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# Note

## A new approach to *cis*-chrysanthemic acid*

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The current world market for pyrethrin insecticides is around £700 million[1], and is increasing as the demand for other less environmentally acceptable insecticides declines. Thus, there is a continuing interest in new routes for the production of *cis*-chrysanthemic acids of general structure **1**. We have described[2] the synthesis of 3-oxabicyclo[3.1.0]hexan-2-ones like **2** from D-ribono-1,4-lactone, and have converted them into various *cis*-chrysanthemic acids[3]. A key step in this route involved the addition of diazopropane to butenolides like **3**, but this method is unsuitable for large-scale syntheses. A new, more viable route is now described.

Reaction of (*S*)-5-hydroxymethylfuran-2(5*H*)-one (**3**, R = H), easily prepared from 1,2:5,6-di-*O*-isopropylidene-D-mannose[4], with 2-propanol under irradiation with a low-pressure mercury lamp yielded the photoadduct **4** in yields of up to 94% on the multi-gramme scale. The relative stereochemistry was established using n.O.e. studies, and the stereochemical purity was assured following formation of the Mosher ester[5], which gave $^{1}$H-, $^{13}$C-, and $^{19}$F-n.m.r. spectra with descrete signals. Benzoylation of **4** provided **5**, which reacted with $PCl_5$ to yield a 5:1 mixture of the alkenes **6** and **7**. The mixture was treated with anhydrous hydrogen bromide in dichloromethane and produced the bromide **8** (98% from **5**). Reaction of **8** with potassium *tert*-butoxide in *tert*-butyl alcohol then yielded the key bicyclo-compound **9** (51%).

The enantiomer (**10**) of **9** was prepared in a similar fashion from (*R*)-5-hydroxymethylfuran-2(5*H*)-one (**11**), easily obtained from 1,2-*O*-isopropylidene-L-glyceraldehyde via the Wittig product **12** and acid-catalysed cyclisation. The enantiomers **4** and **13**, and **9** and **10**, had identical spectral and analytical data, but approximately equal and opposite $[\alpha]_D$ values.

The key intermediates **9** and **10** are ideally functionalised for conversion into *cis*-chrysanthemic acids, as established by the conversion of **2** (R = $SiPh_2Bu^t$) into (2*R*)-*cis*-chrysanthemic acid (**1**, $R^1$ = $R^2$ = Me) (ref. 3). The scope of these transformations is being investigated.

* Dedicated to Professor Grant Buchanan on the occasion of his 65th birthday.
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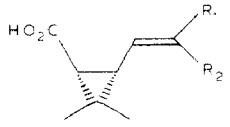


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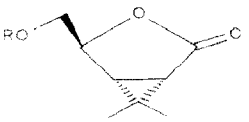


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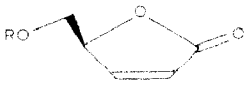


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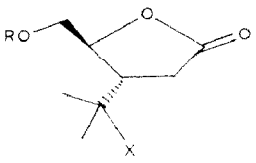
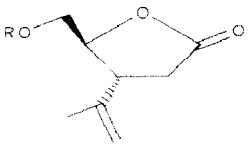



4 R = H, X = OH
5 R = Bz, X = OH
8 R = Bz, X = Br

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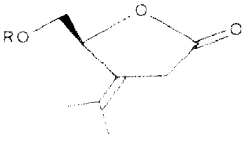
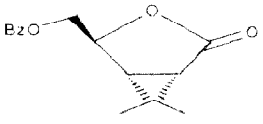



7 R = Bz

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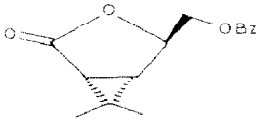


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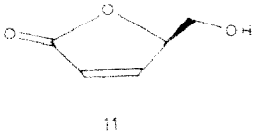


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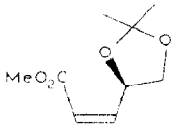


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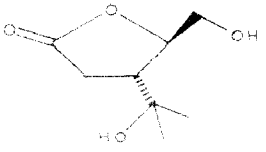


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## EXPERIMENTAL

I.r. spectra were recorded with a Perkin–Elmer 157 spectrophotometer. N.m.r. spectra were recorded with a Perkin–Elmer R34 (220 MHz) or Bruker WM 400 (400 MHz) instrument (University of Warwick). Flash chromatography was performed using Crossfield silica gel (250–400 mesh). Solvents were distilled from calcium hydride when required anhydrous, and light petroleum refers to the fraction b.p. 40–60°.

*(4S,5S)-5-Hydroxymethyl-4-(1-hydroxy-1-methylethyl)tetrahydrofuran-2-one* (**4**). — A solution of butenolide **3** (R = H) (4.0 g, 35 mmol) in 2-propanol (50 mL) was degassed with a stream of nitrogen, then irradiated with two low-pressure mercury lamps (254 nm) for 48 h. After removal of the solvent, the crystalline residue was

recrystallised from ethyl acetate to yield **4** (5.72 g, 94%), m.p. 104°, $[\alpha]_D^{20}$ +25° (*c* 0.29, water), $R_F$ 0.26 (ethyl acetate); $\nu_{max}^{KBr}$ 3420 (OH), 1750 $cm^{-1}$ (lactone C=O). N.m.r. data: $^1H$ [$(CD_3)_2SO$, 400 MHz], $\delta$ 1.04 (s, 3 H, Me), 1.07 (s, 3 H, Me), 2.26 (m, 1 H, H-4); 2.39 (dd, 1 H, *J* 18 and 5.5 Hz, H-3), 2.57 (dd, 1 H, *J* 10 and 18 Hz, H-3), 3.41 (ddd, 1 H, *J* 12, 5.5, and 4 Hz, $CH_2O$), 3.61 (ddd, 1 H, *J* 12 and 3 Hz, $CH_2O$), 4.48 (dt, 1 H, *J* 4.5 and 4 Hz, H-5), 4.60 (s, 1 H, OH), 5.05 (t, 1 H, *J* 5.5 Hz, OH); $^{13}C$ [$(CD_3)_2SO$, 22.5 MHz], $\delta$ 26.67 (Me), 29.29 (Me), 30.61 (C-4), 45.94 (C-2), 63.70 (C=O), 69.37 ($CH_2O$), 81.97 (CHO), 177.27 (C=O).

*Anal.* Calc. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.19; H, 8.16.

*(4S,5S)-5-Benzoyloxymethyl-4-(1-hydroxy-1-methylethyl)tetrahydrofuran-2-one* (**5**). – Benzoyl chloride (1.3 mL, 11 mmol) was added to a solution of **4** (1.77 g, 10 mmol) in dry pyridine (25 mL) under nitrogen at 0°. The mixture was stirred for 2 h, water (25 mL) and ether (100 mL) were added, and the ethereal extract was washed with saturated aqueous citric acid (3 × 30 mL), sat. aq. $NaHCO_3$ (3 × 25 mL) and brine (3 × 25 mL), dried, and concentrated. The residue was recrystallised from ethyl acetate–light petroleum, to give **5** (2.58 g, 97%), m.p. 121°, $R_F$ 0.27 (ether); $\nu_{max}^{KBr}$ 3345 (OH), 1785 (lactone C=O), 1725 (ester C=O), 1590 $cm^{-1}$ (C=C). $^1H$-N.m.r. data ($CDCl_3$, 220 MHz): $\delta$ 1.24 (s, 3 H, Me), 1.28 (s, 3 H, Me), 1.78 (br, 1 H, OH), 2.43 (m, 1 H, H-4), 2.60 (dd, 1 H, *J* 18 and 6.5 Hz, H-3), 2.78 (dd, 1 H, *J* 18 and 9.5 Hz, H-3), 4.48 (dd, 1 H, *J* 12 and 5.4 Hz, $CH_2O$), 4.62 (dd, 1 H, *J* 12 and 2.2 Hz, $CH_2O$), 4.92 (m, 1 H, H-5), 7.43–8.01 (m, 5 H, Ph).

*Anal.* Calc. for $C_{15}H_{18}O_4$: C, 64.74; H, 6.52. Found: C, 64.58; H, 6.50.

*(4S,5S)-5-Benzoyloxymethyl-4-isopropenyltetrahydrofuran-2-one* (**6**) *and the isomer* **7**. — To a solution of **5** (2.0 g, 7.3 mmol) in dry dichloromethane (20 mL) was added a slurry of phosphorus pentachloride (3.1 g, 15 mmol) in dichloromethane (6 mL) at 0°. The mixture was stirred for 5 min, water (80 mL) and ether (100 mL) were added, and the ethereal layer was washed with brine (3 × 25 mL), dried, and concentrated. The white crystalline solid (1.88 g) comprised a 5:1 mixture of **6** and **7**. It was impossible to separate these compounds efficiently by chromatography, but small amounts of the pure compounds were obtained.

Compound **6**: $\nu_{max}^{KBr}$ 1785 (lactone C=O), 1720 (ester C=O), 1600 (aromatic ring), 1580 (alkene), 1450, 1268, 1172, 1107, 1053, 940 $cm^{-1}$. $^1H$-N.m.r. data ($CDCl_3$, 400 MHz): $\delta$ 1.79 (s, 3 H, Me), 2.56 (dd, 1 H, *J* 17.7 and 8.8 Hz, H-3), 2.79 (dd, 1 H, *J* 9.1 and 17.7 Hz, H-3), 3.06 (m, 1 H, H-4), 4.42 (dd, 1 H, *J* 12.3 and 5.5 Hz, $CH_2O$), 4.52 (dd, 1 H, *J* 12.3 and 2.9 Hz, $CH_2O$), 4.66 (m, 1 H, H-5), 4.94 (m, 2 H, alkene-H), 7.43–8.01 (m, 5 H, Ph).

Compound **7**: $^1H$-N.m.r. data ($CDCl_3$, 400 MHz): $\delta$ 1.68 (s, 3 H, Me), 1.76 (s, 3 H, Me), 3.18 (m, 2 H, H-3,3), 4.46 (dd, 1 H, *J* 12.4 and 4.5 Hz, $CH_2O$), 4.52 (dd, 1 H, *J* 12.4 and 2.6 Hz, $CH_2O$), 5.41 (m, 1 H, H-5), 7.43–8.05 (m, 5 H, Ph).

*Anal.* Calc. for $C_{15}H_{18}O_5$ (mixture): C, 69.22; H, 6.20. Found: C, 69.42; H, 6.17.

*(4S,5S)-5-Benzoyloxymethyl-4-(1-bromo-1-methylethyl)tetrahydrofuran-2-one* (**8**). — A solution of the mixture **6** and **7** (2.0 g, 7.2 mmol) in acetic acid (10 mL) was added to a solution of acetic acid (20 mL) saturated with HBr. The mixture was stirred at

room temperature for 5 min, then an ice–water mixture was added followed by ether. The ethereal extract was washed successively with saturated aqueous sodium sulphate (3 × 25 mL) and then brine (3 × 25 mL), dried ($MgSO_4$), and concentrated to leave **8** as an unstable crystalline solid (2.4 g, 98%), $R_F$ 0.65 (ethyl acetate); $\nu_{max}^{KBr}$ 1781 (lactone C=O), 1720 (ester C=O), 1600 (aryl C=C), 1580, 1450, 1275, 1178, 1120, 970, and 615 $cm^{-1}$. $^1$H-N.m.r data ($CDCl_3$, 220 MHz): $\delta$ 1.74 (s, 3 H, Me), 1.82 (s, 3 H, Me), 2.62 (m, 1 H, H-4), 2.70 (dd, 1 H, *J* 18 and 4 Hz, H-3), 2.91 (dd, 1 H, *J* 18 and 8.8 Hz, H-3), 4.48 (dd, 1 H, *J* 12 and 4 Hz, $CH_2O$), 4.60 (dd, 1 H, *J* 12 and 3 Hz, $CH_2O$), 4.93 (m, 1 H, H-5), 7.42–8.02 (m, 5 H, Ph). Mass spectrum: *m/z* 342 ($M^+$ + 1, $^{81}$Br), 340 ($M^+$ + 1, $^{79}$Br), 261 ($M^+$ – Br).

*(1R,4S,5S)-4-Benzoyloxymethyl-6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one* (**9**). — A solution of potassium *tert*-butoxide (1.3 equiv.) in tetrahydrofuran (25 mL) was added to a solution of **8** (1.18 g, 5.3 mmol) in dry tetrahydrofuran (60 mL). The mixture was stirred at 0° for 5 min, brine (35 mL) was added, and then dichloromethane. The aqueous layer was extracted with dichloromethane (2 × 25 mL), and the combined organic extract was dried and concentrated. Flash chromatography (ether–light petroleum, 6:4) of the residue gave **9** (0.71 g, 51%), m.p. 92°, $[\alpha]_D^{20}$ –51° (*c* 0.2, dichloromethane); $\nu_{max}^{KBr}$ 1769 (lactone C=O), 1727 (ester C=O), and 1600 $cm^{-1}$ (aryl C=C). N.m.r. data: $^1$H [$(CD_3)_2SO$, 400 MHz], $\delta$ 0.52 (s, 3 H, Me), 0.82 (s, 3 H, Me), 1.13 (d, 1 H, *J* 6.1 Hz, H-5), 1.59 (d, 1 H, *J* 0.8 Hz, H-1), 3.84 (m, 1 H, H-4), 4.09 (dd, 1 H, *J* 12 and 3.4 Hz, $CH_2O$), 4.11 (dd, 1 H, *J* 12 and 4.6 Hz, $CH_2O$), 7.05–8.23 (m, 5 H, Ph); $^{13}$C ($CDCl_3$, 22.5 Hz), $\delta$ 14.87 (Me), 23.14 (Me), 25.24 (C-6), 30.63 (C-5), 32.00 (C-1), 65.64 (C-4), 75.16 (C-5), 128.5–133.38 (aryl C), 166.123 (ester C=O), 173.64 (lactone C=O).

*Anal.* Calc. for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 68.97; H, 6.23.

*Methyl* (R)-(Z)-*4,5-(dimethylmethylenedioxy)pent-2-enoate* (**12**). — A solution of L-glyceraldehyde (12.0 g, 94 mmol) in methanol (Analar, 100 mL) was added to a solution of methoxycarbonylmethylenetriphenylphosphorane (1.1 equiv.) at 0°, and the mixture was stirred for 1 h, then concentrated. The residue was extracted with hot light petroleum–ether (7:3, 3 × 100 mL), and the combined extracts were concentrated. Flash chromatography (light petroleum–ether, 7:3) gave **12** (14.3 g, 82%) and the corresponding *trans*-ester (1.1 g). Compound **12** had $R_F$ 0.62 (ethyl acetate), $[\alpha]_D^{20}$ –118° (*c* 1.8, chloroform); $\nu_{max}^{KBr}$ 1725 (ester C=O), 1649 (C=C), 1210, and 1068 $cm^{-1}$. $^1$H-N.m.r. data ($CDCl_3$, 220 MHz): $\delta$ 1.42 (s, 3 H, Me), 1.48 (s, 3 H, Me), 3.62 (dd, 1 H, *J* 8.5 and 4 Hz, H-5), 3.76 (s, 3 H, OMe), 4.41 (dd, 1 H, *J* 7 Hz, H-5), 5.54 (m, 1 H, H-4), 5.88 (dd, 1 H, *J* 11.5 and 1.5 Hz, H-2), 6.40 (dd, *J* 11.5 and 6.5 Hz, H-3).

(R)-*5-Hydroxymethylfuran-2(5H)-one* (**11**). — A solution of **12** (13.0 g, 70 mmol) in methanol (35 mL) containing conc. sulphuric acid (0.5 mL, 30%) was stored for 1.5 h at room temperature, then concentrated. Flash chromatography (ethyl acetate) of the residue gave **11** (7.22 g, 91%), m.p. 37–39°, $[\alpha]_D^{20}$ +174° (*c* 0.2, water); $\nu_{max}^{KBr}$ 3343 (OH), 1745 (lactone C=O), 1607 (C=C), 1163, 1115, 1078, 1058, and 862 $cm^{-1}$. $^1$H-N.m.r. data ($CDCl_3$, 220 MHz): $\delta$ 3.28 (s, 1 H, OH), 3.84 (dd, *J* 13 and 5.6 Hz, $CH_2O$), 4.04 (dd, 1 H, *J* 13 and 3.2 Hz, $CH_2O$), 5.22 (m, 1 H, H-5), 6.23 (dd, 1 H, *J* 6 and 2.2 Hz, H-3), 7.66 (dd, 1 H, *J* 6 and 1.5 Hz, H-4).

*Anal.* Calc. for $C_5H_6O_3$: C, 52.63; H, 5.30. Found: C, 52.37; H, 5.30.

(4*R*,5*R*)-5-Hydroxymethyl-4-(1-hydroxy-1-methylethyl)tetrahydrofuran-2-one (**13**) had $[\alpha]_D^{20}$ $-25°$ (*c* 0.3, water); and (*1*S,*4*R,*5*R)-4-benzoyloxymethyl-6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one (**10**) had $[\alpha]_D^{20}$ $-51°$ (*c* 0.2, dichloromethane).

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