for 12 h at room temperature. After filtration and removal of the solvent in vacuo, the residue was chromatographed on silica gel with ethyl acetate as eluant, to give **14** (3.7 g; 98%) as a colorless oil: IR 3350, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (d, 6 H, J = 5.5 Hz), 3.5 (d, 2 H), 3.2–3.8 (m, 2 H), 3.9–4.3 (m, 1 H), 4.5–4.9 (m, 1 H), 4.8 (br s, 1 H, OH); MS, m/e (relative intensity) 159 (M^+, 8), 144 (85), 86 (25), 70 (35), 56 (100). Anal. Calcd for $C_7H_{13}NO_3$: C, 52.81; H, 8.23. Found: C, 52.79; H, 8.20.

3-Isopropyl-5-[((methylsulfonyl)oxy)methyl]oxazolidin-2-one (15). To a solution of CH_2Cl_2 (30 mL) containing **14** (21 mmol; 3.3 g), Et_3N (30 mmol; 3.0 g), and a catalytic amount of (*N,N*-dimethylamino)pyridine (0.1 g) was added methanesulfonyl chloride (23 mmol; 2.6 g), and the mixture was stirred for 2 h at 0 °C. Then water was added, and the mixture was extracted with CH_2Cl_2 (150 mL). After removal of the solvent, **15** was recovered in a quantitative yield: IR 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (d, 6 H, J = 5.5 Hz), 3.1 (s, 3 H), 3.2–3.8 (m, 2 H), 3.9–4.3 (m, 1 H, J = 5.5 Hz), 4.4 (d, 2 H), 4.5–4.9 (m, 1 H). Anal. Calcd for $C_8H_{15}NO_5S$: C, 40.50; H, 6.37. Found: C, 40.47; H, 6.34.

3-Isopropyl-5-[(naphthyloxy)methyl]oxazolidin-2-one (16). To a solution of **15** (20 mmol; 4.7 g) in benzene (35 mL) was added Amberlyst A 26 in the naphtolate form (20 g; ~3.8 mequiv/g), and the suspension was stirred for 24 h at room temperature. The resin was then filtered off, the solvent removed in vacuo, and the residue purified by column chromatography over silica gel with cyclohexane–ethyl acetate (1:1) as eluant, to give **16** (4.0 g; 70%) as a white solid: mp 124 °C; IR 1730, 1590, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (d, 6 H, J = 6 Hz), 3.5–4.0 (m, 2 H), 4.1–4.4 (m, 1 H), 4.4 (d, 2 H), 4.5–5.2 (m, 1 H), 6.9–8.4 (m, 7 H_{Ar}); ^{13}C NMR (CD_3COCD_3) δ 127.7, 126.7, 126.2, 125.4, 121.9, 120.9, 105.4, 71.3, 69.1, 44.9, 41.5, 19.2; MS, m/e (relative intensity) 285 (M^+, 88), 226 (20), 144 (90), 100 (100). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71. Found: C, 71.54; H, 6.68.

1-(Isopropylamino)-3-[(1-naphthyl)oxy]propan-2-ol (Propranolol) (17). A solution containing **16** (10 mmol; 2.88 g) in ethanol (10 mL) was added to a 4 N KOH solution (10 mL), and the mixture was refluxed for 24 h. The reaction was then extracted with benzene, and the solvent was stripped off in vacuo. The product **17** was obtained in a quantitative yield: mp 93–94 °C (lit.[17] mp 96 °C); IR 3400, 3300, 1590, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1 (d, 6 H, J = 5.5 Hz), 2.6–3.2 (m, 4 H + OH), 4.0–4.4 (m, 3 H), 6.75–8.4 (m, 7 H_{Ar}); ^{13}C NMR (CD_3OD) δ 128.4, 127.3, 126.9, 126.1, 122.9, 121.4, 105.9, 74.1, 69.8, 51.0, 50.1, 22.7, 22.5; MS, m/e (relative intensity) 259 (M^+, 85), 244 (24), 215 (50), 144 (100). Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16. Found: C, 74.08; H, 8.14.

Acknowledgment. This work was supported by a grant from M.P.I. (Rome).

Registry No. **1a**, 2305-21-7; **1b**, 80885-30-9; **1c**, 110-64-5; **3a**, 59874-89-4; **3b**, 93667-62-0; **3c**, 97186-55-5; **4a**, 4181-11-7; **4a**·HCl, 99726-00-8; **4b**, 99726-01-9; **4b**·HCl, 99726-02-0; **4c**, 99726-03-1; **4d**, 99726-04-2; **4e**, 99726-05-3; **5**, 99726-06-4; *cis*-**6a**, 99726-07-5; *trans*-**6a**, 99726-08-6; *cis*-**6b**, 99726-09-7; *trans*-**6b**, 99726-10-0; *cis*-**6c**, 99726-11-1; *trans*-**6c**, 99726-12-2; *cis*-**6d**, 99726-13-3; *trans*-**6d**, 99726-14-4; *cis*-**6e**, 99726-15-5; *trans*-**6e**, 99726-16-6; *cis*-**6f**, 99726-17-7; *trans*-**6f**, 99726-18-8; *cis*-**7a**, 99726-19-9; *trans*-**7a**, 99726-20-2; *cis*-**7b**, 99726-21-3; *trans*-**7b**, 99726-22-4; *cis*-**7c**, 99726-23-5; *trans*-**7c**, 99726-24-6; **8a** (isomer 1), 97186-68-0; **8a** (isomer 2), 99726-25-7; **8b** (isomer 1), 97224-13-0; **8b** (isomer 2), 99726-26-8; *cis*-**9a**, 99726-27-9; *trans*-**9a**, 99726-28-0; *cis*-**9b**, 99726-29-1; *trans*-**9b**, 99726-30-4; *cis*-**9c**, 99726-31-5; *trans*-**9c**, 99726-32-6; **10a** (isomer 1), 99726-33-7; **10a** (isomer 2), 99726-34-8; **10b** (isomer 1), 99726-35-9; **10b** (isomer 2), 99726-36-0; **11**, 99726-37-1; **12**, 99726-38-2; **13**, 95360-67-1; **14**, 83277-30-9; **15**, 99726-39-3; **16**, 70693-88-8; **17**, 13013-17-7; CCl_3CN, 545-06-2; allylamine, 107-11-9; 2-bromopropane, 75-26-3.

(17) Howe, R.; Shanks, R. G. *Nature* (London) **1966**, *210*, 1336.

Thermorubin II: 1,3-Dihydroxy-9*H*-xanthones and 1,3-Dihydroxy-9*H*-xanthenes. New Methods of Synthesis

Radhakrishna K. M. Pillai, Prakash Naiksatam, Francis Johnson,* Raghavan Rajagopalan, Paul C. Watts, Renato Cricchio, and Sonia Borras

Department of Chemistry and the Department of Pharmacological Sciences, State University of New York, Stony Brook, New York 11794

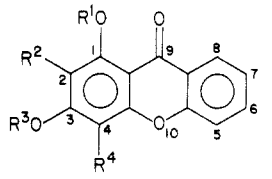
Received July 2, 1985

Two new efficient methods for the synthesis of 1,3-dihydroxy-9*H*-xanthones have been developed. The first, an adaptation of the classical method of Grover, Shah, and Shah, utilizes Eaton's reagent (P_2O_5/CH_3SO_3H) in place of $ZnCl_2/POCl_3$ to effect the acylation step. The second, an entirely new method, is based on the Friedel–Crafts acylation of a *O,O,O*-tris(trimethylsilyl)phloroglucinol by a 2-chlorobenzoyl chloride. Both methods give good yields. Improvements have been made in the Tanase synthesis of 1,3-dihydroxy-9*H*-xanthenes and the methyl ethers of the latter have been shown to undergo formylation at the 4-position. By contrast, related xanthones are known to undergo substitution at the 2-position. The structures in a series of 2-substituted 9*H*-xanthones including the previously known 2- and 4-methyl-1,3-dihydroxy-9*H*-xanthones have been examined by the use of an NMR shift reagent.

In previous papers[1,2] dealing with the structure of the antibiotic thermorubin, we had cause to synthesize several derivatives of 1,3-dihydroxy-9*H*-xanthone (**1**) amongst which were compounds designated as having structures **2–4**. The regiochemistry of the carboxy group in these substances was assigned solely on the basis of mass spectral data. In view of the fact that these compounds were used[1,2] in structural arguments concerning thermorubin, we decided to seek additional evidence for the position assignment of this group. Our initial intention was to convert the carboxyl to a methyl group and then to compare the product with the known 2- and 4-methyl-1,3-dihydroxyxanthones (**5** and **6**) or their derivatives. However, in our

(1) Moppett, C. E.; Dix, D. T.; Johnson, F.; Coronelli, C. *J. Am. Chem. Soc.* **1972**, *94*, 3269–3272.
(2) Johnson, F.; Chandra, B.; Iden, C. R.; Naiksatam, P.; Kahen, R.; Okaya, Y.; Lin, S.-Y. *J. Am. Chem. Soc.* **1980**, *102*, 5580–5585.

0022-3263/86/1951-0717$01.50/0



1, $R^1=R^2=R^3=R^4=H$
2, $R^1=R^3=R^4=H$; $R^2=CO_2H$
3, $R^1=R^4=H$; $R^2=CO_2CH_3$; $R^3=CH_3$
4, $R^1=R^3=CH_3$; $R^2=CO_2CH_3$; $R^4=H$
5, $R^1=R^3=R^4=H$; $R^2=CH_3$
6, $R^1=R^2=R^3=H$; $R^4=CH_3$

opinion, neither the synthetic methods nor the NMR spectral data described in the literature[3,4] for the latter compounds allows unambiguous assignment of their structures. We therefore devoted some effort to finding other evidence that would confirm or disprove the original assignments. In the course of both this work and of preparing compounds **1–6** we have evolved new and more satisfactory general methods for the synthesis of the simpler 1,3-dihydroxyxanthones. These are discussed first.

Synthesis of 1,3-Dihydroxyxanthones

An almost universal approach to the synthesis of hydroxylated xanthones is the original method of Grover, Shah, and Shah,[5] and this is illustrated in Scheme I. In some instances the xanthone **10** is obtained directly; in others the intermediate benzophenone **9** is isolated, and this on heating in aqueous solution cyclizes to the desired xanthone. Yields range from 18–48%.

In our hands the crude product of this type of reaction always contained a large amount of a brown slimy material, which on a large scale proved extremely difficult to remove by either mechanical or chemical means.

A little-known but attractive alternative route for the synthesis of 1,3-dihydroxyxanthones is the procedure of Tanase.[6] This approach and its utilization will be discussed later. At this point suffice it to say that the method is rather lengthy and as described in the literature contains a capricious hydrogenation step. We therefore sought to improve the direct method of Grover et al.[5] and initially we attempted to use other milder reagents in place of $POCl_3/ZnCl_2$. However neither BF_3 etherate, $(CF_3CO)_2O/ZnCl_2$ nor $(CF_3CO)_2O/CF_3CO_2H$ gave any of the desired product. Success was achieved, however, when Eaton's reagent[7] (P_2O_5/CH_3SO_3H) was employed as the condensing agent. Yields in this one-step procedure are eminently satisfactory (Table I, method A); the product is clean, and the xanthone, rather than the benzophenone, is always the major product. The procedure, however, appears to be restricted to phloroglucinols because neither hydroquinone nor resorcinol nor pyrogallol gives any significant yield of the expected xanthone. Only starting materials and/or O-acylated products are obtained. Parallel with these experiments we examined a novel approach to the desired xanthones. This consists in treating the tris(trimethylsilyl) derivative[8] of phloroglucinol (**11**)

Scheme I

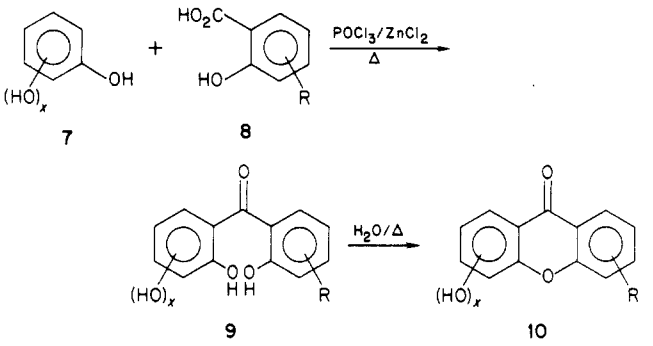
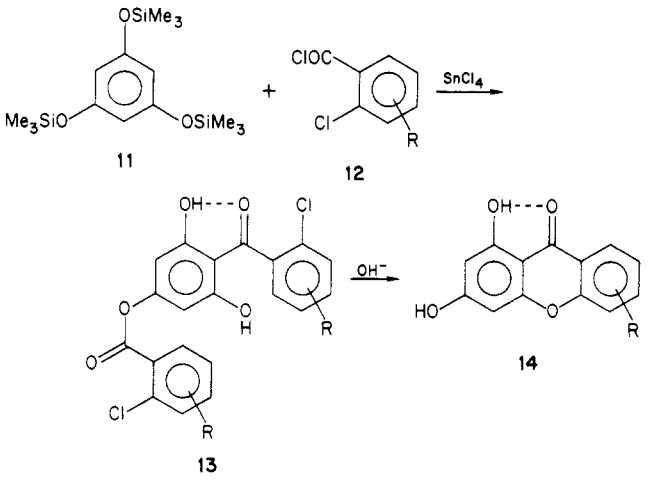


Table I

1,3-Dihydroxyxanthone	yield, (%) method A	method B
parent	91	67
6-chloro	93	63
7-chloro	79	58
8-chloro	89	
7-bromo	83	
6-methoxy	92	69

with 2 equiv of a 2-chlorobenzoyl chloride (**12**) in the presence of stannic chloride in methylene chloride. The



major product of this reaction is the acylated benzophenone **13**, which when heated with base undergoes both hydrolysis and cyclization to afford **14**. In practice, **13** need not be purified and overall yields of **14** are satisfactory (Table I, method B). Again the method appears restricted to 1,3-dihydroxyxanthones[9] because the corresponding silyl derivatives of dihydric phenols such as resorcinol and catechol give largely the bis-O-aroylated product and little of the required intermediate benzophenone, thus limiting the usefulness of the procedure.

Synthesis and Proof of Structure of 2, 5, and 6

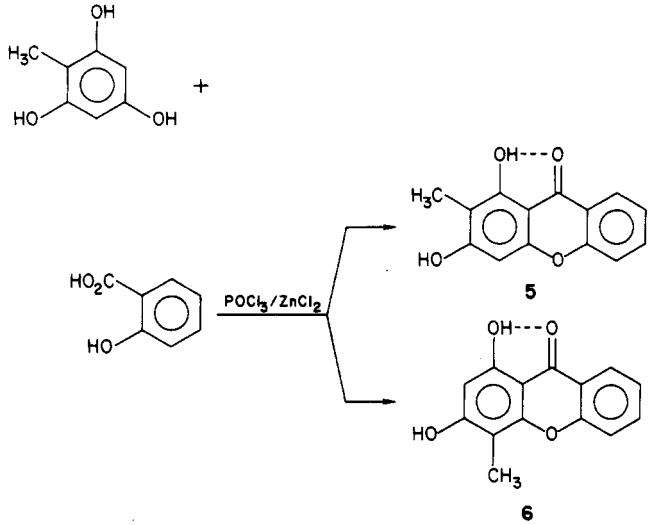
The synthesis of the carboxylic acid, to which structure **2** was assigned,[1] was achieved by the treatment of **1** with Stiles' reagent. Brief contact of **2** with diazomethane afforded **3**, whereas prolonged treatment led to the permethylated product **4**.

As noted previously the structural assignments for these compounds were based on mass spectral data that were

(3) Jain, A. C.; Khanna, V. K.; Seshadri, T. R. *Tetrahedron* **1969**, *25*, 275–282.
(4) Pinto, M. M.; Polonia, J. *Helv. Chim. Acta* **1974**, *57*, 2613–2617.
(5) Grover, P. K.; Shah, G. D.; Shah, R. C. *J. Chem. Soc.* **1955**, 3982–3985.
(6) Tanase, Y. *J. Pharm. Soc. Jpn.* **1941**, *61*, 341–356. This article by Tanase was not abstracted by Chemical Abstracts and has rarely been employed in xanthone and xanthene synthesis. Hence a more detailed outline is given in the present article. For another application, see: Davies, J. E.; Kirkcaldy, D.; Roberts, J. C. *J. Chem. Soc.* **1960**, 2169–2178.
(7) Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071–4073.
(8) Henglein, F. A.; Kramer, J. *Chem. Ber.* **1959**, *92*, 2585–2592.

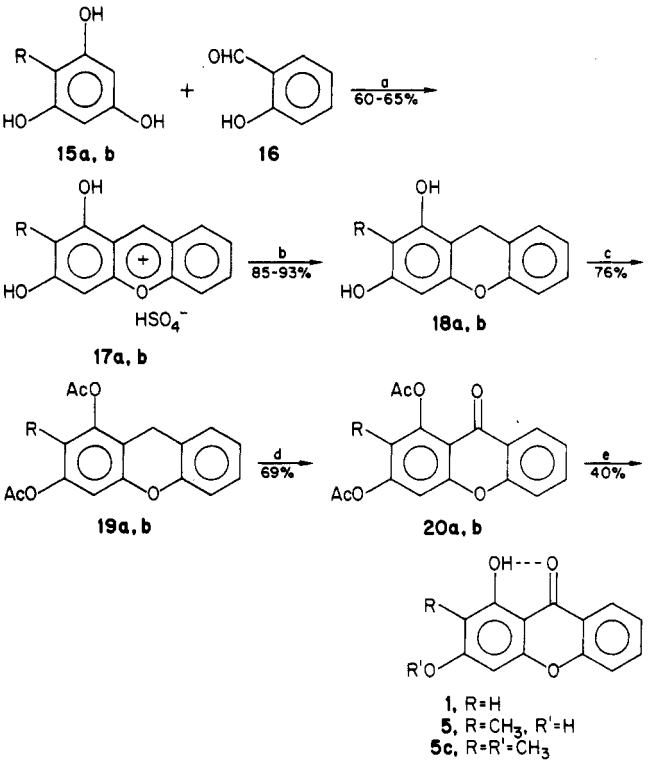
(9) Given that phloroglucinol exhibits a character partially representative of cyclohexane-1,3,5-trione, the fact that **11**, but not lower homologues, undergoes facile acylation probably reflects its greater enol silyl ether character. Such ethers are well-known to undergo C-acylation under Friedel–Crafts conditions, but yields are usually good only with polyhalo acid halides or anhydrides (Murai, S.; Kuroki, Y.; Hasegawa, K.; Tsutsumi, S. *J. Chem. Soc., Chem. Commun.* **1972**, 946–947).

not unequivocal. We decided therefore to attempt to correlate these substances chemically with the 2- and 4-methyl-1,3-dihydroxyxanthones, **5** and **6**, respectively, since these seemed to be the closest known related compounds. Both of these substances had been prepared[3,4] previously, the most significant paper being that of Pinto and Polonia,[4] who used the procedure of Grover et al.[5] The yields of **5** and **6** were 28% and 0.6%, respectively, and their separation required extensive chromatography.



Regiochemical assignments were made[4] using the finding by Barraclough et al.[10] that the C-4 hydrogen atom, in isomers of this type, usually absorbs in the NMR spectrum at lower field than the C-2 hydrogen. Nevertheless the assignments are ambiguous because the positions of absorption of both of the hydrogen atoms in question (**5**, 4-H, δ 6.52; **6**, 2-H, δ 6.35) lie well within the limits of deviation (δ ±0.17) of the mean experimental value (δ 6.44) quoted[10] for the C-4 hydrogen atom. The latter was obtained from a series of 17 xanthones having dioxy and alkyl substituents. The mean value obtained for the C-2 hydrogen atom was δ 6.32 ± 0.06. Because of both this uncertainty of assignment and the extremely poor yield of **6**, we decided to look for an alternative method of synthesis and to ascertain their regiochemistry using a different procedure. With regard to synthesis we examined the approach used by Tanase.[6] Scheme II shows our own adaptation which involves two modifications of the original procedure. The first is the use of acetic acid as a diluent in the condensation reaction. This allows easy removal of the brick-red xanthenium salt **17** by filtration. The second is the change to sodium borohydride or better triethyl silane as the reducing agent for the conversion of **17** to the xanthene **18** instead of the palladium-catalyzed hydrogenation of the alkali-neutralized xanthenium salt as recommended by Tanase.[6] In our hands the hydrogenation method proved to be capricious, giving highly variable yields of **18**. In the **a** series (Scheme II) this approach led to the well-known 1,3-dihydroxyxanthone as previously reported by Tanase,[6] whereas in the **b** series the sole product was the compound assigned[4] as being the 2-methyl homologue (**5**) (reported[4] mp 250–251 °C). This on brief treatment with diazomethane gave the monomethoxy derivative **5c**, as expected; the hydroxyl of 1-hydroxyanthones is known[11] to be resistant to methylation under these conditions, an effect that is undoubtedly due to its low acidity because of H bonding to the 9-carbonyl.

Scheme II[a]

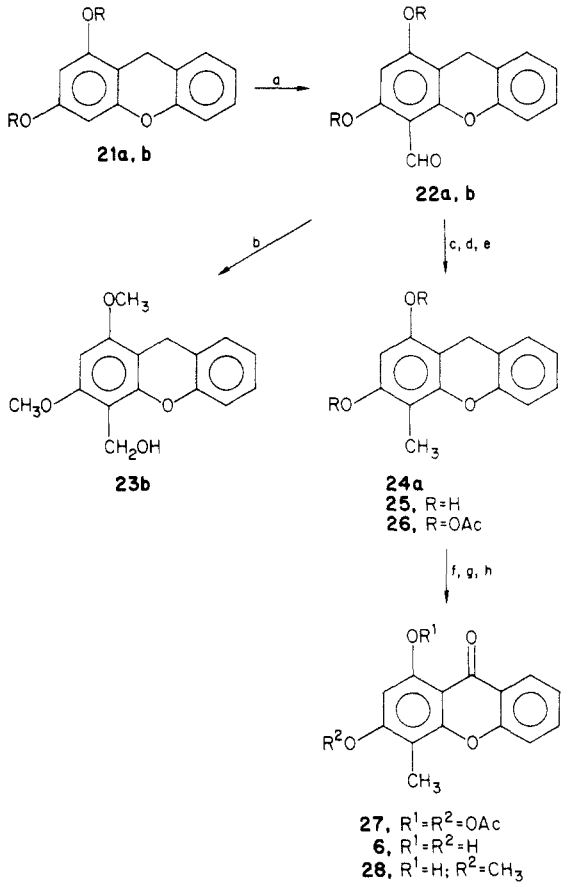


[a] **a** series R = H; **b** series R = CH_3. Reagents: (a) H_2SO_4/AcOH; (b) $CF_3CO_2H/CF_3CO_2Na/Et_3SiH$ or $NaBH_4$; (c) Ac_2O; (d) CrO_3; (e) OH^-.

In an attempt to find a better route to the compound designated[4] as the 4-methyl isomer (**6**), the chemistry of **18a** was explored. Protection of the hydroxyl groups as the dibenzyl ether **21a** (Scheme III) followed by formylation ($POCl_3/PhN(CH_3)CHO$)[12] afforded an aldehyde which we now regard as **22a**. Reduction of the latter under Clemmensen conditions gave **24a**, which when hydrogenated over a palladium catalyst led to **25**. The corresponding diacetate **26**, when oxidized with chromium trioxide in acetic acid followed by hydrolysis gave the compound described[3,4] in the literature as **6** (reported[4] 241–242 °C). This behaves in the same way as **5**, yielding a monomethyl ether **28** when treated briefly with diazomethane at 0 °C. Having developed a series of intermediates related to both 1,3-dihydroxymethylxanthones of interest, we now attempted to relate them to the product of carboxylation (Stiles' reagent)[13] of 1,3-dihydroxyxanthone. Toward this end the permethylated derivative **4**, obtained by the exhaustive action of diazomethane on the acid **2**, was reduced with lithium aluminum hydride (Scheme IV). This led to a complex mixture from which it was possible to isolate an (hydroxymethyl)dimethoxyxanthene (**29**) in 28% yield. Palladium-catalyzed hydrogenation of the latter then gave a methyl dimethoxyxanthene **30**, which also could be obtained from diazomethane treatment of **18b**. In an attempt to put the position assignments of the 2- and 4-methyl compounds on a firmer basis we decided to examine the ^1H NMR behavior of the two isomeric hydroxymethyl xanthenes **29** and **23b** in the presence of a shift reagent. We expected, in the case of the 4-hydroxymethyl compound, that with increasing quantities of shift reagent ($Eu(fod)_3$), the signal

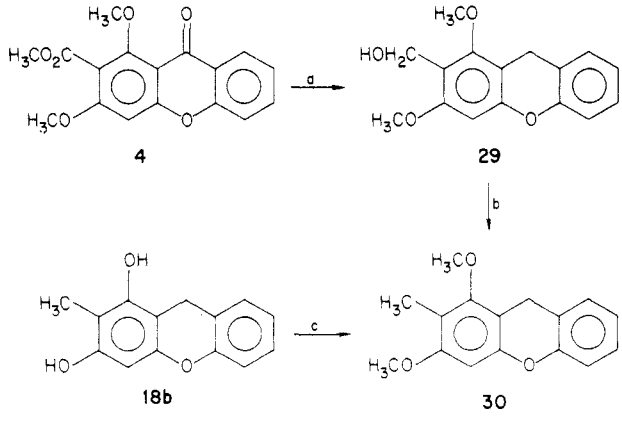
(10) Barraclough, D.; Locksley, H. D.; Scheinmann, F.; Taveira-Magalhaes, M.; Gottleib, O. R. *J. Chem. Soc. B* **1970**, 603–612.
(11) Robertson, A.; Waters, R. B. *J. Chem. Soc.* **1929**, 2239–2243.
(12) Gutsche, C. D.; Jason, E. F.; Coffey, R. S.; Johnson, E. E. *J. Am. Chem. Soc.* **1958**, *80*, 5756–5767.
(13) Stiles, M. *J. Am. Chem. Soc.* **1959**, *81*, 2598–2599. Mechoulam, R.; Ben-Zvi, Z. *J. Chem. Soc., Chem. Commun.* **1969**, 343–344.

Scheme III[a]



[a] **a** series, R = CH_2Ph; **b** series, R = CH_3. Reagents: (a) $POCl_3$/PhN(CH_3)CHO; (b) $NaBH_4$; (c) Zn/HCl (**24a**); (d) Pd/H_2 (**25**); (e) Ac_2O (**26**); (f) CrO_3 (**27**); (g) OH^- (**6**); (h) CH_2N_2 (**28**).

Scheme IV[a]



[a] Reagents: (a) $LiAlH_4$; (b) Pd–C/H_2; (c) CH_2N_2.

of one of the methoxy groups would be moved downfield considerably more than that of the other whereas in the case of the 2-hydroxymethyl compound the shift differences should be much less. The required **23b** was prepared (Scheme III) by sodium borohydride reduction of **22b**, the latter having been obtained by formylation of **21b**.

Maximum shifts were obtained at molar ratios of shift reagent: xanthene of 1:5 in both cases. For **29** one of the methoxy shifted from δ 3.85 to 4.05 (Δ = δ 0.20) whereas the other moved from δ 3.85 to 4.36 (Δ = δ 0.51). For **23b** the corresponding shifts were from δ 3.87 to 3.98 (Δ = δ 0.11) and from δ 3.87 to 3.44 (Δ = δ 0.57). Although one of the methoxys in **23b** undergoes a relatively small shift (δ 0.11) as expected, the corresponding shift for **29**, namely, δ 0.20, is not that much greater. Thus the most that can be said is that although the difference in relative shifts observed for the 1-methoxy groups in **29** and **23b** is in the expected direction (in relationship to the structures proposed for **5** and **6** by Pinto and Polonia[4]) and thus is supportive, the magnitude[14] is not sufficient to argue strongly for an indisputable structure proof.

Experimental Section

^1H NMR spectra were measured on an 80-MHz Varian CFT-20 instrument, IR spectra were taken on a Perkin-Elmer 257 spectrometer, and UV spectra were recorded on a Cary 12 spectrometer. Mass spectra were obtained from a Hewlett-Packard HP5983 GC/MS spectrometer (low resolution) or a Kratos MS-30 instrument (high resolution). All new compounds were shown to be homogeneous by TLC in two solvent systems, viz., methylene chloride–ethyl acetate (9:1) and chloroform–methanol (98:2). Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

Preparation of 1,3-Dihydroxy-9*H*-xanthones. Method A. A mixture of phosphorus pentoxide (5 g) and methanesulfonic acid (35 mL) was heated on a steam bath until a clear solution was obtained (0.5 h). To this was added a mixture of phloroglucinol (2.52 g, 10 mmol) and the respective substituted salicylic acid (10 mmol). Heating was continued for 15 min, and the reaction mixture was poured into ice–water. The resulting solid was collected by filtration, washed with water, dried in air, and recrystallized from aqueous ethanol to afford the requisite xanthone. Physical data for the 1,3-dihydroxyxanthones prepared by either this method or method B are noted below. Yields are given in Table I.

Method B. A solution of phloroglucinol tris(trimethylsilyl) ether[8] (3.42 g, 10 mmol) in methylene chloride (20 mL) was added at 0 °C to a methylene chloride solution (50 mL) of the requisite 2-chlorobenzoyl chloride (20 mmol) and stannic chloride (6.60 g, 25 mmol). The reaction mixture was allowed to stand for 48 h at room temperature and then filtered to remove a small amount of precipitate which had formed. This was discarded and the filtrate was decomposed by pouring it into ice–water. The organic layer was separated, washed with water and sodium bicarbonate solution, followed again by water, dried, and concentrated under reduced pressure. The residue, without purification, was dissolved in aqueous potassium hydroxide (4.0 N, 30 mL) and heated on a steam bath for 4 h. The dark solution was cooled and washed with ethyl acetate and the aqueous layer acidified with HCl. Extraction with ethyl acetate, followed by the usual isolation procedure afforded the crude xanthone, which was crystallized from aqueous ethanol.

In the case where 2-chlorobenzoyl chloride itself was used, the crude oil obtained from the acylation part of the procedure was examined further. A sample (0.43 g) was submitted to preparative TLC on silica gel (eluant; 5% ether in benzene) and the major (least polar) band proved to be a viscous oil, which slowly crystallized. Recrystallization (ether–light petroleum) afforded pure **13** (R = H) as microcrystals (0.25 g): mp 140.5–142.5 °C; IR ($CHCl_3$) λ_{max} 3150 (broad), 1750, 1630, 1595, 1300, 1220, 1164, 1154, 1100 (broad), 1054, 994, 926 cm^{-1}; ^1H NMR ($CHCl_3$) δ 5.93 (d, J = 2 Hz; 1 H, Ar H), 6.11 (d, J = 2 Hz, 1 H, Ar H), 7.0 (m, 8 H, Ar H), 12.37 (s, OH). Anal. Calcd for $C_{20}H_{12}Cl_2O_5$: C, 59.57; H, 3.0; Cl, 17.59. Found: C, 59.47; H, 3.11; Cl, 17.65.

1,3-Dihydroxy-6-chloro-9*H*-xanthone: mp 325–327 °C; IR (Nujol) λ_{max} 3250, 1655 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.19 (s, 1 H, H-2), 6.31 (s, 1 H, H-4), 7.29–8.06 (m, 3 H, Ar H), 11.10 (s, 1 H, OH), 12.57 (s, 1 H, OH); HRMS, calcd for $C_{13}H_7ClO_4$ m/z 262.6514, found m/z 262.6513.

1,3-Dihydroxy-7-chloro-9*H*-xanthone: mp 283–285 °C: IR (Nujol) λ_{max} 3250, 1660 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.15 (s, 1 H, H-2), 6.25 (s, 1 H, H-4), 7.46–7.99 (m, 3 H, Ar H), 11.12 (s, OH) 12.54 (s, 1 H, OH); HRMS, found m/z 262.6508.

1,3-Dihydroxy-8-chloro-9*H*-xanthone: mp 307–308 °C; IR (Nujol) λ_{max} 3250, 1660 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.19 (s, 1

(14) In a case that might be considered related, it was found that in the presence of Eu(Fod)$_3$ the ^1H NMR absorption of the 2-methyl group of 2,4-dimethylphenol underwent a downfield shift of 1.35 ppm, whereas that of the 4-methyl substituent was shifted only 0.25 ppm (Schoffner, J. P. *J. Am. Chem. Soc.* **1974**, *96*, 1599–1601).

H, H-2), 6.29 (s, 1 H, H-4), 737–773 (m, 3 H, Ar H), 11.04 (s, 1 H, OH), 12.81 (s, 1 H, OH); HRMS, found m/z 262.6543.

2,4-Dihydroxy-7-bromo-9*H*-xanthone: mp 282–283 °C; IR (Nujol) λ_{max} 3250, 1665 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 6.25 (s, 1 H, H-2), 6.35 (s, 1 H, H-4), 7.66–7.99 (m, 3 H, Ar H), 11.41 (s, 1 H, OH), 12.53 (s, 1 H, OH): HRMS, calcd for $C_3H_7BrO_4$ m/z 306.1166, found m/z 306.1180.

2,4-Dihydroxy-7-methoxy-9*H*-xanthone: mp 280–282 °C; IR (Nujol) λ_{max} 3250, 1655 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 6.11 (s, 1 H, H-2), 6.21 (s, 1 H, H-4) 6.92–7.10 (m, 2 H, Ar H), 7.85–795 (m, 1 H, Ar H), 10.92 (s, 1 H, OH), 12.91 (s, 1 H, OH). HRMS, calcd for $C_{14}H_{10}O_5$ m/z 258.2328, found m/z 258.2332.

1,3-Dihydroxyxanthenium Bisulfate (17a). Dry phloroglucinol (23.5 g) was dissolved in a mixture of sulfuric acid (90 mL) and acetic acid (200 mL). A solution of salicylaldehyde (23 g 1.9 mL) in acetic acid (50 mL) was then added dropwise over a period of 30 min. The mixture was stirred for 15 h and the bright red precipitate removed by filtration through a sintered-glass funnel. The resulting crystalline **17a** was washed with a 1:1 mixture of acetic acid and ether (200 mL) and finally with ether and then allowed to air-dry (38.5 g, 60% yield); mp 195–198 °C; IR (Nujol) λ_{max} 1640, 1600, 1170, 1040, 902, 845, 763, 595 cm^{-1}. The salt was used as such in further experiments.

1,3-Dihydroxy-2-methylxanthenium Bisulfate (17b). Methylphloroglucinol (1.3 g, 1.0 mmol) was dissolved in a mixture of sulfuric acid (5 mL) and acetic acid (11 mL). There was then added dropwise, during 10 min, a solution of salicylaldehyde (1.22 g, 1.06 mL) in acetic acid (2.7 mL). The mixture was stirred for 17 h, and the bright red precipitate was removed by filtration through a sintered-glass funnel. The material was washed first with a 50:50 mixture of acetic acid and ether (100 mL) and then with pure ether and allowed to air-dry (3.1 g, quantitative) (mp 220 °C dec). The salt was used as such for further experiments. IR (Nujol) λ_{max} 1640, 1600, 1170, 1040, 902, 845, 763, 595 cm^{-1}.

1,3-Dihydroxy-2-methyl-9*H*-xanthene (18b) and Its Diacetate (19b). A solution of the xanthenium salt **17b** (1.0 g, 3.1 mmol) in trifluoroacetic acid (4 mL) was treated with sodium trifluoroacetate (0.4 g), and the mixture was stirred for 30 min. Triethylsilane (1.78 mL) was then added dropwise at 10 °C during 5 min. Immediately after the addition had been completed, the red solution decolorized, and a yellow precipitate appeared. The mixture was allowed to stand for 15 h, and the excess trifluoroacetic acid was then removed under reduced pressure. The residue was dissolved in ether, and the ethereal solution was washed with sodium bicarbonate solution and then dried ($MgSO_4$). Removal of the ether afforded **18b** as a faintly yellow solid (0.66 g, 39%), mp 188–190 °C dec, which was immediately acetylated because it darkened rapidly when exposed to air. A mixture of crude **18b** (0.86 g, 3.8 mmol), acetic anhydride (2 mL), and a few drops of pyridine was heated on a steam bath for 2 h. The solution was poured into cold water, and after 1 h it was acidified with 5 N HCl and extracted with EtOAc. The organic extract after evaporation yielded a solid (0.9 g, 76%), which was recrystallized from methanol: mp 150 °C; IR (Nujol) λ_{max} 1740, 1460, 1375, 1200, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.93 (s, 3 H, methyl), 2.31 (s, 3 H, OAc), 2.38 (s, 3 H, OAc), 3.81 (s, 2 H, CH_2), 6.72 (s, 1 H, Ar H), 7.0–7.25 (m, 4 H, ArH); MS, m/z (relative intensity) 312 (M^+, 5.34), 253 (44), 228 (36), 227 (88), 213 (10), 212 (15), 211 (100), 181 (10), 69 (52); HRMS, calcd for $C_{18}H_{16}O_5$ m/z 312.0997, found m/e 312.1004.

1,3-Diacetoxy-2-methyl-9*H*-xanthone (20b). To a solution of **19b** (0.21 g) in acetic acid (16 mL) solution was added dropwise chromium trioxide (70 mg) in water (1 mL). The solution was allowed to stand at room temperature for 4 h and then diluted with water and extracted with ethyl acetate. Evaporation of the solvent gave an oil, which crystallized from ethanol to give **20b** (150 mg, 68.5%): mp 184 °C; IR (Nujol) λ_{max} 1760, 1665, 1615, 1460, 1375, 1305, 1305, 1200, 1080, 890 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.09 (s, 3 H, CH_3), 2.38 (s, 3 H, OAc), 2.52 (s, 3 H, OAc), 7.09–8.25 (m, 5 H, Ar H); MS, m/z (relative intensity) 326 (M^+, 0.01), 284 (29), 243 (14), 242 (100), 241 (26), 213 (30), 92 (10). Anal. Calcd for $C_{18}H_{14}O_6$: C, 66.26; H, 4.32. Found: C, 66.37; H, 4.56.

1,3-Dihydroxy-2-methyl-9*H*-xanthone (5). The preceding diacetate (**20b**) (100 mg) was heated with potassium hydroxide (250 mg) and water (10 mL) on a steam bath for 4 h. The solution was cooled, acidified with dilute hydrochloric acid, and thoroughly extracted with ethyl acetate. Evaporation of the solvent gave a solid (75 mg), which when recrystallized from aqueous alcohol led to pure **5** as yellow needles: mp 251–252 °C (lit.[4] mp 250–251 °C); IR (Nujol) λ_{max} 1740, 1650, 1610, 1660, 1455, 1375, 1330, 1155, 1130, 1090 cm^{-1}; ^{1}H NMR (CF_3CO_2H) δ 10.4 (s, 2 H, phenolic OH), 8,23 (m, 4 H, Ar H), 7.1 (s, 1 H, Ar H), 2.33 (s, 3 H, methyl); MS, m/z (relative intensity) 242 (M^+, 100), 241 (75), 213 (30), 121 (22). Anal. Calcd for $C_{14}H_{10}O_4$: C, 69.41; H, 4.16. Found: C, 68.90; H, 4.22.

1,3-Dihydroxy-9*H*-xanthene (18a). (a) To a suspension of 1,3-dihydroxyxanthenium bisulfate (3.0 g) in water (100 mL) and ethyl acetate (15 mL) was added sodium borohydride in small portions until the suspended solid had dissolved and the solution was only faintly red. A small amount of charcoal was added, and the solution was filtered and then acidified. Extraction with ethyl acetate and evaporation of the solvent afforded **18a** as a crystalline solid (1.75 g, 83% yield), mp 207 °C (202–207 °C dec). This material was identical with that prepared by the method described below.

(b) A solution of the xanthenium salt (38.5 g) in trifluoroacetic acid (100 mL) was treated with sodium trifluoroacetate (35 g), and the mixture was stirred for 30 min. Neat triethylsilane (20 g) was then added dropwise at 10 °C during 15 min. At the end of the addition the red color was discharged and a yellow precipitate had appeared. The mixture was allowed to stand overnight, and the excess trifluoroacetic acid was removed under reduced pressure. Ether and water were added to the crystalline residue, and the ether layer was separated, washed with sodium bicarbonate solution, and then dried ($MgSO_4$). Removal of the ether afforded a faintly yellow solid (30.5 g), which was then dissolved in a mixture of ether (250 mL) and hexane (50 mL), filtered, and treated with charcoal and the solvent removed. The recovered solid was recrystallized from aqueous methanol to afford the desired **18a** (24.6 g, 85%): mp 204–205 °C; IR (Nujol) λ_{max} 3400, 3300 (shoulder), 1635, 1525, 1263, 1141, 1040, 744 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.92 (s, $ArCH_2Ar$, 2 H), 6.22 (s, Ar H, 2 H), 7.15 (m, Ar H, 4 H); MS, m/z (relative intensity) 214 (M^+ 58), 213 (100), 197 (32), 171, 139, 130, 115, 100, 69. Anal. Calcd for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.86; H, 4.83.

1,3-Bis(benzyloxy)-9*H*-xanthene (21a). 1,3-Dihydroxyxanthene (**18a**; 2.12 g) was added to a suspension of finely powdered anhydrous potassium carbonate (4.2 g), in dimethylformamide (50 mL). Benzyl chloride (3 g) was then added, and the mixture was heated under reflux for 1 h. The reaction solution was cooled, water (80 mL) was added, the mixture was extracted with methylene chloride, and the extract was washed with water and dried ($MgSO_4$). Removal of the solvent afforded a solid (3.9 g), which was recrystallized from methylene chloride–methanol to give pure **21a** (2.9 g, 74%): mp 123 °C; IR (Nujol) λ_{max} 1633, 1600, 1580, 1500, 1480, 1232, 1184, 1038, 817, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 2 H, $ArCH_2Ar$), 5.01 (s, 4 H, benzylic CH_2), 6.30 (2 H, Ar H), 7.01–7.45 (14 H, m, Ar H); MS, m/z (relative intensity) 394 (M^+, 2.4), 100 (9.6), 92 (7.6), 91 (100), 65 (54). Anal. Calcd for $C_{27}H_{22}O_3$: C, 82.21; H, 5.62. Found: C, 82.59; H, 5.71.

1,3-Bis(benzyloxy)-4-formyl-9*H*-xanthene (22a). A mixture of *N*-methylformanilide (3 g) and phosphorus oxychloride (0.5 g) was allowed to stand at room temperature for 30 min. A solution of **9** (0.784 g) in methylene chloride (1 mL) was added, and the solution then was heated on the steam bath to ensure complete dissolution of the xanthene. After the mixture was allowed to stand at room temperature overnight, methylene chloride (20 mL) and water were added, the organic layer was separated, washed with 15% HCl, water, and sodium bicarbonate solution, and finally dried over magnesium sulfate. Removal of the solvent gave a crystalline solid (1.15 g), which was recrystallized from methylene chloride–ether to give crystals of pure **22a** (0.74 g, 88%): mp 186–187 °C; IR (Nujol) λ_{max} 1670, 1615, 1600, 1480, 1395, 1370, 1258, 1230, 1150, 1093, 800, 760, 735, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 2 H, $ArCH_2Ar$), 5.06–5.10 (2 s, 2 H each, benzylic CH_2), 6.23 (s, 1 H, Ar H), 7.11–7.88 (m, 4 H, Ar H), 10.55 (s, 1 H, CHO); MS, m/z (relative intensity) 422 (M^+, 1.1), 92 (7.9) 91 (100), 65 (50). Anal. Calcd for $C_{28}H_{22}O_4$: C, 79.60; H, 5.25. Found: C, 79.39; H, 5.09.

1,3-Bis(benzyloxy)-4-methyl-9*H*-xanthene (24a). To a suspension of 1,3-bis(benzyloxy)-4-formylxanthene (**22a**; 4.0 g) in dioxane (10 mL) were added a zinc–mercury amalgam (freshly

prepared from 0.3 g of zinc dust and 0.3 g of mercuric chloride) and 4 N HCl (15 mL). The mixture was heated under reflux for 2 h and then filtered hot. Water (100 mL) was added to the filtrate, and it was then extracted with methylene chloride (3 × 25 mL). The extract was washed with water, dried ($MgSO_4$), and evaporated. The residue on crystallization from dioxane–ethanol led to pure **24a** (3.5 g, 90%): mp 148 °C; IR (Nujol) λ_{max} 1620, 1600, 1580, 1375, 1250, 1230, 1200, 1180, 1110, 1090, 1040, 980, 930, 860, 800, 750, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.1 (s, 3 H, methyl), 3.82 (s, 2 H, $ArCH_2Ar$), 6.1 (s, 1 H, Ar H), 7.0 (4 H, m, Ar H); MS, m/z (relative intensity) 408 (M^+, 181 (8.1), 92 (8.2), 91 (100), 65 (6.4); HRMS, calcd for $C_{28}H_{24}O_3$ m/z 408.1725, found m/z 408.1710.

1,3-Dihydroxy-4-methyl-9*H*-xanthene (25) and Its Diacetate (26). 1,3-bis(benzyloxy)-4-methylxanthene (**11**; 100 mg) was dissolved in ethyl acetate (15 mL) and hydrogenated over a 10% Pd–C catalyst (100 mg) for 15 min at room temperature. The catalyst was removed by filtration through Celite, and the filtrate on evaporation afforded crude **25** (37 mg, 66%): mp 142–143 °C; ^1H NMR (acetone-d_6) δ 2.83 (s, 3 H, CH_3), 3.85 (s, 2 H, CH_2), 6.24 (s, 1 H, H-2), 7.13 (m, 4 H, Ar H). Because this compound tended to oxidize rapidly in air, without further purification, a sample (98 mg) of **25** was mixed with acetic anhydride (2 mL) containing pyridine (4 drops) and heated on a steam bath for 2 h. The solution was poured into cold water and after 1 h acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic extract on evaporation yielded a solid, which recrystallized from aqueous ethanol to afford **26** (94 mg, 70%): mp 122 °C; IR (KBr) λ_{max} 1750, 1610, 1680, 1480, 1440, 1380, 1210, 1120, 1090, 900, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (s, 3 H, 2.28 (s, 3 H, OAc), 2.31 (s, 3 H, CHOAc), 3.80 (s, 2 H, $ArCH_2Ar$), 6.56 (s, 1 H, Ar H), 7.08 (m, 4 H, Ar H); MS, m/z (relative intensity) 312 (M^+, 7.36), 253 (41.23), 228 (53.97), 227 (100), 212 (11.53), 211 (73.47), 181 (9.97), 69 (31.4); HRMS, calcd for $C_{18}H_{16}O_5$ m/e 312.0997, found m/z 312.1006.

1,3-Diacetoxy-4-methyl-9*H*-xanthone (27). This xanthone was obtained from **26** by using the same oxidative procedure that was employed to convert **19b** to **20b**. The yield of pure **27** was 68%: mp 189 °C; IR (KBr) λ_{max} 1760, 1650, 1610, 1475, 1400, 1375, 1320, 1280, 1200, 1100, 910, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (s, 3 H, methyl), 2.35 (s, 3 H, CH_3CO_2), 2.45 (s, 3 H, CH_3CO_2), 6.76 (s, 1 H, Ar H), 7.46–8.23 (m, 4 H, Ar H); MS, m/z (relative intensity) 326 (M^+), 284 (32), 243 (15), 242 (100), 241 (29). Anal. Calcd for $C_{18}H_{14}O_6$: C, 66.26; H, 4.32. Found: C, 66.46; H, 4.38.

1,3-Dihydroxy-4-methyl-9*H*-xanthone (6). Hydrolysis of **27** in a manner analogous to that used with **20b** to obtain **5** led after crystallization from aqueous ethanol, to pure **6**: mp 240–241 °C (lit.[4] mp 241–242 °C); MS, m/z (relative intensity) 242 (M^+, 100), 241 (72), 213 (47), 185 (14), 139 (20), 129 (12), 128 (35), 127 (14), 121 (29), 115 (26), 93 (17), 92 (33), 69 (90); HRMS, calcd for $C_{14}H_{10}O_4$ m/z 242.0578, found m/z 242.0544.

1-Hydroxy-3-methoxy-2-methyl-9*H*-xanthone (5c). A solution of 1,3-dihydroxy-2-methylxanthone (**5**; 100 mg) in methanol (3 mL) was treated with excess diazomethane in ether at 0 °C for 10 min. The solution was evaporated, and the resulting brown solid was crystallized from aqueous alcohol to afford **5c** (57 mg, 54%): mp 220 °C; MS, m/z (relative intensity) 256 (M^+, 100), 255 (37), 241 (16), 239 (11), 238 (42), 228 (9.5), 227 (57), 226 (31), 225 (43), 213 (15), 197 (21), 128 (13) 121 (13), 69 (55.5); HRMS, calcd for $C_{14}H_{10}O_4$ m/z 256.0735, found m/z 256.0738.

1-Hydroxy-3-methoxy-4-methyl-9*H*-xanthone (28). Exactly the same procedure that was used for the preparation of **5c** was followed using **6** to obtain **28**: recrystallized from aqueous ethanol; yield 70%, mp 255 °C; ^1H NMR (acetone-d_6) δ 2.22 (s, 3 H, CH_3), 3.92 (s, 3 H, OCH_3), 6.46 (s, 1 H, H-2), 7.33 (m, 4 H, Ar H); MS, m/z (relative intensity) 256 (M^+, 100), 255 (29.5), 241 (31.9), 227 (25), 226 (12), 225 (39), 226 (12), 225 (39), 213 (16), 197 (12), 128 (12), 77 (11), 69 (36); HRMS, calcd for $C_{15}H_{12}O_4$ m/z 256.0735, found m/z 256.0738.

1,3-Dihydroxy-2-carboxy-9*H*-xanthone (2) and Its Dimethyl Derivative 3. 1,3-hydroxyxanthone (0.5 g) and Stiles' reagent[13] (15 mL) were heated for 2 h under argon. The cooled solution then was added carefully to 6 N HCl (25 mL) and the pale yellow precipitate removed by filtration. The amorphous solid was dried overnight in vacuo to give an amorphous solid (0.527 g), partial melting at 229–231 °C with gas evolution and resolidification followed by remelting at 263–266 °C: IR (Nujol) λ_{max} 3110, 1680, 1615, 1580, 1475, 1440, 1380, 1340, 1300, 1255, 1233, 1182, 1096 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.37 (s, 1 H, H-4), 7.44–8.06 (m, 4 H, Ar H), 10.40 (br s, 3 H, Ar H and CO_2H); MS, m/z (relative intensity) 272 (M^+, 24 (100), 228 (12), 226 (16), 198 (30), 170 (15), 142 (18), 113 (20); HRMS, calcd for $C_{14}H_8O_6$ m/z 272.0321, found m/z 272.0312.

A sample (0.5 g) of this acid was suspended in ether and treated briefly with an excess of an ethereal solution of diazomethane. When the brisk evolution of nitrogen ceased (15–20 min), the ether was removed, and the residue was crystallized from ethanol to give pure 1-hydroxy-2-(methoxycarbonyl)-3-methoxyxanthone (**3**; 0.41 g): mp 179–181 °C; IR (Nujol) λ_{max} 3800–3220 (m, broad) 1740, 1655, 1610, 1565, 1270, 1230, 1170, 1115, 1105 ($CHCl_3$) 3200–2300 (m, broad) 1735, 1650, 1610, 1270, 1220, 1165, 1115 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 246 (38500), 300 (16020), 340 nm (7080); ^1H NMR ($CDCl_3$) δ 3.90 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 6.34 (s, 1 H, Ar H), 7.34 (m, 1 H, Ar H) 7.62 (m, 2 H, Ar H), 8.08 (m, 1 H, Ar H), 1320 (s, 1 H, OH); HRMS, calcd for $C_{16}H_{12}O_6$ m/z 300.0634, found m/z 300.0646. Anal. Calcd for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03. Found: C, 63.73; H, 4.16.

1,3-Dimethoxy-2-(methoxycarbonyl)-9*H*-xanthone (19). A sample of 1.0 g of 1,3-dihydroxyxanthone-2-carboxylic acid was suspended in anhydrous ether, and a solution of diazomethane (0.5 g) in ether was added. After the mixture was allowed to stand overnight at 0 °C the ether and excess diazomethane were removed by evaporation at 35 °C. The residue was recrystallized from aqueous alcohol to afford **19** (1.05 g, 91%): mp 190 °C; IR ($CHCl_3$) λ_{max} 1745, 1660, 1630, 1615, 1470, 1440, 1307, 1261, 1107, 1048 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.92, 3.96, 4.03 (3 s, 3 H each, OMe groups), 6.66 (s, 1 H, H at C-4), 7.2–8.4 (m, 4 H, Ar H); MS, m/z (relative intensity) 314 (M^+), 282 (44), 253 (60), 174 (100), 128 (44). Anal. Calcd for $C_{17}H_{14}O_6$: C, 64.96; H, 4.49. Found: C, 64.85; H, 4.42.

Reduction of 4 by Lithium Aluminum Hydride: Isolation of 1,3-Dimethoxy-2-(hydroxymethyl)-9*H*-xanthene (29). To a dry flask flushed with nitrogen and equipped with a reflux condenser, drying tube, and a magnetic stirrer were added LAH (25 mg, excess) and anhydrous ether (15 mL). The dimethoxy ester **4** (50 mg) in ether (5 mL) was added dropwise at 25 °C, and the mixture then was heated at reflux for 1 h. The reaction mixture was cooled and worked up by destroying excess LAH with ethyl acetate. Saturated ammonium chloride (5 mL) was added, and the solution was stirred for a 5 min and then filtered. The filtrate was extracted with methylene chloride, and the organic solution was dried ($MgSO_4$) and then evaporated to yield the crude reduction product (50 mg). This was further purified by preparative TLC using 5% ethyl acetate in methylene chloride as the eluting agent. This led to pure **29** as an oil (12 mg, 28%): IR (Nujol) λ_{max} 3350, 2950, 1625, 1600, 1575, 1480, 1440, 1255, 1080, 1000, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.3 (t, 1 H, OH), 3.85 (s, 6 H, OCH_3), 3.96 (s, 2 H, $ArCH_3Ar$), 4.71 (d, 2 H, CH_2OH), 6.44 (s, 1 H, Ar H), 7.04–7.25 (m, 4 H, Ar H); MS, m/z relative intensity) 272 (M^+, 35), 271 (82), 241 (100), 239 (34); HRMS, calcd for $C_{16}H_{14}O_4$ m/z 272.1048, found m/z 272.1018.

1,3-Dimethoxy-9*H*-xanthene (21b). To a suspension of 1,3-dihydroxyxanthene (**18a**; 0.7 g) in ether was added excess diazomethane in ether, and the solution was allowed to stand at room temperature for 24 h. Evaporation of the solvent then gave crude **21b** (0.7 g). This material was recrystallized from methanol at 0 °C as thick hard faintly brown crystals: mp 85–86 °C (lit.[15] mp 85–86 °C); 0.3 g (38%); IR (Nujol) λ_{max} 1635, 1610, 1580, 1460, 1375, 1255, 1230, 1200, 1140, 1110, 1090, 1045, 795, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.78 and 3.81 (s, 3 H each, OCH_3), 3.85 (s, 2 H, $ArCH_2Ar$), 6.19 (d, 2 H, J = 2.8 Hz, Ar H), 7.02 and 7.12 (m, 4 H, Ar H); MS, m/z (relative intensity) 242 (M^+, 64), 241 (100), 226 (19), 211 (51.0); HRMS, calcd for $C_{14}H_{14}O_3$ m/z 242.0942, found m/z 242.0951.

1,3-Dimethoxy-4-formyl-9*H*-xanthene (22b). *N*-methylformanilide (0.8 mL) and phosphorous oxychloride (0.2 mL) were mixed and allowed to stand at room temperature for 30 min. A solution of 1,3-dimethoxyxanthene (**21b**: 80 mg) in methylene

(15) Kulkarni, N. A.; Kudar, N. A.; Kulkarni, A. B. *Indian J. Chem.* **1975**, *13*, 856–857.

chloride (0.5 mL) was added, and the mixture was warmed on a steam bath for 5 min to ensure a homogeneous solution and then left at room temperature overnight. Water and methylene chloride were added, and the organic layer was removed, washed with dilute hydrochloric acid and then water, dried ($MgSO_4$), and evaporated to give **22b** as a viscous oil (20 mg, 23%): IR (Nujol) λ_{max} 1680, 1620, 1575, 1460, 1415, 1380, 1320, 1240, 1210, 1190, 1120, 1100, 790, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (s, 2 H, Ar H), 3.91 (s, 6 H, OCH_3), 6.14 (s, 1 H), 7.12 (m, 4 H, Ar H), 10.51 (s, 1 H, CHO); MS, m/z (relative intensity) 270 (M^+, 91), 269 (100), 241, 240, 239 (36.5), 226, 225, 224, 223, 213, 212, 211, 210, 198, 197, 196, 195, 184, 183, 182, 181, 169, 168, 167, 155, 154, 153, 139 (19); HRMS, calcd for $C_{16}H_{14}O_4$ m/z 270.0891, found m/z 270.0867.

1,3-Dimethoxy-4-(hydroxymethyl)-9*H*-xanthene (23b). To a solution of 1,3-dimethoxy-4-formylxanthene (**22b**: 33 mg) in a mixture of THF (5 mL) and ethanol (5 mL) was added sodium borohydride and the reaction mixture was stirred overnight. The excess sodium borohydride was destroyed by 20% acetic acid, and the solvents were removed in vacuo. The residue was extracted with ethyl acetate, and the extract was washed with sodium bicarbonate solution and water, then dried ($MgSO_4$), and evaporated. The crude product was purified by preparative TLC on silica gel plates using 10% EtOAc in methylene chloride as the eluent, to afford **23b** as an oil (29 mg, 87%): ^1H NMR ($CDCl_3$) δ 2.35 (t, 1 H, OH), 3.87 (s, 6 H, OCH_3), 4.84 (d, 2 H, CH_2OH), 6.20 (s, 1 H, Ar H), 7.06-7.25 (m, 4 H, Ar H); MS, m/z (relative intensity) 272 (M^+), 271 (100), 241 (83), 139 (28); HRMS, calcd for $C_{16}H_{14}O_4$ m/z 272.1048, found m/z 272.1036.

1,3-Dimethoxy-2-methyl-9*H*-xanthene (30). (a) Methylation of 18b. A suspension of **18b** in ether was treated with excess ethereal diazomethane at 0 °C. The mixture was allowed to stand at room temperature for 24 h. Evaporation of the solvent and trituation of the residue with ether gave a solid (0.03 g, 27%); mp 204-207 °C, which when recrystallized from methylene chloride-methanol gave the pure **30**: mp 208-209 °C; ^1H NMR ($CDCl_3$) δ 2.16 (s, 3 H, Ar CH_3), 3.81 (s, 6 H, OCH_3), 3.95 (s, 2 H, $ArCH_2Ar$), 6.54 (s, 1 H, Ar H), 6.89-7.24 (m, 4 H, Ar H); MS, m/z (relative intensity) 256 (M^+, 1.7), 240 (15), 226 (28), 225 (100), 211 (18), 210 (28), 182 (15), 181 (17), 67 (15); HRMS, calcd for $C_{16}H_{16}O_3$ m/z 256.1099, found m/z 256.1159.

(b) Hydrogenolysis of 29. 1,3-Dimethoxy-2-hydroxymethylxanthene (**29**; 10 mg) dissolved in ethyl acetate (5 mL) was hydrogenated over a 10% Pd-C catalyst for 2 h. The catalyst was removed by filtration and the solvent by evaporation. This afforded **24**, which was purified by preparative TLC (10% EtOAc in methylene chloride) to give a material (6 mg, 60%) mp and mixed mp 208-209 °C, identical in all spectroscopic properties with the sample prepared by method a.

Acknowledgment. We thank Dr. C. R. Iden, who provided all of the mass spectral data reported in this paper, and Linda Nadjek and Ruby Hope for technical assistance. This work was partially supported by Grants NIH 5ROIAI 13988 and NIH 5ROIAI19709, for which we express gratitude.

Stereo- and Regiochemistry in Palladium-Catalyzed Nucleophilic Substitution of Optically Active (*E*)- and (*Z*)-Allyl Acetates

Tamio Hayashi,* Akihiro Yamamoto, and Toshiya Hagihara

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Kyoto 606, Japan

Received June 27, 1985

Optically active (*E*)- and (*Z*)-allyl acetates, 3-acetoxy-1-phenyl-1-butene (**1**) and its regioisomer, 1-acetoxy-1-phenyl-2-butene (**2**), were allowed to react with sodium dimethyl malonate, sodium acetylacetonate, and sodium methyl acetoacetate in the presence of a palladium catalyst. The reaction of (*E*)-acetates proceeded with retention of configuration and that of (*Z*)-acetates proceeded with inversion accompanied by geometrical isomerization from *Z* to *E*. The stereochemistry observed in the reaction with phenylzinc bromide was opposite to that with the soft nucleophiles.

Palladium-catalyzed allylation of nucleophiles is recognized to be useful for organic synthesis, and increasing attention has recently been paid to the reaction mechanism.[1] Stereochemical studies on the allylation with diastereomeric allylic substrates[2] and the intramolecular allylation[3] have shown that the reaction of soft nucleophiles represented by sodium dimethyl malonate proceeds with retention of configuration and that of hard nucleophiles proceeds with inversion of configuration. Here we report stereo- and regiochemical results obtained for the reaction of a set of regioisomeric optically active (*E*)- and (*Z*)-allyl acetates.

Results and Discussion

Reaction of optically active (*E*)- and (*Z*)-3-acetoxy-1-phenyl-1-butene (**1**) and 1-acetoxy-1-phenyl-2-butene (**2**) with sodium dimethyl malonate, sodium acetylacetonate, sodium methyl acetoacetate, and phenylzinc bromide was carried out in the presence of a phosphine/palladium catalyst. The results are summarized in Table I.

The allyl acetate with an *E* configuration, (*S*)-(*E*)-**1** ($[\alpha]^{20}_D$ -53.1° (*c* 1.2, CCl_4), 39% ee),[4] was allowed to react

(1) For reviews: (a) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. (b) Tsuji, J. "Organic Synthesis with Palladium Compounds"; Springer-Verlag: New York, 1980. (c) Trost, B. M.; Verhoeven, T. R. In "Comprehensive Organometallic Chemistry"; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: New York, 1982; Vol. 8, p 799. (d) Tsuji, J. *Pure Appl. Chem.* **1982**, *54*, 197.

(2) (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 3435. (b) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730. (c) Fiaud, J.-C.; Malleron, J.-L. *Tetrahedron Lett.* **1981**, *22*, 1399. (d) Trost, B. M.; Schmuff, N. R. *Tetrahedron Lett.* **1981**, *22*, 2999. (e) Trost, B. M.; Klun, T. P. *J. Am. Chem. Soc.* **1979**, *101*, 6756. (f) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2591. (g) Fiaud, J.-C.; Malleron, J.-L. *J. Chem. Soc., Chem. Commun.* **1981**, 1159. (h) Trost, B. M.; Keinan, E. *J. Am. Chem. Soc.* **1978**, *100*, 7779. (i) Hayasi, Y.; Riediker, M.; Temple, J. S.; Schwartz, J. *Tetrahedron Lett.* **1981**, *22*, 2629. (j) Matsushita, J.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1982**, 160. (k) Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833. (l) Keinan, E.; Greenspoon, N. *Tetrahedron Lett.* **1982**, *23*, 241. (m) Fiaud, J.-C. *J. Chem. Soc., Chem. Commun.* **1983**, 1055.

(3) (a) Yamamoto, K.; Deguchi, R.; Ogimura, Y.; Tsuji, J. *Chem. Lett.* **1984**, 1657. (b) Takahashi, T.; Jinbo, Y.; Kitamura, K.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 5921.

0022-3263/86/1951-0723$01.50/0