The Synthesis and Absolute Configuration of the Novel Ichthyotoxic Diacylglycerols, Umbraculumin A and Umbraculumin C

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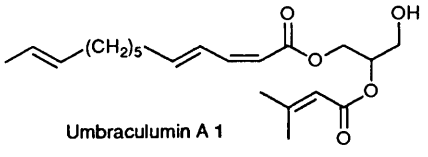
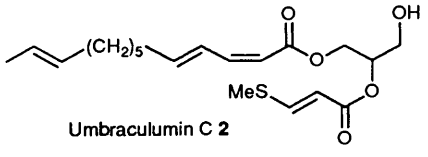
The total syntheses of umbraculumin A **1** and umbraculumin C **2** in homochiral form are described. Noteworthy steps involve (i) the preparation of the key *Z,E*-acid **10** by organolithium addition to pyrylium salts, (ii) the use of the 4-methoxyphenylmethyl protecting group for the preparation of 1,2-diacyl glycerols and its removal using trifluoroacetic acid–anisole without significant acyl migration (DDQ removal having proved inefficient) and (iii) a new procedure for the stereoselective preparation of (*Z*)- and (*E*)-3-methylthiopropenoic acid.

Skin extracts of the opisthobranch mollusc *Umbraculum mediterraneum* were recently shown to contain the novel diacylglycerols umbraculumin A **1** and umbraculumin C **2**, their structures being determined by spectroscopic means.[1] These compounds were shown to be very toxic to the mosquito fish *Gambusia affinis* at 10 and 0.1 μg cm^{-3}, respectively.[1] Given the current interest in marine defense allomones[1–3] and our own involvement with the development of stereospecific routes to conjugated polyenes[3–6] and the synthesis and biological screening of novel diacylglycerols,[7] we embarked upon the synthesis of the umbraculumins. The successful syntheses, which are shown in Schemes 1–3, also serve to establish the absolute configurations of umbraculumin A and umbraculumin C.[6] Sodano *et al.* reached the same conclusions by derivatisation of the natural compounds using a chiral isocyanate, saponification, treatment with dimethoxypropane, and comparison of the derived acetal-urethanes with those obtained from the two enantiomeric isopropylidene glycerols.[8]



Umbraculumin A 1



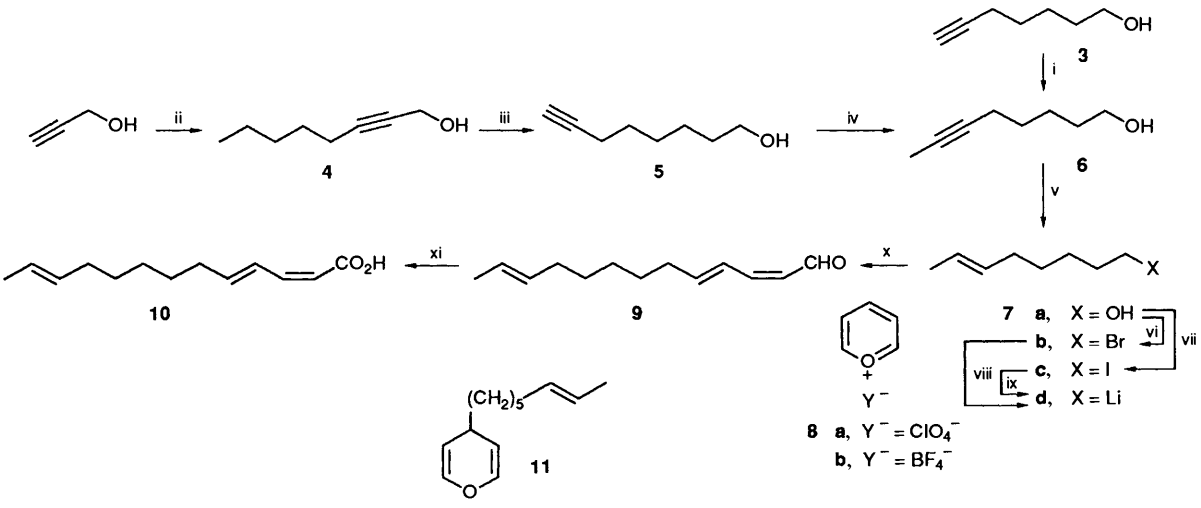
Umbraculumin C 2

The key carboxylic acid **10**, required for the synthesis of both compounds, was prepared by oxidation of aldehyde **9**, readily available by organolithium addition to pyrylium salts using our recently published methodology[3–6] as shown in Scheme 1.

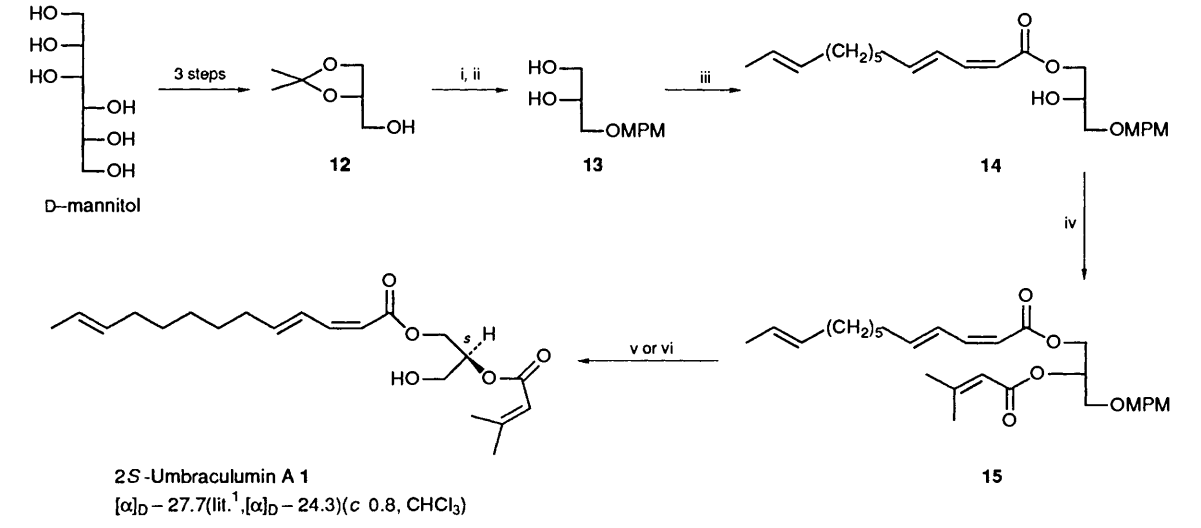
Oct-6-yn-1-ol **6** was identified as a suitable precursor for the preparation of compound **9** and initially it was prepared by methylation of the dianion derived from hept-5-yn-1-ol **3**. The yields obtained from this process were rather variable, however, and an improved method was developed based on Brandsma's procedure[9] for the conversion of alk-1-ynes into the isomeric alk-2-ynes. Thus, homologation of the prop-2-ynyl alcohol dianion using amyl bromide gave oct-2-yn-1-ol **4** which, *via* 'zipper' isomerisation,[10] gave the alk-1-yne **5**. Treatment[9] of **5** with potassium *tert*-butoxide (Bu'OK) in dimethyl sulphoxide (DMSO) at 80 °C for 5 min gave efficient (84.5%) 'mono-unzipping' producing the required isomeric alk-2-yne **6**. Alkyne reduction using lithium in liquid ammonia followed by treatment of the resulting alkenyl alcohol **7a** with 1,2-bis-(diphenylphosphino)ethane (diphos)–bromine[11] or imidazole–triphenylphosphine iodine[12] gave the *E*-alkenyl halides **7b** and **7c**, respectively, in high overall yield. The corresponding organolithium reagent **7d** was prepared by treatment of bromide **7b** with lithium metal or, more reproducibly, from iodide **7c** and *tert*-butyllithium.[13] Addition of the organometallic reagent **7d** to pyrylium perchlorate **8a**[4] or pyrylium tetrafluoroborate **8b**[5] and *in situ* rearrangement of the resulting 2*H*-pyran produced the requisite *Z,E*-dienal **9** in 53–56% yield. The 4*H*-pyran **11** was formed as a by-product in these reactions in 20–30% yield. The choice of pyrylium salt makes little difference to the reaction yield, although the tetrafluoroborate salt[5] obviously presents less of a safety hazard. The oxidation of *Z,E*-dienal **9** to *Z,E*-acid **10** without isomerisation was accomplished efficiently using buffered sodium chlorite in the presence of a halogen scavenger.[14]

With acid **10** in hand, we were in a position to attempt the mono-acylation of a protected glycerol derivative. Careful consideration was given to the choice of protecting group as we envisaged removing it in the final stage of the synthesis and it was of paramount importance that the deprotection conditions did not lead to acyl migration[15] or diene isomerisation. We chose to use the 4-methoxyphenylmethyl (MPM) derivative **13**[16,17] as it is well established that the MPM group can be removed using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) under neutral conditions.[18] We also investigated the use of the *tert*-butyldiphenylsilyl protecting group, but studies on model 3-silylated diacylglycerols indicated that it would be extremely difficult to carry out desilylation without concomitant acyl migration. The preparation of umbraculumin A **1** using MPM protection is shown in Scheme 2.

Solketal **12** is readily available in chiral (*S*) form from D-mannitol using published procedures.[19] Alkylation of **12** with NaH–MPMCl followed by removal of the acetal protecting group gave diol **13** as a crystalline solid in high yield. Although a known[16,17] compound, **13** has been reported[17] to be an oil. Acylation of **13** with the carboxylic acid **10** in the presence of dicyclohexylcarbodiimide–4-dimethylaminopyridine (DCC–DMAP)[20] gave the 1-acyl derivative **14** in 50% yield after chromatography to remove the isomeric 2-acyl isomer and diacylated material. Acylation of **14** with 3,3-dimethylacrylic acid proceeded slowly but provided the MPM protected form of the target molecule **15** in high yield. There was no sign of acyl migration during this step. Despite our carefully laid plans, the removal of the MPM protecting group using DDQ in aqueous dichloromethane proved to be extremely difficult,



Scheme 1 *Reagents:* i, excess $LiNH_2$, NH_3 (liq.), CH_3I (variable yields and low reproducibility); ii, excess $LiNH_2$, NH_3 (liq.), $C_5H_{11}Br$ (84%); iii, $H_2N(CH_2)_3NH_2$, Li, Bu^{t}OK (78%), iv, Bu^{t}OK, DMSO, 80 °C, 5 min (84.5%); v, Li, NH_3 (liq.) (97%); vi, $Ph_2PCH_2CH_2PPh_2$, $2Br_2$ (93%); vii, Ph_3P, I_2, imidazole (98%); viii, Li, ether; ix, Bu^{t}Li, Et_2O; x, **8a** or **8b** (56% from **8a** and **7b**, 53% from **8b** and **7c**); xi, $NaClO_2$, aq. Bu^{t}OH, 2-methylbut-2-ene (72%)

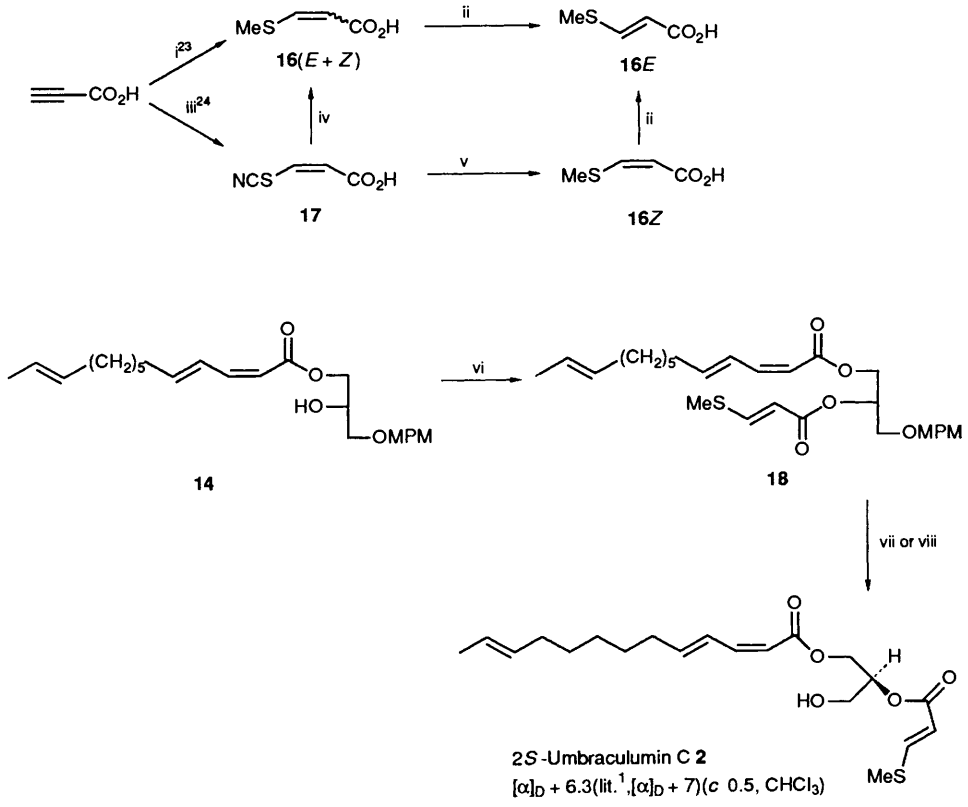


Scheme 2 *Reagents:* i, NaH, THF, *p*-$MeOC_6H_4CH_2Cl$; ii, 1 mol dm^{-3} HCl, MeOH (68% over 2 steps); iii, **10**, DCC, DMAP, 0 °C, 12 h (50%); iv, $Me_2C{=}CHCO_2H$, DCC, DMAP, 6 d (93%); v, DDQ, aq. CH_2Cl_2 (26% + 16% recovered **15**); vi, CF_3CO_2H, CH_2Cl_2, anisole (74%)

umbraculumin A **1** being obtained in a maximum yield of 26% after extensive optimisation. Given that a saturated 1-acyl-2-alkyl MPM-protected glycerol has been successfully deprotected using standard conditions,[16] and that we have prepared 1,2-dihexanoyl- and 1,2-didecanoyl-glycerol from the corresponding MPM derivatives using DDQ, it is possible that the low yield for the deprotection of **15** is in some way associated with the presence of an unsaturated side chain. Additional studies would be required to clarify this point.

Fortunately, we discovered that MPM removal could be accomplished efficiently (74%) by the use of trifluoroacetic acid (TFA) in dichloromethane containing anisole as a carbonium ion trap.[20–22] It is noteworthy, particularly in view of our original fears, that neither acyl migration nor isomerisation was observed. Umbraculumin A **1** was isolated as an oil, $[\alpha]_D$ −27.7 (*c* 0.7, $CHCl_3$) [lit.,[1] $[\alpha]_D$ −24.3 (*c* 0.8, $CHCl_3$)], with spectral data (see Experimental section) entirely consistent with the literature[1] values. The use of D-mannitol as starting material establishes that umbraculumin A has the 2*S*-configuration as shown in Scheme 2, *i.e.* it is an *sn*-1,2-diacylglycerol.

With all of the necessary methodology established, the synthesis of umbraculumin C was straightforward (Scheme 3). The published[23] procedure for the preparation of (*E*)-3-methylthiopropenoic acid **16***E* involves heating methanethiol, propiolic acid and an amine in a sealed tube at 80–90 °C for 12 h to give the required product as an *E*/*Z* mixture which is then isomerised to the *E*-alkene by heating in boiling xylene for 24 h, and purified by chromatography and recrystallisation. We have developed an alternative sequence, based on work on the corresponding thiols recently published by Giffard and Léauté,[24] which avoids the need to generate and use methanethiol as shown in Scheme 3. Treatment of propiolic acid with KSCN–H_2SO_4 according to the published procedure,[24] gives the *Z*-thiocyanate **17**. Alkaline hydrolysis of **17** using sodium hydroxide in the presence of methyl iodide gives **16***Z* directly without contamination by **16***E*. If the hydrolysis is carried out using lithium hydroxide, however, and the reaction left for several days to allow equilibration to occur before addition of methyl iodide, then a 5.5:1 ratio of **16***E*:**16***Z* was obtained (when NaOH–MeI were used under similar conditions the corresponding ratio was 2.7:1). Isomerisation of **16***Z* following literature conditions[23] required prolonged heating (24 h). We found that the presence of a catalytic quantity of



Scheme 3 *Reagents:* i, MeSH, 80 °C, 12 h (ref. 23); ii, Xylene, PTSA, heat (31–68%, see text); iii, KSCN, H_2SO_4 (ref. 24); iv, Aq. LiOH, MeOH, 8 d then MeI (62%, *E*:*Z ca.* 5.5:1); v, Aq. NaOH, MeI, MeOH, 0.5 h (63%); vi, **16***E*, DCC, DMAP, 0 °C, 49 h (92%); vii, DDQ, aq. CH_2Cl_2 (28% + 30% recovered **18**); viii, CF_3CO_2H, CH_2Cl_2, anisole, 6 h (84%)

toluene-4-sulphonic acid (PTSA) promoted the reaction (9 h) but it still proceeded in low yield (31%). In xylene/PTSA, the isomerisation process was faster (4 h) with the 5.5:1 **16***E*:**16***Z* mixture and **16***E* was isolated in 68% yield.

Acylation of the monoacylglycerol **14** with (*E*)-3-methylthiopropenoic acid **16***E* proceeded efficiently to give the adduct **18** but deprotection with DDQ again proved to be a low yielding reaction (Scheme 3). The combination of trifluoroacetic acid in dichloromethane–anisole was successful here too, producing umbraculumin C **2** in 84% yield. Again the spectroscopic and rotational data were entirely consistent with the literature[1] values confirming[8] that umbraculumin C has the 2*S*-configuration as shown in Scheme 3.

Preliminary experiments were carried out to establish the scope of the MPM–trifluoroacetic acid protocol for the preparation of 1,2-diacylglycerols. Interestingly, the MPM derivatives of 1,2-dihexanoyl- and 1,2-didecanoyl-glycerol underwent only slow deprotection under the conditions used for the umbraculumins and a significant amount of acyl migration (to the 1,3-isomer) was detected. It would appear, therefore, that the MPM–trifluoroacetic acid procedure is limited in its generality, although the efficiency of the procedure for the production of the umbraculumins is noteworthy.

Experimental

^1H NMR spectra (δ_H) were recorded using JEOL PMX 60 and JEOL FX 400 (unless otherwise stated) spectrometers. ^{13}C NMR spectra (δ_C) were recorded using JEOL EX 90 and JEOL FX 400 (unless otherwise stated) spectrometers. Samples for NMR spectrometry were prepared as solutions in $CDCl_3$, containing tetramethylsilane as an internal standard, unless otherwise stated; *J* values are given in Hz. IR spectra (ν_{max}) were recorded on a Perkin-Elmer FT IR 1720X spectrophotometer as neat films (liquid samples) or emulsions in Nujol (solid samples); UV spectra (λ_{max}) were recorded on a Pye-Unicam PU 8800 spectrophotometer and optical rotations on a Perkin-Elmer 141 polarimeter ($[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}). Mass spectra were recorded on a Kratos MS 25 (low resolution) or a Kratos VG Zab-E (high resolution) instrument. For Kugelrohr distillations, the b.p.s quoted refer to oven temperatures.

Reactions involving organometallic reagents were carried out under a nitrogen atmosphere using flame-dried apparatus. Light petroleum refers to the fraction of boiling range 40–60 °C, which was redistilled before use. Diethyl ether and THF (tetrahydrofuran) were dried over sodium–benzophenone ketyl and distilled immediately before use. Dry DMSO, CH_2Cl_2 and propane-1,3-diamine were distilled from CaH_2 and stored over 4 Å molecular sieves. DDQ was recrystallised from chloroform before use, *tert*-butyllithium (in pentane) was purchased from Aldrich Chemical Company and was used as received as were all other reagents with the exception of the pyrylium salts **8** which were prepared by literature procedures.[4,5] Sodium hydride refers to a 60% dispersion in oil which was washed twice with petroleum before use. Analytical thin layer chromatography (TLC) was performed on Merck 5554 aluminium-backed silica gel plates. Preparative centrifugal chromatography was carried out on a Chromatotron Model 7924T using silica gel (Merck 7749). M.p.s were recorded on a Kofler hot-stage melting point apparatus and are uncorrected. Oct-2-yn-1-ol **4** and oct-7-yn-1-ol **5** were prepared by modification of a literature[25] route (see Scheme 1 and text).

Oct-6-yn-1-ol **6**.—A mixture of oct-7-yn-1-ol **5** (37.11 g, 0.294 mol) and potassium *tert*-butoxide (5.93 g, 0.053 mol) in dry DMSO (580 cm^3) was heated at 80–83 °C for 5 min.[9] After cooling, the reaction mixture was poured into water and

extracted with light petroleum–diethyl ether (1:1). The organic phase was washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Kugelrohr distillation under reduced pressure gave the *title compound* **6** (31.36 g, 84.5%) as a pale yellow oil, b.p. 62–72 °C/0.2–0.5 mmHg (Found: C, 76.0; H, 11.2. $C_8H_{14}O$ requires C, 76.1; H, 11.2%); ν_{max}/cm^{-1} 3350; δ_H(PMX 60) 1.33–1.37 (6 H, m), 1.75 (3 H, t, *J* 2.4), 1.95–2.30 (2 H, m), 3.25 (1 H, br s, exch.) and 3.60 (2 H, br t, *J* 7.2); δ_C(EX 90) 3.3, 18.6, 24.9, 28.8, 32.15, 62.5, 75.5 and 79.0; *m/z* 125 ($M^+ - 1$, 1.5%), 69 (46), 67 (100) and 32 (77).

(6E)-*Oct*-6-*en*-1-*ol* **7a**.—A solution of the alcohol **6** (31.15 g, 0.247 mol) in dry THF (150 cm^3) was added dropwise to a stirred blue mixture of lithium wire (5.74 g, 0.827 mol) in liquid ammonia (640 cm^3) over a period of 35 min. After further stirring for 2 h, ammonia was evaporated and the residue was diluted with water and extracted with light petroleum–diethyl ether (1:1). The organic phase was washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. Kugelrohr distillation under reduced pressure afforded the title compound **7a** [26] (30.57 g, 97%), as a colourless oil, b.p. 56–64 °C/0.7 mmHg; spectral data was consistent with the assigned structure.

(6E)-1-*Bromooct*-6-*ene* **7b**.—A solution of bromine (2.56 g, 16 mmol) in dichloromethane (6.5 cm^3) was added dropwise to a stirred solution of 1,2-bis(diphenylphosphino)ethane (3.19 g, 8.0 mmol) in dichloromethane (40 cm^3) at 0 °C. A solution of alcohol **7a** (1.02 g, 7.97 mmol) in dichloromethane (10 cm^3) was then added and the reaction mixture was warmed up to room temp. and stirred for 40 min. By-products were precipitated with diethyl ether (140 cm^3) and light petroleum (280 cm^3) and removed by filtration through a pad of silica gel. The solids were washed with diethyl ether–light petroleum (1:2). Concentration of the combined filtrates under reduced pressure and Kugelrohr distillation of the residue under reduced pressure gave the title compound **7b** (1.41 g, 93%), as a colourless oil, b.p. 50–90 °C/0.5 mmHg (lit.,[27] 86–89 °C/3 mmHg); spectral data was consistent with the assigned structure.

(6E)-1-*Iodooct*-6-*ene* **7c**.—Imidazole (2.04 g, 30 mmol) was added to a solution of triphenylphosphine (7.86 g, 30 mmol) in CH_2Cl_2 (100 cm^3) stirred under N_2 followed by portionwise addition of I_2 (7.59 g, 29.91 mmol). After 30 min, a solution of the alcohol **7a** (3.23 g, 25.23 mmol) in CH_2Cl_2 (25 cm^3) was added and the orange mixture stirred for 1.5 h. The bulk of the solvent was evaporated and the remainder filtered through a short column of silica with light petroleum. After washing of the column several times with light petroleum, the combined filtrates were concentrated under reduced pressure to give the *title compound* **7c** (5.82 g, 98%) as a colourless oil (Found: C, 40.6; H, 6.4. $C_8H_{15}I$ requires C, 40.35; H, 6.35; I, 53.3%); R_f 0.49 (light petroleum); ν_{max}/cm^{-1} 965; δ_H(PMX 60) 1.25–1.53 (6 H, m), 1.57–1.77 (3 H, m), 1.80–2.17 (2 H, m), 3.20 (2 H, t, *J* 7.2) and 5.45 (2 H, m); δ_C 7.1, 17.9, 28.4, 30.0, 32.3, 33.4, 125.0 and 131.0; *m/z* 239 ($M^+ + 1$, 2.6%), 238 (M^+, 20%), 111 ($M^+ - I$, 14%) and 55 (100).

(2Z,4E,11E)-*Trideca*-2,4,11-*trienal* **9**.—(*a*) *From bromide* **7b** *and pyrylium perchlorate* **8a**. A solution of the bromide **7b** (383 mg, 2.0 mmol) in dry diethyl ether (1.5 cm^3) was added dropwise to finely cut lithium metal (33 mg, 4.76 mmol) in dry diethyl ether (1.5 cm^3) stirred under N_2 at 0 °C. After 3 h the resulting grey suspension of organolithium reagent **7d** was added *via* a cannula to a suspension of pyrylium salt **8a** (182 mg, 1.01 mmol) in dry THF (6 cm^3) stirred at −78 °C under N_2. The orange reaction mixture was quenched with saturated aqueous NH_4Cl at −78 °C after 1 h and then extracted with diethyl ether. The combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to afford the trienal **9** and the 4*H*-pyran **11** (*ca.* 2:1 by ^1H NMR spectroscopy). Purification by preparative centrifugal chromatography using light petroleum–CH_2Cl_2 (1:1) as eluent gave the *trienal* **9** (109 mg, 56%) as a colourless oil (Found: C, 81.0; H, 10.2. $C_{13}H_{20}O$ requires C, 81.2; H, 10.5%); R_f 0.36 (light petroleum–CH_2Cl_2, 1:1); ν_{max}/cm^{-1} 2855, 1669, 1637 and 965; δ_H 1.28–1.40 (4 H, m), 1.46 (2 H, appt. quint., *J* 7.3), 1.64 (3 H, d, *J* 4.6), 1.97 (2 H, br s), 2.23 (2 H, appt. q, *J* 7.0), 5.40–5.43 (2 H, m), 5.78 (1 H, dd, *J* 10.7 and 7.9), 6.13–6.21 (1 H, m), 6.90–6.95 (1 H, m), 7.00–7.07 (1 H, m) and 10.17 (1 H, d, *J* 7.9); δ_C 17.8, 28.4, 28.6, 29.2, 32.3, 32.9, 124.2, 124.7, 125.7, 131.2, 147.0, 147.8 and 190.2; *m/z* 192 (M^+, 7%) and 81 ($C_5H_5O^+$, 100).

(*b*) *From iodide* **7c** *and pyrylium tetrafluoroborate* **8b**. *tert*-Butyllithium (1.7 mol dm^{-3} in pentane, 2.5 cm^3, 4.25 mmol) was added to a solution of the iodide **7c** (478 mg, 2.0 mmol) in dry ether (4 cm^3) stirred under N_2 at −78 °C. After 2 h the temperature was brought up to 0 °C for 30 min; then the solution of organolithium reagent **7d** was added *via* a cannula to a suspension of pyrylium tetrafluoroborate (167 mg, 0.99 mmol) in dry THF (6.0 cm^3) stirred at −78 °C. After 1 h the reaction mixture was worked up and the product was purified as described above giving the *trienal* **9** (100 mg, 53%) identical with the product obtained from procedure (*a*).

(2Z,4E,11E)-*Trideca*-2,4,11-*trienoic Acid* **10**.—A solution of $NaClO_2$ (0.84 g, 6.1 mmol) and KH_2PO_4 (0.83 g, 6.1 mmol) in water (8 cm^3) was added to a solution of the aldehyde **9** (188 mg, 0.98 mmol) and 2-methylbut-2-ene (5.3 cm^3) in *tert*-butyl alcohol (20 cm^3) and the mixture vigorously stirred at room temp. for 20 h. The volatile compounds were removed by evaporation under reduced pressure and the residue was extracted with diethyl ether. The combined organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by preparative centrifugal chromatography using light petroleum–ethyl acetate (4:1) containing 1 to 5% of methanol as eluent afforded the *acid* **10** (155 mg, 72%) as a colourless oil (Found: C, 74.85; H, 9.9. $C_{13}H_{20}O_2$ requires C, 75.0; H, 9.7%); R_f 0.35 (light petroleum–ethyl acetate, 4:1 + 1% MeOH); ν_{max}/cm^{-1} 2950, 1685, 1635 and 963; δ_H 1.23–1.37 (4 H, m), 1.37–1.45 (2 H, m), 1.61–1.62 (3 H, m), 1.95 (2 H, br s), 2.16–2.21 (2 H, m), 5.37–5.40 (2 H, m), 5.55 (1 H, d, *J* 11.3), 6.10 (1 H, dt, *J* 15.0 and 7.3), 6.63 (1 H, t, *J* 11.3), 7.31 (1 H, dd, *J* 11.3 and 15.0) and 10.0 (1 H, exch.); δ_C 17.9, 28.65, 28.7, 29.3, 32.4, 33.0, 114.7, 124.7, 127.0, 131.4, 147.1, 147.7 and 172.2; *m/z* 209 ($M^+ + 1$, 1.3%), 208 (M^+, 24%), 97 (55), 81 (59), 55 (100) and 41 (56.5).

(R)-3-(4-*Methoxybenzyloxy*)*propane*-1,2-*diol* **13**.—A solution of (*S*)-isopropylideneglycerol **12** [19] (5.83 g, 44.1 mmol) in dry THF (190 cm^3) was added dropwise to NaH (1.28 g, 53.3 mmol) in dry DMSO (60 cm^3) and the mixture stirred at room temp. under N_2. After 30 min, a solution of 4-methoxybenzyl chloride (6.91 g, 44.1 mmol) in dry THF (20 cm^3) was added to the alkoxide and the mixture stirred for 18 h; it was then quenched by pouring onto ice and saturated aq. NH_4Cl. The product was extracted with ethyl acetate and the organic phase was washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude acetonide was hydrolysed without further purification by stirring with 1 mol dm^{-3} HCl (10 cm^3) in MeOH (15 cm^3) at room temp. for 2 h and then worked up as before with ethyl acetate. The resulting solid was recrystallised from toluene–light petroleum to give the title *diol* **13** (6.38 g, 68%) as square plates, m.p. 43.5–45.1 °C (lit.,[17] reported as an oil) (Found: C, 62.25; H, 7.7. $C_{11}H_{16}O_4$ requires C, 62.25; H, 7.6%); $[\alpha]_D$ −1.54 (*c* 3.7 in $CHCl_3$); R_f 0.38 (CH_2Cl_2–MeOH,

9:1); ν_{max}/cm^{-1} 3279 and 1612; δ_H 2.30–2.98 (2 H, br s, exch.), 3.47–3.93 (5 H, m), 3.77 (3 H, s), 4.47 (2 H, s), 6.87 (2 H, d, *J* 8.4) and 7.23 (2 H, d, *J* 8.4); *m/z* 212 (M^+, 7%), 137 (21) and 121 (CH_2PhOMe^+, 100%).

Monoacylglycerol **14**.—DCC (dicyclohexylcarbodiimide) (267 mg, 1.29 mmol) was added to a solution of acid **10** (203 mg, 0.98 mmol) and diol **13** (242 mg, 1.14 mmol) in dry CH_2Cl_2 (11 cm^3) at 0 °C. Then DMAP (dimethylaminopyridine) (33 mg, 0.27 mmol) was added and the mixture stirred at 0 °C for 12 h. The precipitated dicyclohexylurea was filtered off and the filtrate eluted through a pad of SiO_2 with ether. After evaporation of the solvent under reduced pressure, the residue was purified by preparative centrifugal chromatography using light petroleum–EtOAc (1 to 25% of EtOAc) as eluent to give the *title compound* **14** (196 mg, 50%) as a colourless oil (Found: C, 71.4; H, 8.6. $C_{24}H_{34}O_5$ requires C, 71.6; H, 8.5%); R_f 0.11 (light petroleum–EtOAc, 4:1); ν_{max}/cm^{-1} 3457, 1717, 1637 and 965; δ_H 1.25–1.38 (4 H, m), 1.43 (2 H, app. quint., *J* 7.3), 1.64 (3 H, dd, *J* 3.4 and 1.2), 1.93–1.97 (2 H, m), 2.20 (2 H, m), 2.61 (1 H, d, *J* 4.9, exch.), 3.48 (1 H, dd, *J* 6.1 and 9.5), 3.54 (1 H, dd, *J* 4.3 and 9.5), 3.80 (3 H, s), 4.03–4.07 (1 H, m), 4.17 (1 H, dd, *J* 6.1 and 11.6), 4.23 (1 H, dd, *J* 4.6 and 11.6), 4.50 (2 H, s), 5.39–5.42 (2 H, m), 5.58 (1 H, d, *J* 11.3), 6.09 (1 H, dt, *J* 15.3 and 7.0), 6.57 (1 H, t, *J* 11.3), 6.88 (2 H, d, *J* 8.85), 7.25 (2 H, d, *J* 8.5) and 7.35 (1 H, ddt, *J* 15.3, 11.3 and 1.2); δ_C 17.9, 28.7, 28.8, 29.4, 32.5, 33.0, 55.3, 65.1, 69.0, 70.7, 73.2, 113.9, 114.7, 124.8, 126.9, 129.4, 129.8, 131.4, 146.3, 146.4, 159.4 and 166.5; *m/z* 403 ($M^+ + 1$, 1%), 402 (M^+, 4%), 121 (MPM^+, 100%) and 55 (31%).

Diacylglycerol **15**.—The monoacylglycerol **14** (173 mg, 0.43 mmol) was stirred at room temp. with 3,3-dimethylacrylic acid (53 mg, 0.53 mmol) in the presence of DCC (115 mg, 0.56 mmol) and DMAP (56 mg, 0.46 mmol) in dry CH_2Cl_2 (4.5 cm^3). The reaction was monitored by TLC and additional 3,3-dimethylacrylic acid (43 mg, 0.43 mmol) and DCC (113 mg, 0.55 mmol) were added until the monoacylglycerol was consumed. After 6 d the reaction mixture was worked up as described in the preceding experimental. Purification by preparative centrifugal chromatography using light petroleum–ethyl acetate (9:1) as eluent afforded the *title compound* **15** (196 mg, 94%) as a colourless oil (Found: C, 71.7; H, 8.6. $C_{29}H_{40}O_6$ requires C, 71.9; H, 8.3%); R_f 0.39 (light petroleum–EtOAc, 4:1); ν_{max}/cm^{-1} 1718, 1637, 1612, 1614 and 965; δ_H 1.28–1.34 (4 H, m), 1.39–1.46 (2 H, m), 1.63 (3 H, d, *J* 4.3), 1.89 (3 H, d, *J* 0.9), 1.95 (2 H, m), 2.16 (3 H, d, *J* 0.9), 2.16–2.21 (2 H, m), 3.58–3.61 (2 H, m), 3.79 (3 H, s), 4.29 (1 H, dd, *J* 11.9 and 6.1), 4.37 (1 H, dd, *J* 11.9 and 4.0), 4.45 (1 H, d, *J* 11.6), 4.50 (1 H, d, *J* 11.6), 5.25–5.29 (1 H, m), 5.39–5.42 (2 H, m), 5.53 (1 H, d, *J* 11.3), 5.70–5.71 (1 H, m), 6.06 (1 H, dt, *J* 15.0 and 7.0), 6.54 (1 H, t, *J* 11.3), 6.86 (2 H, d, *J* 8.5), 7.23 (2 H, d, *J* 8.5) and 7.32 (1 H, dd, *J* 15.0 and 12.5); δ_C 17.8, 20.1, 27.3, 28.55, 28.6, 29.2, 32.3, 32.8, 55.05, 62.4, 67.9, 69.2, 72.8, 113.65, 114.8, 115.7, 124.6, 126.9, 129.1, 129.8, 131.3, 145.7, 145.9, 157.45, 159.1, 165.5 and 165.9; *m/z* 484 (M^+, 0.5%), 157 (52%), 121 (MPM^+, 100%), 83 (85%) and 55 (32%).

Umbraculumin A **1**.—A solution of TFA (915 mg, 8.0 mmol) in CH_2Cl_2 (5 cm^3) was added to a stirred solution of the diacylglycerol **15** (0.095 mg, 0.196 mmol) and anisole (673 mg, 6.2 mmol) in CH_2Cl_2 (13 cm^3) at *ca.* −15 °C. After the mixture had been stirred at this temperature for 5 h, the volatile components were removed under reduced pressure and the residue was purified by preparative centrifugal chromatography using light petroleum–EtOAc (4:1) as eluent to give umbraculumin A **1** (53 mg, 74%) as a colourless oil (Found: $M^+ + 1$, 365.2328. Calc. for $C_{21}H_{33}O_5$: $M^+ + 1$, 365.232 799); R_f 0.57 (light petroleum–EtOAc, 4:1); $[\alpha]_D$ −27.7 (*c* 0.7 in $CHCl_3$) [lit.,[1] $[\alpha]_D$ −24.3 (*c* 0.8 in $CHCl_3$)]; ν_{max}/cm^{-1} 3478, 1719, 1638 and 965; λ_{max}(hexane)/nm 216 (ε 15 940) and 261 (ε 24 261); δ_H 1.29–1.38 (4 H, m), 1.39–1.47 (2 H, m), 1.64 (3 H, m), 1.91 (3 H, d, *J* 1.2), 1.97 (2 H, m), 2.18 (3 H, d, *J* 1.2), 2.21 (2 H, m), 2.34 (1 H, t, *J* 6.4, exch.), 3.76 (2 H, t, *J* 5.5), 4.35 (2 H, d, *J* 5.3), 5.12 (1 H, appt. quint., *J* 5.2), 5.39–5.42 (2 H, m), 5.58 (1 H, d, *J* 11.3), 5.73 (1 H, m), 6.10 (1 H, dt, *J* 15.3 and 7.0), 6.59 (1 H, t, *J* 11.3) and 7.32 (1 H, ddd, *J* 15.25, 11.3 and 1.2); δ_C(22.4 MHz) 17.9, 20.4, 27.5, 28.8, 28.8, 29.4, 32.5, 33.0, 61.8, 61.8, 71.7, 114.5, 115.6, 124.8, 127.0, 131.4, 146.5, 146.5, 158.4, 166.0 and 166.4.

Deprotection of **15** using DDQ in CH_2Cl_2–H_2O (20:1)[18] gave umbraculumin A **1** (26%) in addition to unchanged starting materials (16%).

(Z)-β-*Methylthiopropenoic Acid* **16***Z*.—A solution of acid **17**[24] (385 mg, 3.0 mmol) and MeI (1.28 g, 9.0 mmol) in MeOH (6.0 cm^3) was added to a cooled suspension of NaOH (*ca.* 0.5 g) in MeOH (12 cm^3). The resulting fine suspension was stirred at room temp. for 30 min and then carefully acidified with dilute HCl and extracted with EtOAc. The organic phase was washed with water and brine, dried ($MgSO_4$) and evaporated under reduced pressure to give a solid. Recrystallization from toluene afforded the *title compound* **16***Z* (226 mg, 63%) as colourless needles, m.p. 123.0–123.9 °C (lit.,[27] 119–120 °C) with spectral data in accord with literature[27] values (vinylic *J* 9.6).

(E)-β-*Methylthiopropenoic Acid* **16***E*.—(*a*) *From thiocyanate* **17**. A suspension of thiocyanate **17**[24] (383 mg, 3.0 mmol) in MeOH (6 cm^3) and water (4 cm^3) containing LiOH (0.24 g) was stirred at room temp. under N_2 for 8 d. Then the reaction mixture was cooled to 0 °C and MeI (1.28 g, 9.0 mmol) was added. After being stirred at room temp. for 15 min the reaction mixture was cooled again to 0 °C and carefully neutralized with dilute HCl and worked up as described above to give the thiomethylpropenoic acid **16** as a mixture of *E*- and *Z*-isomers in a ratio of 5.5:1 (^1H NMR spectroscopy) (219 mg, 62%) as a crystalline solid. A mixture (*ca.* 5.5:1) of compounds **16***E* and **16***Z* (680 mg, 5.76 mmol) was heated under reflux in xylene[23] (100 cm^3) containing a catalytic amount of toluene-4-sulphonic acid under N_2 for 4 h. The solvent was evaporated under reduced pressure. Sublimation of the solid product at 60 °C/0.7 mmHg gave (*E*)-β-thiomethylpropenoic acid **16***E* (460 mg, 68%) as a crystalline solid, m.p. 136.5–138.6 °C (lit.,[28] 137–139 °C) with spectral data in accord with literature[28] values (vinylic *J* 14.95).

(*b*) *From acidic isomerisation of compound* **16***Z*.[23] The *cis*-isomer **16***Z* (274 mg, 0.71 mmol) was isomerised using toluene-4-sulphonic acid in xylene (50 cm^3) for 9 h as described above. Sublimation gave **16***E* in only 31% yield.

Diacylglycerol **18**.—Monoacylglycerol **14** (297 mg, 0.74 mmol), (*E*)-β-thiomethylpropenoic acid **16***E* (205 mg, 1.74 mmol), DCC (352 mg, 1.71 mmol) and DMAP (89 mg, 0.73 mmol) in dichloromethane (7.5 cm^3) following the procedure used for the conversion of **14** into **15**. After 49 h, work-up and chromatography as before gave *diacylglycerol* **18** (341 mg, 92%) as a colourless oil (Found: C, 67.1; H, 7.9; S, 6.6. $C_{28}H_{38}O_6S$ requires C, 66.9; H, 7.6; S, 6.4%); R_f 0.29 (light petroleum–EtOAc, 4:1); ν_{max}/cm^{-1} 1713, 1637, 1612, 1583 and 966; δ_H 1.28–1.34 (4 H, m), 1.42 (2 H, m, appt. quint., *J* 7.0), 1.62–1.64 (3 H, m), 1.96 (2 H, br s), 2.19 (2 H, appt. q, *J* 7.0), 2.30 (3 H, s), 3.60–3.62 (2 H, m), 3.78 (3 H, s), 4.30 (1 H, dd, *J* 6.4 and 12.2), 4.38 (1 H, dd, *J* 4.0 and 12.2), 4.44 (1 H, d, *J* 11.9), 4.49 (1 H, d, *J* 11.9), 5.28–5.33 (1 H, m), 5.38–5.41 (2 H, m), 5.53 (1 H, d, *J* 11.6), 5.66 (1 H, d, *J* 14.6), 6.06 (1 H, dt, *J* 15.0 and 7.6), 6.54 (1 H, appt. t, *J* 11.6), 6.86 (2 H, d, *J* 8.8), 7.22 (2 H, d, *J* 8.8), 7.32 (1 H, dd, *J* 11.6 and 15.0) and 7.76 (1 H, d, *J* 14.9); δ_C 14.1,

17.8, 28.55, 28.6, 29.2, 32.3, 32.8, 55.0, 62.3, 67.8, 70.1, 72.8, 112.5, 113.7, 114.7, 124.6, 126.8, 129.1, 129.7, 131.3, 145.85, 146.0, 147.9, 159.2, 164.2 and 165.8; *m/z* 502 (M^+, 0.8%), 265 (25) and 175 (60).

Umbraculumin C **2**.—The diacylglycerol **18** (107 mg, 0.21 mmol) was treated with TFA (684 mg, 6.0 mmol) and anisole (645 mg, 6.0 mmol) in CH_2Cl_2 (24 cm^3) as described for the preparation of umbraculumin A **1**. After 6 h, work-up and chromatography as before gave umbraculumin C **2** (68 mg, 84%) as a colourless oil (Found: C, 62.9; H, 8.2. Calc. for $C_{20}H_{30}O_5S$: C, 62.8; H, 7.9%); R_f 0.09 (light petroleum–EtOAc, 4:1); $[\alpha]_D$ +6.3 (*c* 0.49 in $CHCl_3$) {lit.,[1] $[\alpha]_D$ +7 (*c* 0.5 in $CHCl_3$)}; ν_{max}/cm^{-1} 3471, 1713, 1637, 1583 and 966; λ_{max}(hexane)/nm 267 (ε 44 000); δ_H 1.30–1.39 (4 H, m), 1.43 (2 H, appt. quint. *J* 7.0), 1.63–1.64 (3 H, m), 1.96 (2 H, br s), 2.20 (2 H, appt. q, *J* 7.0), 2.34 (3 H, s), 2.51 (1 H, m, exch.), 3.77 (2 H, d, *J* 4.9), 4.37 (2 H, d, *J* 4.9), 5.16 (1 H, appt. quint., *J* 4.9), 5.40–5.42 (2 H, m), 5.57 (1 H, d, *J* 11.3), 5.69 (1 H, d, *J* 14.9), 6.10 (1 H, dt, *J* 15.2 and 7.6), 6.59 (1 H, t, *J* 11.3), 7.32 (1 H, dd, *J* 11.3 and 15.2) and 7.81 (1 H, d, *J* 14.9); δ_C 14.3, 17.9, 28.6, 28.7, 29.3, 32.4, 33.0, 61.5, 61.7, 72.3, 112.2, 114.3, 124.7, 126.8, 131.4, 146.6, 146.7, 148.6, 164.7 and 166.3; *m/z* 381 ($M^+ - 1$, 1.4%), 175 (74), 101 (100) and 55 (21).

Deprotection of **18** using DDQ in CH_2Cl_2–H_2O (20:1)[18] gave umbraculumin C **2** (28%) in addition to unchanged starting materials (30%).

Acknowledgements

We are grateful to the SERC for a postdoctoral research assistantship (J. M. H.) and to CNPq, Brazil for a scholarship (E. F. D. M.). We would also like to thank Dr. C. H. Frydrych (SmithKline Beecham) for helpful advice concerning the removal of MPM protecting groups.

References

1 G. Cimino, A. Crispino, A. Spinella and G. Sodano, *Tetrahedron Lett.*, 1988, **29**, 3613.
2 G. Cimino, S. De Rosa, S. De Stefano, R. Morrone and G. Sodano, *Tetrahedron*, 1985, **41**, 1093 and refs. therein.
3 B. C. Borer and R. J. K. Taylor, *J. Chem. Res. (S)*, 1990, 162.
4 M. Furber, J. M. Herbert and R. J. K. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1989, 683 and refs. therein.
5 Y. Y. Belosludtsev, B. C. Borer and R. J. K. Taylor, *Synthesis*, 1991, 320.
6 Preliminary communication on part of this work: E. F. De Medeiros, J. M. Herbert and R. J. K. Taylor, *Tetrahedron Lett.*, 1990, **31**, 5843.
7 J. C. Briggs, A. H. Haines and R. J. K. Taylor, unpublished results.
8 M. Gavagnin, A. Spinella, G. Cimino and G. Sodano, *Tetrahedron Lett.*, 1990, **31**, 6093.
9 L. Brandsma, *Preparative Acetylenic Chemistry*, 2nd ed., Elsevier, 1988, (pp. 231–234).
10 S. R. Abrams and A. C. Shaw, *Org. Synth.*, 1987, **66**, 127.
11 S. P. Schmidt and D. W. Brooks, *Tetrahedron Lett.*, 1987, **28**, 797.
12 G. L. Lange and C. Gottardo, *Synth. Commun.*, 1990, **20**, 1473.
13 W. F. Bailey and E. R. Punzalan, *J. Org. Chem.*, 1990, **55**, 5404; E. Negishi, D. R. Swanson and C. J. Rousset, *J. Org. Chem.*, 1990, **55**, 5406.
14 B. S. Bal, W. E. Childers and H. W. Childers, *Tetrahedron*, 1981, **37**, 2091; G. A. Kraus and M. J. Taschner, *J. Org. Chem.*, 1980, **45**, 1175.
15 S. J. Cockman, Cynthia A. Joll, B. C. Mortimer, T. G. Redgrave and R. V. Stick, *Aus. J. Chem.*, 1990, **43**, 2093 and refs. therein.
16 S. F. Martin and J. A. Josey, *Tetrahedron Lett.*, 1988, **29**, 3631.
17 P. W. Manley, D. P. Tuffin, N. M. Allanson, P. E. Buckle, N. Lad, S. M. F. Lai, D. O. Lunt, R. A. Porter and P. J. Wade, *J. Med. Chem.*, 1987, **30**, 1812.
18 K. Horita, T. Yoshioka, T. Tanaka, Y. Oikawa and O. Yonemitsu, *Tetrahedron*, 1986, **42**, 3021.
19 G. Hirth and W. Walther, *Helv. Chim. Acta*, 1985, **68**, 1863.
20 A. Hassner and V. Alexanian, *Tetrahedron Lett.*, 1978, 4475.
21 H. Yamada, K. Jimpo, H. Tobiki, T. Komatsu, H. Noguchi, K. Irie and T. Nakagome, *J. Antibiot.*, 1983, **36**, 522.
22 Dr. C. H. Frydrych (SmithKline Beecham, Brockham Park, Surrey RH3 7AJ), personal communication.
23 F. Ikegami, T. Sekine, S. Duangteraprecha, N. Matsushita, N. Matsuda, N. Ruangrungsi and I. Murakoshi, *Phytochemistry*, 1989, **28**, 881 and refs. therein.
24 M. Giffard and I. Léauté, *J. Chem. Res.*, 1990, 320.
25 P. P. Waanders, L. Thijs and B. Zwanenberg, *Tetrahedron Lett.*, 1987, **28**, 2409.
26 M. Jacobson, I. Keiser, D. L. Chambers, D. H. Miyashita and C. Harding, *J. Med. Chem.*, 1971, **14**, 236.
27 K. Naya, M. Hayashi, I. Takagi, S. Nakamura and M. Kobayashi, *Bull. Chem. Soc. Jap.*, 1972, **45**, 3673.
28 N. K. Hart and J. A. Lamberton, *Aus. J. Chem.*, 1966, **19**, 1259.

Paper 1/02922C
Received 17*th June* 1991
Accepted 15*th July* 1991