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Synthesis of quinone and xanthone analogs of rhein

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Abstract—A new strategy based on carbonylation of aryl triflates has been developed to prepare 7-methyl rhein from emodin and new xanthone analogs of rhein. This approach avoids the oxidation step of methyl derivatives with toxic chromium salts. Although possessing the same structural arrangement of phenol and carboxylic acid functions as found in rhein, these new xanthone derivatives have no activity against IL-1. Thus, the quinone moiety of rhein appears to be essential for activity. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Diacetylrhein is an effective drug for the treatment of gonarthrosis and coxarthrosis[1] which is rapidly metabolized in humans to rhein.[2] In contrary to other nonsteroidal anti-inflammatory drugs (NSAIDs), rhein does not reduce prostaglandin synthesis.[3] Rhein inhibits the effects of the proinflammatory cytokine interleukin-1 (IL-1) such as NO production,[4] induction of collagenase production and synthesis of proteoglycanes by chondrocytes.[5] Interestingly, rhein has also shown a strong synergistic effect with known antitumor agents such as doxorubicin (Fig. 1).[6]

The mechanism(s) of action of rhein at the molecular level is not clearly understood, although it is known that two molecules of rhein are able to complex bivalent ions such as calcium.[7] Furthermore the quinone moiety of rhein may play a role in oxido-reduction processes.[8] Although only oxidative (hydroxylated) and glucuronylated or sulfated metabolites have been found in human urine,[9] the laxative effect associated with the therapeutic use of diacetylrhein may result from anthrone production by the intestine microflora,[10] since it has been shown that rhein anthrone, the active metabolite of the purgative sennosides[11] and rhein have a synergistic purgative effect in mice.[12] It thus may be interesting to search for analogs to determine the influence of the quinone moiety either by ring substitution (methoxy and fluoro rhein have already been prepared[13a,b,17b]) or by preparation of xanthones[14] which are isosteres of rhein anthrone (or analogs).

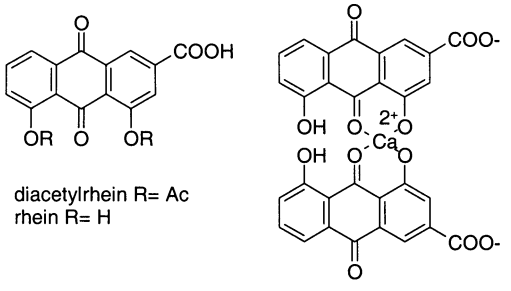
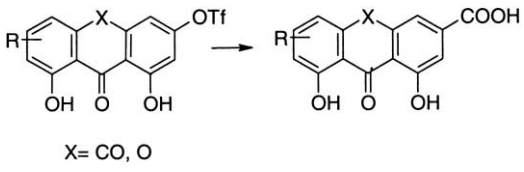


Figure 1.

Although rhein is usually prepared by hemisynthesis implying oxidation of aloin (or aloe emodin)[15] and sennosides[16] rhein itself and several analogs have already been prepared by standard routes based either on Friedel–Crafts acylation,[13] Diels–Alder cycloaddition[17] or phthalide cyclisation.[18] Apart from hemisynthesis, the carboxylic acid moiety was commonly obtained by an oxidation step of a methyl derivative.

It thus seems worthwhile, in order to avoid the use of toxic metal salts, to introduce this function through another methodology and the carbonylation of an aryl triflate may be considered (Scheme 1). This new route has been first tested starting from the commercially available emodin to prepare 7-methyl rhein. For the preparation of xanthones, both strategies have been compared: either oxidation of a



Scheme 1.

Keywords: rhein; xanthone analogs; anthraquinones.

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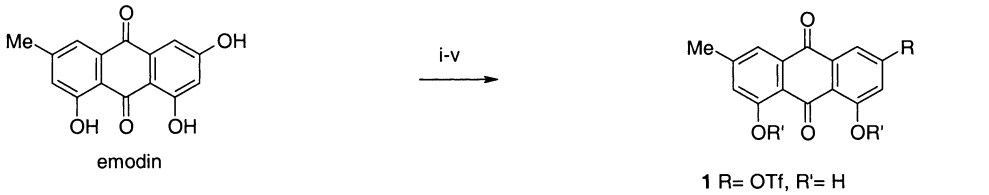


1 R= OTf, R'= H
2 R= OTf, R'= Piv
3 R= $COOCH_2CH_2TMS$, R'= Piv
4 R= COOH, R'= H

i: Tf_2O, pyr, 95%; ii: PivCl, pyr, 80%;
iii: CO, $Pd(OAc)_2$, DPPP, $TMSCH_2CH_2OH$, NEt_3, DMSO, 39%
iv: TBAF, THF then v: NaOH, 77%

Scheme 2.

methyl xanthone or Pd catalyzed carbonylation of a xanthone triflate.

2. Results and discussion

2.1. Conversion of emodin to 7-methyl rhein

The overall strategy implied conversion of emodin to the 3-*O*-triflate and subsequent protection of the resulting phenolic groups followed by carbonylation (Scheme 2). This protection step was required for the carbonylation which otherwise proceeded in low yield (10%).

First, the more reactive, nonchelated, phenolic group was selectively converted to the mono triflate **1** (95%). This material was converted to the bis pivalate **2** (80%) which proved to be stable under the carbonylation conditions (this was not the case of the corresponding acetate). Carbonylation under standard conditions in presence of trimethylsilylethanol[19] gave ester **3** (39%) which was then converted in one pot (TBAF, THF then NaOH 1N) to 7-methyl rhein **4** (77%). Thus emodin was converted to the target quinone in 23% overall yield.

2.2. Synthesis of xanthone analogs

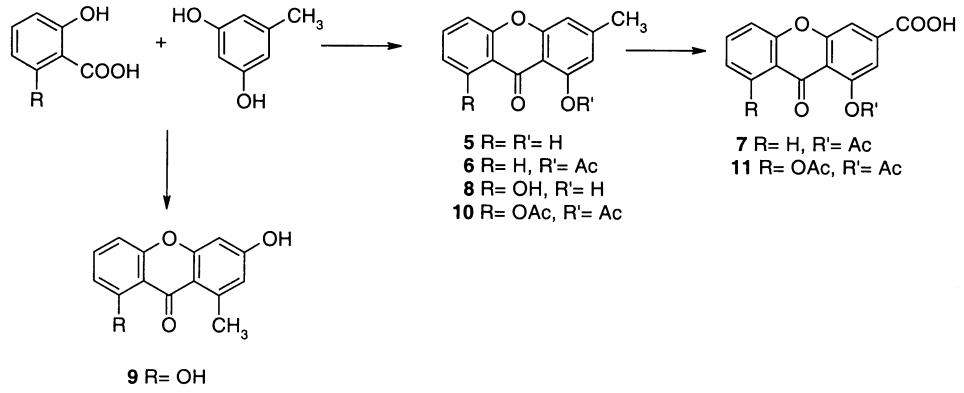
The first approach (Scheme 3) was based on the preparation of known methyl xanthones **5**[20] and **8**[21] upon heating a mixture of a salicylic acid with 5-methyl resorcinol in presence of $ZnCl_2$ and $POCl_3$. Thus **5** was then quantitatively acetylated to **6** and oxidized by CrO_3 in acetic acid/acetic anhydride to give **7** (37%).

The same strategy was then attempted from 2,6-dihydroxy benzoic acid and 5-methyl resorcinol. This afforded a low 10% yield of the desired xanthone **8**. Acetylation to **10** and oxidation as above gave the desired xanthone **11** (45%). The disappointing low yield obtained in the xanthone synthesis led us to study other acidic reaction conditions. The use of polyphosphoric acid (PPA, 80°C, 4 h) gave an improved overall yield, but the unwanted isomer **9** (30%) was then formed together with **8** (10%).

The second route relied on the carbonylation of an appropriately protected triflate. The starting xanthone **12**[22] was prepared in 29% yield upon heating phloroglucinol and 2,6-dihydroxy benzoic acid in presence of $ZnCl_2$–$POCl_3$ (70°C, 6.5 h). A major advantage of this strategy is the production of only one possible isomer. This material was then selectively converted to triflate **13** (75%) and the chelated phenol groups were protected as pivalates to give **14** (95%). Carbonylation under the same conditions as for emodin afforded ester **15** (65%) which was then deprotected to afford xanthone **16** (84%, 11% overall yield from phloroglucinol) (Scheme 4).

2.3. Biological evaluation of xanthones

Xanthones **7**, **11** and **16** were tested according to the method of Schindler[23] (using peripheral blood mononuclear cells) for their potential inhibition of IL1, IL6 and TNFα production. They did not show any activity at 10 μM concentration (reference compounds: cycloheximide (IC_{50}=0.12 μM for IL1), dexamethasone (IC_{50}=9.7 and 4.5 nm, respectively, for IL6 and TNFα)).

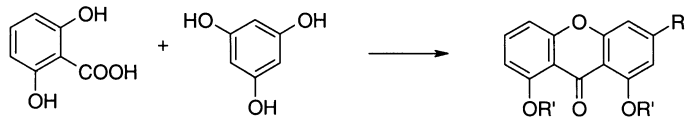


5 R= R'= H
6 R= H, R'= Ac
8 R= OH, R'= H
10 R= OAc, R'= Ac

7 R= H, R'= Ac
11 R= OAc, R'= Ac

9 R= OH

Scheme 3.



12 R= OH, R'= H
13 R= OTf, R'= H
14 R= OTf, R'= Piv
15 R= $COOCH_2CH_2TMS$, R'= Piv
16 R= COOH, R'= H

Scheme 4.

3. Conclusion

A new strategy has been implemented to prepare anthraquinone and xanthone carboxylic acids by carbonylation of aryl triflates, thus avoiding an oxidation step using toxic chromium salts. Protection of chelated phenol groups is essential to carry out this Pd catalyzed carbonylation. Furthermore, the preparation of new xanthone derivatives related to rhein has been completed by this strategy, which turned out to be more efficient than oxidation of methyl xanthones. These compounds have been tested for their potential inhibition of IL-1 and have not demonstrated any significant activity. Since these compounds should be able to complex Ca^{2+} as proposed for rhein itself, it may be suggested that the quinone moiety of rhein may play an important role in the observed inhibition of IL-1.

4. Experimental

4.1. General

Melting points are uncorrected. ^1H and ^{13}C NMR were recorded on a 300 MHz (Bruker Advance DPX300) spectrometer with TMS as internal standard. High resolution MS were performed by the 'Service Central de Microanalyse' (CNRS, Lyon). Organic extract mixtures were dried over anhydrous $MgSO_4$, filtered and the solvent was then removed under reduced pressure. All separations were done under flash chromatography conditions on silica gel (Matrex, 25–40 mμ) and thin layer chromatography (TLC) were performed on silica gel plates (Merck, $60GF_{254}$).

4.2. Preparation of anthraquinones

4.2.1. 3-Trifluoromethanesulfonyloxy-1,8-dihydroxy-6-methyl-anthraquinone (1). To a solution of emodin (800 mg, 2.96 mmol) in dichloromethane (30 ml) was added pyridine (0.96 ml, 11.84 mmol) and trifluoromethanesulfonic anhydride (0.5 ml, 2.96 mmol). The resulting mixture was stirred at 0°C for 4 h. The reaction was quenched with 1N HCl and the mixture was extracted with dichloromethane. The crude compound was recrystallized from dichloromethane to give **1** (1.13 g, 95%): mp 166–169°C; ^1H NMR (300 MHz, $CDCl_3$): δ 2.49 (s, 3H), 7.15 (sl, 1H), 7.19 (d, 1H, J=2.5 Hz), 7.69 (m, 2H), 11.82 and 12.28 (2s, 2H); MS (EI) m/z 402 (M^+); HRMS calcd for $C_{16}H_9O_7F_3S_1$: 402.0021; found: 402.0023.

4.2.2. 3-Trifluoromethanesulfonyloxy-6-methyl-1,8-dipivaloyloxy-anthraquinone (2). To a solution of **1** (89 mg, 0.22 mmol) in pyridine (0.9 ml) was added pivaloyl chloride (0.07 ml, 0.55 mmol) at 0°C. After 48 h at room temperature, the reaction was quenched with 1N HCl and the mixture was extracted with dichloromethane. Flash column chromatography (EtOAc/EP, 5:95–10:90) afforded **2** (101 mg, 80%) as a white solid: mp 163°C; ^1H NMR (300 MHz, $CDCl_3$): δ 1.44 and 1.45 (2s, 2×9H), 2.51 (s, 3H), 7.17 (sl, 1H), 7.27 (m, 1H), 8.03 (sl,1H), 8.10 (d, 1H, J=2.6 Hz); HRMS calcd for $C_{26}H_{25}O_9F_3S_1$: 570.1171; found: 570.1182.

4.2.3. 3-[2-(Trimethylsilyl)ethyloxycarbonyl]-6-methyl-1,8-dipivaloyloxy-anthraquinone (3). A mixture of **2** (300 mg, 0.53 mmol), $Pd(OAc)_2$ (18 mg, 0.08 mmol) and of 1,3-bis(diphenylphosphino)propane (33 mg, 0.08 mmol) was prepared at room temperature, then placed under vacuum and recharged with carbon monoxide three times. A solution of 2-(trimethylsilyl)ethyl alcohol (0.23 ml, 1.58 mmol), triethylamine (0.15 ml, 1.05 mmol) in DMSO (1.4 ml) was added. The mixture was stirred, at 70°C for 3 h, under an atmosphere of carbon monoxide. The reaction mixture was extracted with EtOAc and washed with 1N HCl. Flash column chromatography (EtOAc/EP, 5:95–50:50) afforded **3** (102 mg, 39%). ^1H NMR (300 MHz, $CDCl_3$): δ 0.12 (s, 9H), 1.19 (t, 2H, J=8.2 Hz), 1.44 and 1.46 (2s, 2×9H), 2.50 (s, 3H), 4.48 (t, 2H, J=8.2 Hz), 7.15 (sl, 1H), 7.93 (d, 1H, J=1.6 Hz), 8.04 (sl, 1H), 8.81 (d, 1H, J=1.6 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ −1.46, 17.4, 21.6, 27.2, 39.1, 64.5,123.9, 125.0, 126.0, 128.9, 130.6, 130.9, 134.0, 134.6, 135.7, 146.2, 150.6, 164.2, 176.3, 176.5, 179.5 and 181.6; MS (EI) m/z 566 (M^+).

4.2.4. 3-(1,8-Dihydroxy-6-methyl)anthraquinonecarboxylic acid (4). To a solution of **3** (100 mg, 0.17 mmol) in THF (0.8 ml) was added tetrabutylammonium fluoride (92 mg, 0.35 mmol) at 0°C. After 20 h at room temperature, 1 ml of 1N NaOH was added to the mixture. After 72 h, the reaction mixture was extracted and the aqueous layer was acidified and then extracted with dichloromethane. The crude compound was recrystallized from a mixed solvent of dichloromethane and methanol to give **4** (39 mg, 77%) as an orange solid: mp 246–249°C; ^1H NMR (300 MHz, $(CD_3)_2CO$): δ 2.52 (s, 3H), 7.25 (sl, 1H), 7.68 (sl, 1H), 7.87 (d, 1H, J=1.6 Hz), 8.34 (d, 1H, J=1.6 Hz), 11.89 and 12.06 (s, 2×OH).

4.3. Preparation of xanthones

4.3.1. 1-Hydroxy-3-methyl-9-oxo-xanthene (5). To a solution of 2-hydrobenzoic acid (10.0 g, 72.5 mmol) and 3,5-dihydroxytoluene (9.0 g, 72.5 mmol) was added $ZnCl_2$

(30.0 g, 217.4 mmol) and $POCl_3$ (16.7 g, 108.7 mmol). The resulting mixture was stirred at 60°C for 3 h. The reaction was quenched with ice, and extracted with dichloromethane. Flash column chromatography (petroleum ether/ether, 97:3) afforded **5** (10%): mp 134°C, lit.[20] 142–143°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H), 6.47 (s, 1H), 6.55 (s, 1H), 7.27 (dd, 1H, J=7.8, 7.2 Hz), 7.30 (d, 1H, J=8.2 Hz), 7.62 (ddd, 1H, J=8.2, 7.2, 1.3 Hz), 8.11 (dd, 1H, J=7.8, 1.3 Hz), 12.41 (s, OH); ^{13}C NMR (300 MHz, $CDCl_3$): δ 23.0, 107.2, 107.8, 111.5, 118.2, 120.8, 124.2, 126.1, 135.6, 149.2, 156.31, 156.35, 161.8 and 182.0.

4.3.2. 1-Acetoxy-3-methyl-9-oxo-xanthene (6). To a solution of **5** (100 mg, 0.44 mmol) in acetic anhydride (5 ml) was added sodium acetate (50 mg, 0.61 mmol). The resulting mixture was stirred at 50°C for 15 h and then quenched with ice. The precipitate was filtrated, washed and dried. Flash column chromatography (EtOAc/petroleum ether, 10:90) provided **6** (95%): mp 150°C, lit.[20] 153–154°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.49 (s, 6H), 6.82 (sl, 1H), 7.20 (sl, 1H), 7.35 (ddd, 1H, J=7.9, 7.2, 1.0 Hz), 7.42 (dl, 1H, J=8.4 Hz), 7.69 (ddd, 1H, J=8.4, 7.2, 1.5 Hz), 8.23 (dd, 1H, J=7.9, 1.5 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 21.9, 21.2, 112.7, 116.1, 117.6, 119.4, 124.0, 122.2, 126.5, 134.2, 146.4, 149.8, 155.3, 157.3, 169.9 and 175.6.

4.3.3. 3-(1-Acetoxy-9-oxo-xanthene)carboxylic acid (7). To a solution of **6** (50 mg, 0.17 mmol) in glacial acetic acid (1.5 ml) and acetic anhydride (1.5 ml) was added, at 50–60°C and during 30 min, a solution of chromium trioxide in 0.2 ml of water and 1.5 ml of acetic acid. The resulting mixture was stirred at 65–70°C for 3 h and then quenched with water. The precipitate was filtrated, washed with water and dried under vacuum to provide **7** (37%): mp 208°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3H), 7.50 (dd, 1H, J=7.2, 7.9 Hz), 7.62 (sl, 1H), 7.66 (d, 1H, J=8.3 Hz), 7.89 (ddd, 1H, J=8.3, 7.2, 1.5 Hz), 8.08 (sl, 1H), 8.20 (dd, 1H, J=7.9, 1.5 Hz).

4.3.4. 1,8-Dihydroxy-3-methyl-9-oxo-xanthene (8). A mixture of 2,6-dihydroxybenzoic acid (1.00 g, 6.49 mmol), 3,5-dihydroxytoluene (0.92 g, 6.49 mmol) and polyphosphoric acid (10.00 g) was heated at 80–90°C for 4 h. The resulting mixture was quenched with ice and extracted with EtOAc. Flash column chromatography (EtOAc/petroleum ether, 5:95–30:70) afforded **8** (0.16 g, 10%) and **9** (0.47 g, 30%).

8: mp 189–191°C; lit.[21] 193–194°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H), 6.59 (s, 1H), 6.69 (s, 1H), 6.77 (dd, 1H, J=8, 2 Hz), 6.86 (dd, 1H, J=8, 2 Hz), 7.56 (t, 1H, J=8 Hz), 11.86 and 11.70 (2s, 2OH); ^{13}C NMR (300 MHz, $CDCl_3$): δ 22.7, 105.8, 107.1, 107.7, 107.8, 110.7, 111.6, 137.2, 149.9, 156.2, 156.3, 161.0, 161.4 and 185.7; HRMS (M^+) calcd 242.0579, found 242.0579.

9: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.76 (s, 3H), 6.66–6.69 (m, 3H), 6.83 (dd, 1H, J=8, 2 Hz), 7.56 (t, 1H, J=8 Hz), 9.80 (s, OH), 13.18 (s, OH).

4.3.5. 1,8-Diacetoxy-3-methyl-9-oxo-xanthene (10). To a solution of **8** (200 mg, 0.82 mmol) in acetic anhydride (45 ml) was added sodium acetate (275 mg). The resulting mixture was refluxed for 16 h and then quenched with ice. The precipitate was filtrated, dried to provide **10** as a white solid: mp 194–196°C, lit.[21] 196–197°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.41 (m, 9H), 6.78 (s, 1H), 6.93 (dd, 1H, J=8, 2 Hz), 7.13 (s, 1H), 7.31 (dd, 1H, J=8, 2 Hz), 7.62 (t, 1H, J=8 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 21.2, 21.9, 112.9, 115.2, 115.7, 115.8, 118.3, 119.6, 134.3, 146.4, 149.7, 150.0, 156.4, 156.5, 169.7, 169.8 and 174.2; HRMS (M^+) calcd 326.0790, found 326.0792.

4.3.6. 3-(1,8-Diacetoxy-9-oxo-xanthene)carboxylic acid (11). To a solution of **10** (165 mg, 0.5 mmol) in acetic acid (4.8 ml) and acetic anhydride (4.8 ml) was added, at 65°C during 30 min, a solution of chromium trioxide (435 mg, 4.35 mmol) in water (0.6 ml) and acetic acid (4.8 ml). The resulting mixture was stirred at 80°C for 14 h and then quenched with water. After 4 h at 4°C, the precipitate was filtrated, washed and dried to provide **11** (82 mg, 45%) as a white solid: mp 181–183°C; ^{1}H NMR (300 MHz, DMSO d_6): δ 2.45 and 2.50 (2s, 6H), 6.98 (sl, 1H), 7.12 (dl, 1H, J=8 Hz), 7.37 (sl, 1H), 7.53 (dl, 1H, J=8 Hz), 7.84 (t, 1H, J=8 Hz), 9.00–11.00 (sl, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 21.0, 21.4, 115.4, 116.1, 118.9, 120.1, 135.5, 155.9, 156.0, 169.2 and 173.6; HRMS (FAB) m/z (M^+) calcd 356.0532, found 356.0560.

4.3.7. 1,3,8-Trihydroxy-9-oxo-xanthene (12). To a solution of 2,6-dihydroxybenzoic acid (1.00 g, 6.48 mmol) and phloroglucinol (0.82 g, 6.48 mmol) was added $ZnCl_2$ (2.65 g, 19.44 mol) and $POCl_3$ (11 ml). The resulting mixture was heated at 65–70°C for 6.5 h. The reaction was quenched with ice and extracted with EtOAc. Flash column chromatography (EtOAc/petroleum ether, 20:80) afforded **12** (0.45 g, 29%) as a white solid: mp 269–270°C, lit.[22] 258°C; ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 6.24 (d, 1H, J=2.3 Hz), 6.37 (d, 1H, J=2.3 Hz), 6.72 and 6.88 (2dd, 2H, J=8.4, 0.9 Hz), 7.64 (t, 1H, J=8.4 Hz), 10.00 (sl, OH), 11.82 (s, 2OH); ^{13}C NMR (300 MHz, $(CD_3)_2CO$): δ 94.3, 98.5, 101.7, 107.0, 109.6, 110.6, 137.1, 156.0, 158.0, 161.2, 163.2, 166.4 and 184.4; HRMS (FAB) m/z ($M+H^+$) calcd 245.0450, found 245.0465.

4.3.8. 3-Trifluoromethanesulfonyloxy-1,8-dihydroxy-9-oxo-xanthene (13). To a solution of **12** (400 mg, 1.64 mmol) in dichloromethane (16 ml) was added pyridine (0.53 ml, 6.55 mmol) and then trifluoromethanesulfonic anhydride (0.27 ml, 1.64 mmol). After 2 h at 0°C, the resulting mixture was quenched with 1N aqueous HCl and extracted with EtOAc. Flash column chromatography (EtOAc/petroleum ether, 2:98–50:50) afforded **13** (465 mg, 75%): mp 106–108°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.69 (d, 1H, J=2.3 Hz), 6.84 (d, 1H, J=2.3 Hz), 6.81 and 6.89 (2dd, 2H, J=8.3, 0.9 Hz), 7.62 (t, 1H, J=8.4 Hz), 11.47 and 12.07 (2s, 2OH); ^{13}C NMR (300 MHz, $CDCl_3$): δ 100.9, 104.4, 107.2, 107.6, 111.8, 116.5, 138.2, 154.6, 155.9, 156.7, 161.3, 163.0 and 185.2.

4.3.9. 3-Trifluoromethanesulfonyloxy-1,8-dipivaloyloxy-9-oxo-xanthene (14). To a solution of **13** (399 mg, 1.06 mmol) in pyridine (5 ml) was added pivaloyl chloride (0.32 ml, 2.65 mmol) at 0°C. The resulting mixture was stirred at room temperature for 48 h. The reaction was

quenched with 1N HCl and extracted with dichloromethane. Flash column chromatography (EtOAc/petroleum ether) afforded **15** (545 mg, 94%): mp 193–194°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 and 1.45 (2s, 2×9H), 6.84 (d, 1H, J=2.5 Hz), 7.30 (dd, 2H, J=8.0, 1.0 Hz), 7.29 (d, 1H, J=2.5 Hz), 7.63 (t, 1H, J=8.0 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 27.1, 27.2, 39.1, 108.6, 112.3, 115.5, 115.9, 116.0, 119.2, 134.7, 150.6, 151.5, 151.7, 156.2, 156.8, 171.7, 176.0 and 176.6; HRMS (FAB) m/z ($M+H^+$) calcd 545.1093, found 545.1097.

4.3.10. 3-[2-(Trimethylsilyl)ethyloxycarbonyl]-1,8-dipivaloyloxy-9-oxo-xanthene (15). A mixture of **14** (504 mg, 0.55 mmol), $Pd(OAc)_2$ (19 mg, 0.08 mmol) and 1,3-bis(diphenylphosphino)propane (35 mg, 0.08 mmol) was prepared at room temperature, then placed under vacuum and recharged with carbon monoxide three times. To this was added a solution of 2-(trimethylsilyl)ethyl alcohol (0.24 ml, 1.67 mmol), triethylamine (0.16 ml, 1.11 mmol) and DMSO (1.2 ml). The mixture was stirred at 70°C under an atmosphere of carbon monoxide for 3 h and then was extracted with EtOAc. Flash column chromatography (EtOAc/petroleum ether, 5:95–50:50) afforded **15** (191 mg, 65%) as a white solid: mp 157–160°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.10 (s, 9H), 1.17 (t, 2H, J=6.9 Hz), 1.44 and 1.46 (2s, 2×9H), 4.45 (t, 2H, J=6.9 Hz), 7.47 and 7.97 (2d, 2H, J=1.5 Hz), 6.86 and 7.33 (2dd, 2H, J=8.3, 0.8 Hz), 7.61 (t, 1H, J=8.3 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ −1.4, 17.4, 27.1, 39.0, 64.3, 115.7, 116.1, 116.9, 118.5, 118.6, 118.7, 134.4, 135.6, 150.4, 150.6, 156.0, 156.4, 164.3, 173.5, 176.5 and 176.6; HRMS (FAB) m/z ($M+H^+$) calcd 541.2257, found 541.2240.

4.3.11. 3-(1,8-Dihydroxy-9-oxo-xanthene)carboxylic acid (16). A solution of **15** (155 mg, 0.29 mmol) in 1N aqueous NaOH (1.05 ml) was added to a mixture of methanol/water (1/1). After one week at room temperature, the resulting miture was extracted with EtOAc. The crude compound was recrystallized from dichloromethane to give **16** (66 mg, 85%): mp 310–311°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.81 and 6.99 (2d, 2H, J=8.4 Hz), 7.38 and 7.57 (2d, 2H, J=1.4 Hz), 7.68 (t, 1H, J=8.4 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 102.6, 105.2, 105.7, 106.2, 107.6, 108.8, 109.2, 135.9, 137.2, 153.7, 154.2, 158.8, 159.0, 164.2 and 183.8; HRMS (FAB) m/z ($M+H^+$) calcd 273.0399, found 273.0388.

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References

1. Nguyen, M.; Dougados, M.; Berdah, L.; Amor, B. *Arthritis Rheum.* **1994**, *37*, 529–536.
2. (a) Pomarelli, P.; Berti, M.; Gatti, M. T.; Mosconi, P. *Farmaco Ed. Sci.* **1980**, *35*, 836–842. (b) Franchi-Micheli, S.; Lavacchi, L.; Friedmann, C. A.; Ziletti, L. *J. Pharm. Pharmacol.* **1983**, *35*, 262–264.
3. La Villa, G.; Marra, F.; Laffi, G.; Belli, B.; Meacci, E.; Fascetti, P.; Gentilini, P. *Eur. J. Clin. Pharmacol.* **1989**, *37*, 1–5.
4. (a) Pelletier, J. P.; Mineau, F.; Fernandes, J. C.; Duval, N.; Martel-Pelletier, J. *J. Rheumatol.* **1998**, *25*, 2417–2424. (b) Menkes, C. J.; Borderie, D.; Hernvann, A.; Ekindjian, O. *Bull. Acad. Natl. Med.* **1999**, *183*, 785–795. (c) Yaron, M.; Shirazi, I.; Yaron, I. *Osteoarthritis Cartilage* **1999**, *7*, 272–280.
5. Spencer, C. M.; Wilde, M. I. *Drugs* **1997**, *53*, 98–108.
6. Fanciulli, M.; Gentile, F. P.; Bruno, T.; Paggi, M. G.; Benassi, M.; Floridi, A. *Anticancer Drugs* **1992**, *3*, 615–621.
7. Beccerica, E.; Ferretti, G.; Curatola, G.; Cervini, C. *Pharmacol. Res.* **1990**, *22*, 277–285.
8. Kagedal, K.; Bironaite, D.; Ollinger, K. *Free Radical Res.* **1999**, *31*, 419–428.
9. Dahms, M.; Lotz, R.; Lang, W.; Renner, U.; Bayer, E.; Spahn-Langguth, H. *Drug Metab. Disp.* **1997**, *25*, 442–452.
10. De Witte, P.; van Hoestenberghe, A.; Eyssen, H. *Biopharm. Drug Disp.* **1992**, *13*, 243–253.
11. Yamauchi, K.; Shinano, K.; Nakajima, K.; Yagi, T.; Shigeaki, K. *J. Pharm. Pharmacol.* **1992**, *44*, 973–976.
12. Yagi, T.; Yamauchi, K. *J. Pharm. Pharmacol.* **1999**, *51*, 93–95.
13. (a) Owton, W. M.; Brunavs, M.; Miles, M.; Dobson, D. R.; Steggles, D. J. *J. Chem. Soc. Perkin Trans 1* **1995**, 931–934. (b) Gallagher, P. T.; Owton, W. M.; Williams, A. C. Eur Pat. Appl. 698,594, February 28, 1996; *Chem. Abstr.* **1996**, *124*, 316785e. (c) Gallagher, P. T.; Hicks, T. A.; Lightfoot, A. P.; Owton, W. M. *Tetrahedron Lett.* **1994**, *35*, 289–292. (d) Di Napoli, G. Eur. Pat. Appl. EP 822,178, February 4, 1998; *Chem. Abstr.* **1998**, *128*, 167311a.
14. For a review of naturally occuring xanthones see: Sultanbawa, M. U. S. *Tetrahedron* **1980**, *36*, 1465–1506.
15. Robinson, R.; Simonsen, J. L. *J. Chem. Soc.* **1909**, *95*, 1085–1096. Nawa, H.; Uchibayashi, M.; Matsuoka, T. *J. Org. Chem.* **1961**, *26*, 979–981 and references cited therein.
16. Carcasona, A.; Grimminger, W.; Hietala, P.; Zaeske, H.; Witthohm, K. Ger. Offen. DE 4,120,990, January 7, 1993; *Chem. Abstr.* **1993**, *119*, 95158w.
17. (a) Zope, U. R.; Pandey, B.; Ayyangar, N. R. *Chem. Ind. (London)* **1988**, 124. (b) Bloomer, J. L.; Stagliano, K. W.; Gazzillo, J. A. *J. Org. Chem.* **1993**, *58*, 7906–7912. (c) Estanove, C.; Pruvost, F. Intern. Pat. Appl. PCT WO 9,716,404, May 9, 1997; *Chem. Abstr.* **1997**, *127*, 4938a.
18. Hauser, F. M.; Prasanna, S. *J. Org. Chem.* **1982**, *47*, 383–384.
19. Ye, B.; Burke, T. R. *Tetrahedron* **1996**, *52*, 9963–9970.
20. Kane, V. V.; Kulkarni, A. B.; Shah, R. C. *J. Sci. Ind. Res.* **1959**, *18B*, 28–32.
21. Ahluwalia, S. *Proc. Indian Acad. Sci. Sect. A* **1956**, *44*, 1–3.
22. Grover, P. K.; Shah, G. D.; Shah, R. C. *J. Sci. Ind. Res.* **1956**, *15B*, 630–632. Patel, G. N.; Trivedi, K. N. *Indian J. Chim.* **1991**, *30B*, 437–439.
23. (a) Schindler, R.; Mancilla, J.; Endres, S.; Ghorbani, R.; Clark, S. C.; Dinarello, C. A. *Blood* **1990**, *75*, 40–47. (b) Schindler, R.; Gelfand, J. A.; Dinarello, C. A. *Blood* **1990**, *76*, 1631–1638.