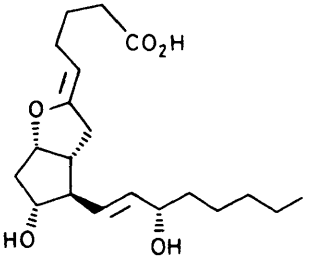
The Synthesis of Heteroaromatic Prostacyclin Analogues *via* Keto Alkyne Cyclisation

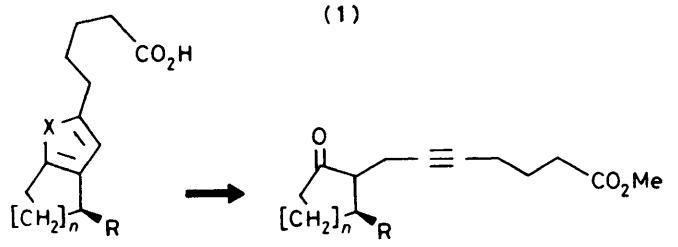
Stuart Cook, Douglas Henderson, Kevan A. Richardson, and Richard J. K. Taylor *
School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ
John Saunders
Searle Research and Development, High Wycombe, Bucks HP12 4HL
Philip G. Strange
Department of Biochemistry, The Medical School, Queen's Medical Centre, Nottingham NG7 2UH

Keto alkyne cyclisation has been used to prepare tetrahydrobenzo[*b*]furans (**4**) and (**15**) but cyclopenta[*b*]furans are not available by this procedure. Compound (**15**) has been converted into benzofuran prostacyclin analogues (**5**) and (**6**) by extremely short routes. Conditions are also described for the conversion of the same keto alkynes into tetrahydrobenzo[*b*]- and cyclopenta[*b*]-thiophenes and -pyrroles, (**7a,b**) and (**9a,b**). Syntheses of thiophene prostacyclin analogues (**8a**) and (**8b**) are also discussed.

The remarkable biological properties of prostacyclin (PGI_2) (**1**), together with its short biological half-life, prompted the search for stable, biologically active synthetic analogues.[1] A number of analogues have been prepared in which hydrolytic stability has been obtained by transformation of the labile alkylidene-tetrahydrofuran moiety into an aromatic heterocycle.[2] We set out to synthesize a range of heteroaromatic prostacyclin analogues of general structure (**2**) for biological studies.[3]



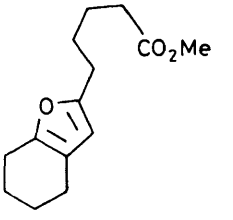
(**1**)



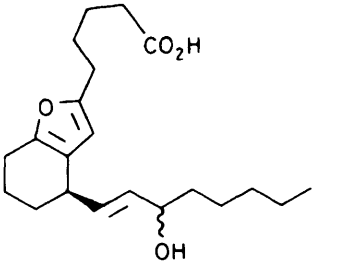
(**2**) X = O, S, NR; n = 1, 2 (**3**) R = H, alkyl

Schulte and Reisch have shown that[4–6] alk-4-ynyl ketones can be transformed into aromatic heterocycles and we decided to investigate the suitability of this procedure for the preparation of the cyclopenta[*b*]- and tetrahydrobenzo[*b*]-heterocycles (**2**) from the keto alkynes (**3**). In this paper we discuss the scope and limitations of the keto alkyne cyclisation route for the preparation of bicyclic heterocyclic systems and demonstrate the utility of the procedure by describing the successful synthesis of the furan, thiophene, and pyrrole prostacyclin analogues (**4**)—(**9**).†

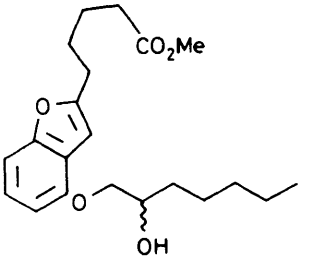
† All synthetic compounds are racemic mixtures. Compounds are named as heterocyclic derivatives rather then as prostaglandin derivatives.



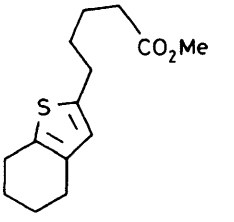
(**4a**)



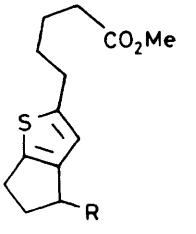
(**5**)



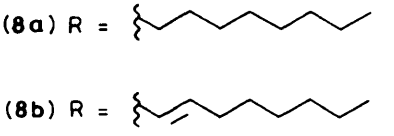
(**6**)



(**7a**)

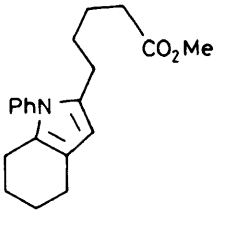


(**7b**) R = H

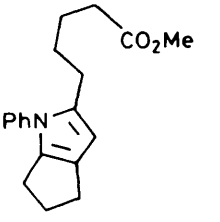


(**8a**) R =

(**8b**) R =



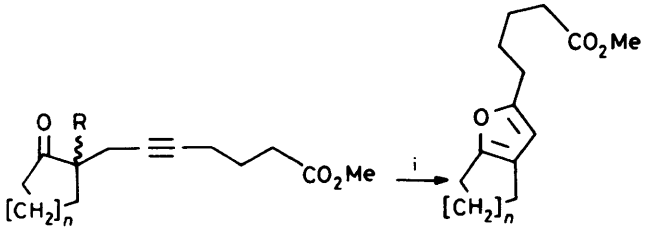
(**9a**)



(**9b**)

Bicyclic Furans.—Prior to this work the only example of a bicyclic furan being prepared by the keto alkyne cyclisation route concerned the preparation of 2-methyl-4-oxotetrahydrobenzo[*b*]furan from 2-(prop-2-ynyl)cyclohexane-1,3-dione.[4] More recent applications of this type of furan synthesis have employed 2,2-dialkylated β-keto esters, cyclisation being accompanied by decarboxyalkylation.[7]

In view of the apparent need for β-dicarbonyl substrates, the readily available[8] alkylated β-keto esters (**10**) were chosen for the *initial* studies. The ease with which the cyclisation precursors can be prepared is one of the attractions of this furan synthesis.



(**10**) R = CO_2Bu^t (**4**)

(**11**) R = H

a; *n* = 2

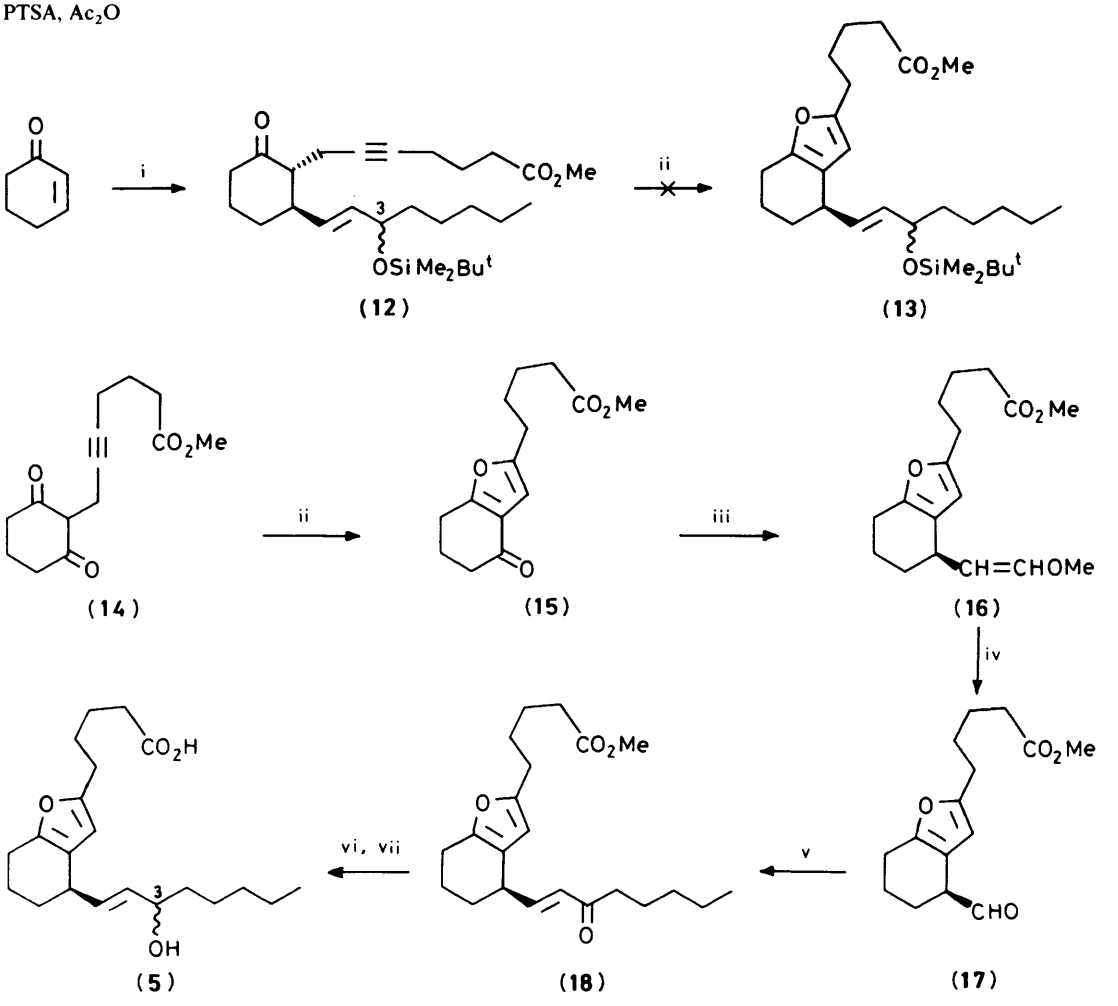
b; *n* = 1

Reagents: i, PTSA, Ac_2O

Treatment of the t-butoxycarbonylcyclohexanone (**10a**) with toluene-*p*-sulphonic acid (PTSA) and acetic anhydride (0.1 mol equiv. of each) in refluxing toluene for 2 h gave the required furan (**4a**) in 68% yield. Subsequently, we found that the same product could also be obtained from the corresponding ketone (**11a**) although the reaction was considerably slower (24 h, 45%).

Unfortunately, this methodology could not be employed for the preparation of the corresponding cyclopenta[*b*]furan (**4b**). β-Keto ester (**10b**) simply underwent decarboxyalkylation to the ketone (**11b**) when heated in toluene containing PTSA–acetic anhydride. Treatment of ketone (**11b**) under a variety of acidic conditions and also with zinc carbonate,[4] mercury(II),[9] palladium(0), palladium(II), or rhodium(I) catalysts failed to effect cyclisation. The difficulties associated with the synthesis of the cyclopenta[*b*]furan system are well recognised[10] and few successful approaches are known.[11] The recent multistep synthesis of a cyclopenta[*b*]furan prostacylin analogue by Nickolson and Vorbruggen is therefore noteworthy.[2d]

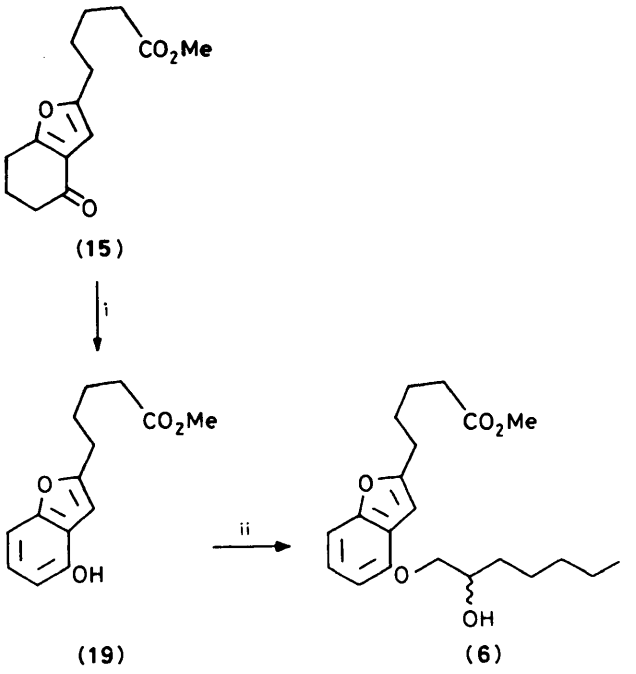
Having established that this strategy is suitable for the construction of tetrahydrobenzo[*b*]furans we turned our attention to the synthesis of the more elaborate prostacylin analogue (**5**) (Scheme 1). The first approach involved the preparation of the dialkylated cyclohexanone (**12**) from cyclohex-2-enone *via* organocuprate conjugate addition–enolate alkylation.[12] Unfortunately, the attempted cyclisation of keto alkyne (**12**) resulted in loss of the C-3 siloxy group prior to furan formation.



Scheme 1. *Reagents:* i, $C_5H_{11}CH(OSiMe_2Bu^t)CH{=}CHCu(C{\equiv}CPr)Li$ then $BrCH_2C{\equiv}C[CH_2]_3CO_2Me$; ii, PTSA, Ac_2O; iii, $Ph_3P{=}CHOMe$; iv, Me_3SiI; v, $(MeO)_2P(O)CH(Na)COC_5H_{11}$; vi, $NaBH_4$; vii, NaOH

We therefore turned to an alternative strategy: early formation of the furan and subsequent elaboration of the ω-side chain. The known[13] 2-alkylated cyclohexanedione (**14**) readily underwent cyclisation to give the 4-oxotetrahydrobenzo-[*b*]furan (**15**), the reaction being complete in 2 h and giving an 80% yield. Ketone (**15**) was converted into aldehyde (**17**) by means of (methoxymethyl)triphenylphosphorane[14,15] followed by unmasking of the resulting mixture of enol ethers (**16**). Not surprisingly, the selective hydrolysis of enol ether (**16**) proved troublesome. The use of aqueous perchloric acid and $Hg(OAc)_2$–KI[15] appeared to hydrolyse the furan in addition to the methyl enol ether moiety. It was eventually found, however, that exposure of enol ether (**17**) to trimethylsilyl iodide[16] for 15 min at −30 °C, followed by aqueous hydrolysis, gave aldehyde (**17**) in 25% yield from ketone (**15**). The use of longer reaction times or higher temperatures gave lower yields of the required aldehyde. The synthesis was completed by Wittig condensation to give enone (**18**) (81%), followed by reduction (83%) and saponification (72%). The C-3 diastereoisomers of alcohol (**5**) (and of the corresponding methyl ester) were chromatographically identical in a range of solvents although the presence of two diastereoisomers was apparent from both ^{13}C and ^{1}H n.m.r. spectroscopy. The other spectroscopic properties (see Experimental section) were typical of a trisubstituted furan.[7] This synthetic sequence is extremely short, prostacyclin analogue (**5**) being prepared from the readily available alkylated dione (**14**) in only six steps.

The cyclohexanedione (**14**) was also employed in preparing the benzofuran prostacyclin analogue (**6**). Dehydrogenation of keto furan (**15**), using either sulphur[17] or palladised charcoal,[18] gave the phenol (**19**) after re-esterification, albeit in low yield. Treatment[2f] of the phenoxide, prepared from the phenol (**19**), with 1,2-epoxyheptane gave prostacyclin analogue (**6**) (Scheme 2). This procedure was not optimised and is inefficient. It does,

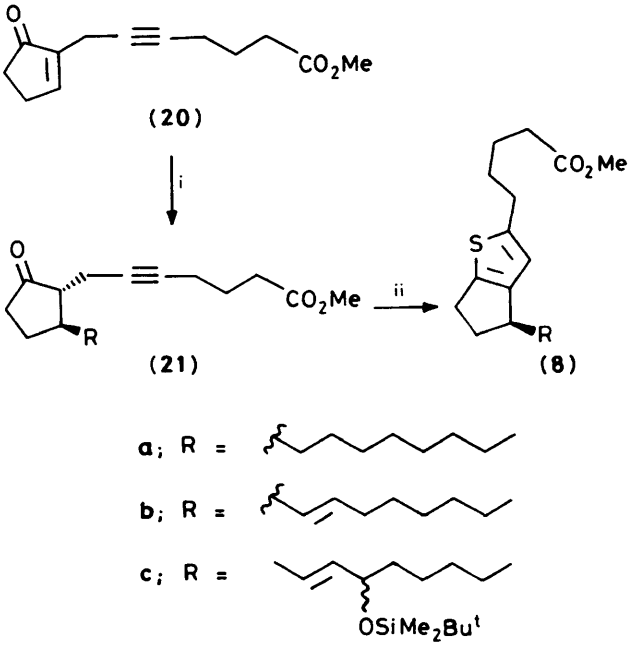


Scheme 2. *Reagents:* i, S or Pd–C; ii, 1,2-epoxyheptane

however, illustrate the ease with which a variety of new furan-based prostacyclin analogues can be prepared using the keto alkyne cyclisation procedure.

Bicyclic Thiophenes.—Schulte *et al.*[5] prepared tetrahydro-2-methylbenzo[*b*]thiophene by the treatment of 2-(prop-2-ynyl)cyclohexanone with H_2S–HCl. The corresponding cyclopenta[*b*]thiophene, though known, was prepared from the pyrrolidine iminium salt derived from 2-(prop-2-ynyl)cyclopentanone.[5] We have shown that both tetrahydrobenzo-*and* cyclopenta-[*b*]thiophenes (**7a**) and (**7b**) can be obtained from the keto alkynes (**11a**) and (**11b**), respectively. Using Schulte's conditions[5] the cyclisation reactions proceeded efficiently but took 72 h at −25 °C and, in the case of the cyclopenta analogue (**7b**), an additional period at higher temperature. When mercury(II) trifluoroacetate was added to the reaction mixture, however, a 66% yield of cyclopenta[*b*]thiophene (**7b**) was obtained after 4 h at room temperature. To our knowledge this is the first time a cyclopenta[*b*]thiophene has been prepared directly by keto alkyne cyclisation.

This cyclisation procedure was next applied to the synthesis of the more elaborate prostacyclin analogues (**8**) which also contain an ω-side chain (Scheme 3). Organocuprate con-



Scheme 3. *Reagents:* i, 'RCu'; ii, H_2S

jugate addition to the known[13,19] cyclopentenone (**20**) was employed to prepare cyclisation precursors (**21**). Treatment of compounds (**21a**) and (**21b**) with H_2S–HCl–$Hg(OCOCF_3)_2$ produced the expected bicyclic thiophene prostacyclin analogues (**8a**) and (**8b**) in 76 and 61% yield respectively. Unfortunately, all attempts to prepare the 15-hydroxylated analogue (**8c**) from the protected allylic alcohol (**21c**) resulted in elimination of the siloxy group. A similar reaction using the acetoxy compound corresponding to (**21c**) was also unsuccessful despite the fact that non-allylic secondary acetates are stable under these conditions.[7]

Pyrrole Analogues.—Reisch has prepared[6] a range of pyrroles by the treatment of keto alkynes with ammonia or primary amines but drastic conditions (acid, high temperature, high pressure) were often required. We have devised relatively mild conditions for this procedure, which are applicable to the synthesis of bicyclic pyrroles. Attention was focussed on the preparation of *N*-phenyl compounds in view of the proven[2c] biological activity of *N*-phenylpyrrole prostacyclin analogues.

Treatment of keto alkynes (**11a**) and (**11b**) with aniline, pyridinium chloride, and mercury(II) trifluoroacetate in refluxing chloroform for *ca.* 5 h gave the tetrahydroindole (**9a**) and cyclopenta[*b*]pyrrole (**9b**) in 55 and 23% yield respectively. No reaction was observed under these conditions in the absence of the mercuric salt catalyst. Although the yields were low the reaction conditions were not optimised.

In summary, we have demonstrated that the keto alkyne cyclisation procedure provides a convenient route to bicyclic furans, thiophenes, and pyrroles. We have also shown that this methodology can be employed for extremely short syntheses of heteroaromatic prostacyclin analogues. The biological screening of the prostacyclin analogues (**4a**) and (**5**)—(**9**) is in progress.

Experimental

^{1}H N.m.r. spectra were recorded on a JEOL PMX-60 spectrometer, and ^{13}C n.m.r. spectra on a JEOL FX-100 spectrometer for $CDCl_3$ solutions unless otherwise stated. Only characteristic ^{13}C absorptions are listed but in all cases the spectra were entirely consistent with the assigned structure. $SiMe_4$ was used as internal standard. I.r. spectra were obtained on a Perkin-Elmer 297 spectrophotometer, and u.v. spectra on a Pye-Unicam SP 800A spectrophotometer with ethanol as solvent. Mass spectra were recorded on a Kratos MS 25 or a VG Analytical ZAB-IF instrument. A normal work-up procedure consisted of three extractions with the specified solvent, washing of the combined extracts where specified, drying ($MgSO_4$), and removal of the solvent on a rotary evaporator under reduced pressure. Light petroleum is the fraction b.p. 40—60 °C. Ether refers to diethyl ether and DME to 1,2-dimethoxyethane. Ether and hexamethylphosphorous triamide were distilled from CaH_2 prior to use, and DME from sodium. Commercial bromo-octane (Aldrich), copper(I) bromide–dimethyl sulphide complex (Fluka), mercury(II) trifluoroacetate (Aldrich), (methoxymethyl)triphenylphosphonium chloride (Aldrich), dimethyl 2-oxoheptylphosphonate (Aldrich), and PTSA monohydrate (Aldrich) were used as received. Methyl 7-(2-oxo-1-t-butoxycarbonylcyclohexyl)hept-5-ynoate (**10a**),[8] methyl 7-(2-oxocyclohexyl)hept-5-ynoate (**11a**),[8] and the corresponding cyclopentyl homologues (**10b**)[8] and (**11b**),[8] methyl 7-(2,6-dioxocyclohexyl)hept-5-ynoate (**14**),[13] methyl 7-(5-oxocyclopent-1-enyl)hept-5-ynoate (**20**),[13,19] copper(I) pent-1-yn-1-ide,[20] (*E*)-oct-1-enyl iodide,[21] and (*E*)-3-dimethyl-t-butylsiloxy)oct-1-enyl iodide[22] were prepared according to literature procedures. Chromatography refers to column chromatography on silica gel 60 (Merck 7734); preparative centrifugal chromatography was carried out on a Chromatotron Model 7924T with silica gel 60 (Merck 7749).

Standard Procedure for the Preparation of Bicyclic Furans.—A solution of the keto alkyne in toluene containing some anti-bumping granules was heated in the dark, to reflux, then a fresh sample of PTSA monohydrate (*ca.* 0.1 mol equiv.) and acetic anhydride (*ca.* 0.1 mol equiv.) were added. When t.l.c. analysis indicated the total consumption of starting material, the reaction mixture was cooled and given a normal ether work-up which included a wash with saturated aqueous sodium hydrogen carbonate. The crude product was then purified by chromatography in the dark.

Methyl 5-(4,5,6,7-*Tetrahydrobenzo*[b]*furan*-2-*yl*)*pentanoate* (**4a**).—(a) *From methyl* 7-(2-*oxo*-1-*t*-*butoxycarbonylcyclohexyl*)*hept*-5-*ynoate* (**10a**).[8] The standard procedure was followed using β-keto ester (**10a**) (0.25 g, 0.74 mmol), PTSA (0.013 g, 0.07 mmol), and acetic anhydride (0.008 g, 0.08 mmol) in toluene (10 ml). After 2 h, preparative centrifugal chromatography with light petroleum–ether (4:1) as eluant gave the *furan* (**4a**) as an oil (0.12 g, 68%), R_F 0.7 (light petroleum–ether, 1:1); $\nu_{max.}$ (film) 1 740 and 1 570 cm^{-1}; δ_H 5.72 (1 H, s), 3.64 (3 H, s), and 2.80—1.40 (16 H, m); δ_C 173.95 (s), 153.23 (s), 148.77 (s), 117.07 (s), and 105.74 (d) (Found: C, 71.4; H, 8.6. $C_{14}H_{20}O_3$ requires C, 71.15; H, 8.53%).

(b) *From methyl* 7-(2-*oxocyclohexyl*)*hept*-5-*ynoate* (**11a**).[8] The standard procedure was followed with ketone (**12a**) (0.50 g, 2.12 mmol), PTSA (0.04 g, 0.21 mmol), and acetic anhydride (0.02 g, 0.20 mmol) in toluene (12 ml). After 24 h, preparative centrifugal chromatography gave the furan (**4a**) as an oil (0.227 g, 45%), identical with the above sample.

Preparation and Attempted Cyclisation of Methyl 7-{2-[(*E*)-3-(*Dimethyl*-*t*-*butylsiloxy*)*oct*-1-*enyl*]-6-*oxocyclohexyl*}*hept*-5-*ynoate* (**12**).—n-Butyl-lithium in hexane (1.53 ml, 2.6 mmol) was added to a stirred solution of (*E*)-3-(dimethyl-t-butylsiloxy)-1-iodo-oct-1-ene (0.885 g, 2.4 mmol) in dry ether (1 ml) under nitrogen −78 °C. The mixture was stirred for 1.7 h and then a freshly prepared solution of pent-1-ynylcopper (0.314 g, 2.4 mmol) in dry ether (4 ml) containing hexamethylphosphorous triamide (0.87 ml, 4.8 mmol) was added dropwise during 15 min, and the mixture stirred for a further 1.25 h at −78 °C. A solution of cyclohex-2-enone (0.19 g, 2.0 mmol) in dry ether (8 ml) was then added slowly during 35 min and the mixture was stirred for 2 h at −78 °C. Dry liquid ammonia (20 ml) was then added and after the mixture had been stirred for 30 min at −78 °C a solution of methyl 7-iodohept-5-ynoate (1.6 g, 6.8 mmol) in dry ether (6 ml) was added. The reaction mixture was left to warm to ambient temperature (2 h) and then quenched with ice–water (50 ml). A normal ether work-up followed by filtration through alumina (light petroleum–ether, 5:1) and preparative centrifugal chromatography (light petroleum–ether, 97:3 ⟶ 80:20) gave unalkylated material (117 mg) followed by the trans-2,3-*disubstituted ketone* (**12**) (258 mg, 27%) $\nu_{max.}$ 2 936, 1 735, 1 716, 1 598, 1 439, 1 254, and 1 074 cm^{-1}; *m*/*z* 476 (M^+), 445 (M^+ − OMe), and 419 (M^+ − Bu^t) [Found: *m*/*z* 419.2617 (M^+ − Bu^t). $C_{24}H_{39}O_4Si$ requires *m*/*z*, 419.2647]. Further elution gave the corresponding 2,3-*cis*-isomer (165 mg, 17%) which was fully characterised. Both ketone (**12**) and the corresponding 2,3-*cis*-isomer gave consistent ^{1}H and ^{13}C n.m.r. spectra.

All attempts to effect the cyclisation of keto alkyne (**12**) into bicyclic furan (**13**) using the standard procedure failed due to the ready loss of the siloxy protecting group under the reaction conditions.

Methyl 5-(4,5,6,7-*Tetrahydro*-4-*oxobenzo*[b]*furan*-2-*yl*)-*pentanoate* (**15**).—The standard procedure for the preparation of furans was followed using compound (**14**),[13,19] (2.0 g, 8.00 mmol), PTSA (0.13 g, 0.70 mmol), and acetic anhydride (0.08 g, 0.80 mmol) in toluene (100 ml). After 2 h, chromatography with light petroleum–ether (4:1) as eluant gave the *title furan* (**15**) as a pale yellow oil (1.61 g, 80%), R_F 0.8 (ether); $\nu_{max.}$(film) 1 735, 1 675, and 1 580 cm^{-1}; $\lambda_{max.}$(EtOH) 217 (ε 9 750) and 271 nm (4 750); δ 6.20 (1 H, s), 3.62 (3 H, s), and 3.00—1.50 (14 H, m) (Found: C, 66.9; H, 7.5. $C_{14}H_{18}O_4$ requires C, 67.18; H, 7.25%).

Methyl 5-(4-*Formyl*-4,5,6,7-*tetrahydrobenzo*[b]*furan*-2-*yl*)-*pentanoate* (**17**).—A suspension of (methoxymethyl)triphenylphosphonium chloride (6.84 g, 0.02 mmol) in dry tetrahydrofuran (THF) (100 ml) under nitrogen was cooled to 0 °C and treated with butyl-lithium in hexane (12 ml of a 1.6M solution, 0.019 mmol). The addition of the butyl-lithium produced a dark red colouration. After the mixture had been stirred at 0 °C for 30 min, a solution of compound (**15**) (2.50 g, 0.01 mmol) in dry THF (5 ml) was added. The reaction mixture was allowed to warm to room temperature and was then stirred until t.l.c.

indicated the total consumption of substrate (**15**) (*ca.* 1 h), then saturated aqueous ammonium chloride (150 ml) was added. A normal ether work-up, which included washes with saturated aqueous sodium hydrogen carbonate and brine, gave a crude mixture of the (*E*)- and (*Z*)-isomers of enol ether (**16**) as an oil (2.5 g), which was used directly in the next reaction.

Sodium iodide (1.10 g, 7.33 mmol) was added to a stirred solution of the crude enol ether (**16**) (2.5 g) in dry acetonitrile (100 ml) under nitrogen at −30 °C. Trimethylsilyl chloride (0.78 g, 7.20 mmol) was then added in one portion. The mixture was kept at −30 °C until t.l.c. analysis, taken at 3 min intervals, showed the completion of the reaction (*ca.* 15 min). After the addition of water (100 ml) and a normal ether work-up, which included two washes with saturated aqueous sodium thiosulphate (200 ml), chromatography with light petroleum–ether (10:1) as eluant gave recovered starting material (**16**) (0.25 g) together with aldehyde (**17**) [0.67 g, 25% from furan (**15**)] as an oil, R_F 0.3 (light petroleum–ether, 4:1); $\nu_{max.}$(film) 2 710, 1 735, 1 725, and 1 570 cm^{-1}; δ_H 9.64 (1 H, d, *J* 2.5 Hz), 5.92 (1 H, br s), 3.62 (3 H, s), 3.36 (1 H, m), and 2.84—1.48 (14 H, m); *m/z* 264 (M^+) and 235 (M^+ − CHO).

Methyl 5-{4,5,6,7-*Tetrahydro*-4-[(*E*)-3-*oxo*-*oct*-1-*enyl*]*benzo*[b]*furan*-2-*yl*}*pentanoate* (**18**).—A solution of dimethyl 2-oxoheptylphosphonate (0.70 g, 3.15 mmol) in dry DME (5 ml) was added to a stirred suspension of sodium hydride (50% in mineral oil; 0.15 g, 3.13 mmol) in dry DME (50 ml) under nitrogen at room temperature. The evolution of hydrogen ceased after 30 min, and a solution of compound (**17**) (0.5 g, 1.89 mmol) in dry DME (5 ml) was then added. When t.l.c. indicated the complete consumption of aldehyde (**17**) (*ca.* 15 min), the reaction was quenched with water (50 ml). After a normal ether work-up, which included a wash with brine, chromatography with light petroleum–ether (10:1) as eluant gave *enone* (**18**) as an oil (0.55 g, 81%), R_F 0.5 (light petroleum–ether, 4:1); $\nu_{max.}$(film) 1 735, 1 670, 1 625, and 1 570 cm^{-1}; δ_H 6.69 (1 H, dd, *J* 17 and 8.5 Hz), 6.10 (1 H, dd, *J* 17 and 1 Hz), 5.78 (1 H, s), 3.64 (3 H, s), 3.39 (1 H, m), 2.58 (6 H, m), 2.34 (2 H, m), 2.14—1.48 (10 H, m), 1.48—1.10 (4 H, m), and 0.88 (3 H, s); *m/z* 360 (M^+) (Found: C, 73.0; H, 9.2. $C_{22}H_{32}O_4$ requires C, 73.30; H, 8.95%).

5-{4,5,6,7-*Tetrahydro*-4-[(*E*)-3-*hydroxyoct*-1-*enyl*]*benzo*[b]*furan*-2-*yl*}*pentanoic Acid.* (**5**).—A stirred solution of the keto ester (**18**) (0.55 g, 1.53 mmol) in methanol (50 ml) was treated with sodium borohydride (0.12 g, 3.17 mmol), added in 4 portions. When t.l.c. indicated that the reaction was complete (*ca.* 15 min), the methanol was removed under reduced pressure and water (50 ml) was added to the residue. After a normal ether extraction, chromatography with light petroleum–ether (4:1) as eluant gave the hydroxy ester as a fully characterised oil (0.46 g, 83%). This ester (0.10 g, 0.276 mmol) was dissolved in methanol–water (4:1; 25 ml) containing potassium hydroxide (0.02 g, 0.36 mmol) and the mixture was stirred at room temperature until all starting material had been consumed (*ca.* 10 h). The methanol was then removed under reduced pressure and the residue was partitioned between ether and water. The aqueous layer was acidified to pH 3 with dil. hydrochloric acid and was then given a normal ether work-up, including a brine wash, to produce pink crystals (0.070 g, 72%). Several recrystallisations from ether–light petroleum gave the *title acid* (**5**) as a diastereoisomeric mixture (0.057 g, 59%) as white crystals, m.p. 80—82 °C. The diastereoisomers were chromatographically identical in a range of solvents, R_F 0.8 (ether), 0.5 (ether–CH_2Cl_2, 1:1); $\nu_{max.}$ 1 710 and 1 570 cm^{-1}; $\lambda_{max.}$(EtOH) 229 nm (10 580); δ_H 6.32 (2 H, br s, exchangeable), 5.84 and 5.80 (1 H, 2 × s), 6.72—5.52 (2 H, m), 4.40—4.00 (1 H, m), 3.40—3.30 (1 H, m), 2.29—1.16 (22 H, m), and 0.96 (3 H, s); δ_C 178.83, 153.35, 148.77, 135.03, 132.80, 119.37, 105.33, 73.21, and 73.04 (diastereoisomeric doubling) (Found: M^+, 348.2295. $C_{21}H_{32}O_4$ requires *M*, 348.2300).

Methyl 5-(4-*Hydroxybenzo*[b]*furan*-2-*yl*)*pentanoate* (**19**).—(*a*) A mixture of the keto ester (**15**) (0.50 g, 2.00 mmol) and flowers of sulphur (0.10 g, 3.13 mmol) were heated in a Wood's metal-bath between 240 and 260 °C for 1 h. The residue was then distilled (Kugelrohr; 200—250 °C, 0.01 mmHg) to give a yellow oil. The oil was partitioned between ice-cold aqueous sodium hydroxide (1M; 50 ml) and ether (50 ml). The aqueous phase was acidified to pH 3 with dil. hydrochloric acid and was then given a normal ether work-up. This gave a yellow acidic gum (0.60 g), which was re-esterified by treatment with acetyl chloride (1 ml) in methanol (20 ml) for 15 min at room temperature. Neutralisation with sodium hydrogen carbonate and a normal ether work-up gave the *title benzofuran* (**19**) (0.04 g, 8%) as white crystals, m.p. 105—110 °C; R_F 0.5 (light petroleum–ether, 1:2); $\nu_{max.}$($CHBr_3$) 3 300, 1 610, 1 715, and 1 595 cm^{-1}; $\lambda_{max.}$(EtOH) 220 (10 560), 246 (6 340), 256 (6 340), and 272 nm (1 690); δ_H 7.60—6.40 (4 H, m), 5.88 (1 H, br s, exchangeable), 3.68 (3 H, s), and 3.12—1.60 (8 H, m) (Found: M^+, 248.1047. $C_{14}H_{16}O_4$ requires *M*, 248.1048).

(*b*) A mixture of ketone (**15**) (0.90 g, 3.60 mmol) and palladium–charcoal (10%; 0.1 g) was refluxed in decalin for 16 h. Light petroleum (50 ml) was then added and the catalyst was removed by filtration through Celite. The solvent was removed under reduced pressure and the residue was extracted into aqueous NaOH; the extract was acidified and esterified as in (*a*). Chromatography (light petroleum–ether, 1:1) gave the benzofuran (**19**) (0.10 g, 11%), identical with that obtained from procedure (*a*).

Methyl 5-{4-(2-*Hydroxyheptyloxy*)*benzo*[b]*furan*-2-*yl*}*pentanoate* (**6**).—Sodium metal (0.003 g, 0.13 mmol) was added to a solution of compound (**19**) (0.020 g, 0.081 mmol) in methanol (15 ml). After the sodium has dissolved, 1,2-epoxyheptane (0.010 g, 0.088 mmol) was added and the mixture was refluxed for 48 h. T.l.c. (light petroleum–ether, 1:1 containing 5% triethylamine) indicated the presence of both product (**6**) and starting material (**19**), but 1,2-epoxyheptane had been completely consumed. Therefore, more sodium (0.004 g, 0.17 mmol) and 1,2-epoxyheptane (0.022 g, 0.19 mmol) were added and the reaction mixture was refluxed for a further 48 h. Dil. hydrochloric acid (25 ml) was then added. After a normal ether work-up which included a wash with brine (50 ml), chromatography with light petroleum–ether (1:1) containing 5% triethylamine as eluant gave unchanged starting material (**19**) (0.008 g, 40%) in addition to the *title benzofuran* (**6**) as a pale yellow oil (0.007 g, 24%), R_F 0.4 (light petroleum–ether, 1:1); $\nu_{max.}$(film) 3 480, 1 735, 1 605, and 1 590 cm^{-1}; $\lambda_{max.}$(EtOH) 232 (14 620), 250 (8 090), 258 (8 880), and 277 nm (5 400); δ_H (CCl_4–10% C_6D_6) (Bruker CXP 200) 7.05—6.52 (3 H, m), 6.46 (1 H, s), 4.02—3.87 (3 H, m), 3.62 (3 H, s), 2.77 (2 H, t, *J* 6 Hz), 2.30 (2 H, t, *J* 6 Hz), 2.10—1.10 (13 H, m), and 0.97 (3 H, t, *J* 6 Hz) (Found: M^+, 362.2084. $C_{21}H_{30}O_5$ requires *M*, 362.2093).

Conjugate Additions to Methyl 7-(5-*Oxocyclopent*-1-*enyl*)-*hept*-5-*ynoate* (**20**): *Preparation of Keto Alkynes* (**21a—c**).—(*a*) Bromo-octane (1.31 g, 6.78 mmol) and a crystal of iodine were added to magnesium turnings (0.17 g, 6.99 g atom) in dry ether (10 ml) at room temperature under nitrogen. The mixture was stirred for 20 min, then cooled to 0 °C; copper(I) bromide–dimethyl sulphide complex (0.68 g, 3.31 mmol) was added and the mixture was stirred for a further 20 min. A solution of enone (**20**)[13,19] (0.675 g, 3.07 mmol) in dry ether (5 ml) was then added, a yellow precipitate resulting, and the reaction mixture was stirred at 0 °C for 30 min. Ether (10 ml) was added and the

mixture was given a normal ether work-up incorporating washes with dil. hydrochloric acid (3 × 20 ml), saturated aqueous sodium hydrogen carbonate (20 ml), and water (2 × 20 ml). The residue was chromatographed (light petroleum–ether, 25:1) to give *methyl* 7-(2-*octyl*-5-*oxocyclopentyl*)*hept*-5-*ynoate* (**21a**) as an oil (0.58 g, 56%), R_F 0.9 (light petroleum–ether, 2:1); $\nu_{max.}$(film) 2 960, 2 920, 2 850, and 1 740 cm^{-1}; δ_H 3.66 (3 H, s) and 2.96—0.90 (31 H, m); *m/z* 334 (M^+) (Found: M^+, 334.2501. $C_{21}H_{34}O_3$ requires *M*, 334.2508).

(*b*) Butyl-lithium (0.84 ml, 1.30 mmol) was added to a solution of (*E*)-oct-1-enyl iodide[21] (0.343 g, 1.44 mmol) in dry ether (5 ml) at −78 °C under nitrogen and the mixture was stirred for 1 h. A freshly prepared homogeneous solution of copper pent-1-yn-1-ide[20] (0.166 g, 1.27 mol) in a mixture of hexamethylphosphorous triamide (0.5 ml) and ether (2 ml) was then added and the reaction mixture was stirred for a further 1 h at −78 °C. A solution of enone (**20**)[13,19] (0.250 g, 1.14 mmol) in ether (3 ml) was then added; the mixture was allowed to warm to −25 °C and was held at this temperature for 2 h. An ether work-up as in (*a*), followed by chromatography (light petroleum–ether, 95:5), gave *methyl* 7-{2-[(*E*)-*oct*-1-*enyl*]-5-*oxocyclopentyl*}*hept*-5-*ynoate* (**21b**) as an oil (0.09 g, 24%), R_F 0.8 (light petroleum–ether, 4:1); $\nu_{max.}$(film) 2 960, 2 920, 2 860, and 1 735 cm^{-1}; δ_H 5.40 (2 H, m), 3.62 (3 H, s), and 2.28—0.80 (27 H, m); *m/z* 332 (M^+) and 301 (M^+ − OMe) [Found: *m/z* 301.2167 (M^+ − OMe). $C_{20}H_{29}O_2$ requires *m/z*, 301.2167].

(*c*) The procedure outlined in (*b*) was followed using (*E*)-3-(dimethyl-t-butylsiloxy)oct-1-enyl iodide[22] (2.87 g, 7.80 mmol), butyl-lithium (4.8 ml, 7.40 mmol), copper(I) pent-1-yn-1-ide (1.02 g, 7.68 mmol), hexamethylphosphorous triamide (2.8 ml), and enone (**20**)[13,19] (1.48 g, 6.73 mmol). Chromatography (light petroleum–ether, 10:1) gave *methyl* 7-{2-[(*E*)-3-(*dimethyl-t-butylsiloxy*)*oct*-1-*enyl*]-5-*oxocyclopentyl*}*hept*-5-*ynoate* (**21c**) (2.0 g, 64%) as an oil, R_F 0.6 (light petroleum–ether, 3:1); $\nu_{max.}$(film) 2 960, 2 940, 2 860, and 1 745 cm^{-1}; δ_H 5.50 (2 H, m), 4.04 (1 H, m), 3.60 (3 H, s), 2.84—1.10 (25 H, m), 0.84 (9 H, s), and 0.00 (6 H, s) (Found: C, 70.4; H, 10.3. $C_{27}H_{46}O_4Si$ requires C, 70.08; H, 10.02%).

Standard Procedure for the Preparation of Bicyclic Thiophenes.—Hydrogen chloride gas and hydrogen sulphide gas were each bubbled into separate portions of methanol (30 ml) at the specified temperature for 30 min. These methanolic solutions (or portions of them, where specified) were then mixed and a solution of the appropriate keto alkyne in methanol (2 ml) was added. The reaction mixture was kept at the specified temperature until completion of the reaction (t.l.c.). The reaction mixture was then neutralised with saturated aqueous sodium hydrogen carbonate, and, after a normal ether work-up, chromatography with light petroleum–ether (10:1) as eluant gave the required thiophene.

Methyl 5-(4,5,6,7-*Tetrahydrobenzo*[b]*thiophen*-2-*yl*)*pentanoate* (**7a**).—The standard procedure for thiophene preparation was followed for methyl 7-(2-oxocyclohexyl)hept-5-ynoate (**11a**) (0.20 g, 0.85 mmol) at −25 °C. After 72 h, chromatography gave the *thiophene* (**7a**) as a pale yellow oil (0.17 g, 80%), R_F 0.7 (light petroleum–ether, 3:1); $\nu_{max.}$(film) 1 735 and 1 440 cm^{-1}; $\lambda_{max.}$ 240 nm (5 500); δ_H 6.38 (1 H, s), 3.62 (3 H, s), and 3.00—1.40 (16 H, m); δ_C 173.84, 141.02, 134.74, 132.98, 124.76, and 51.37 (Found: C, 66.9; H, 8.3; S, 12.7. $C_{14}H_{20}O_2S$ requires C, 66.63; H, 7.99; S, 12.68%).

Methyl 5-(5,6-*Dihydro*-4H-*cyclopenta*[b]*thiophen*-2-*yl*)*pentanoate* (**7b**).—(*a*) The standard procedure for thiophene preparation was followed for methyl 7-(2-oxocyclopentyl)-hept-5-ynoate (**11b**) (0.40 g, 1.80 mmol) at −25 °C. After 72 h at −25 °C the reaction mixture was refluxed for 30 min to complete cyclisation. Chromatography, followed by recrystallisation from ether–light petroleum, gave the *thiophene* (**7b**) as white crystals (0.32 g, 75%), m.p. 33—35 °C; R_F 0.7 (light petroleum–ether, 3:1); $\nu_{max.}$(film) 1 735 and 1 435 cm^{-1}; $\lambda_{max.}$ 232 (4 870) and 253 nm (4 460); δ_H 6.40 (1 H, s), 3.60 (3 H, s), and 3.00—1.40 (14 H, m); δ_C 173.84, 147.77, 145.61, 139.22, 119.47, and 51.43 (Found: M^+, 238.1030. $C_{13}H_{18}O_2S$ requires *M*, 238.1027).

(*b*) The standard procedure for thiophene preparation was followed again for compound (**11b**) (0.05 g, 0.23 mmol), but mercury(II) trifluoroacetate (0.02 g, 0.05 mmol) was also added. After 4 h at room temperature, chromatography gave the thiophene (**7b**) as white crystals (0.035 g, 66%).

Methyl 5-(5,6-*Dihydro*-4-*octyl*-4H-*cyclopenta*[b]*thiophen*-2-*yl*)*pentanoate* (**8a**).—The standard procedure for thiophene formation was followed for the cyclopentanone (**21a**) (0.103 g, 0.31 mmol) and saturated solutions of H_2S and HCl (3 ml each). The reaction mixture was stirred at room temperature for 1 h, mercury(II) trifluoroacetate (0.05 g, 0.12 mmol) was added, and the mixture was stirred at room temperature overnight with the exclusion of light. A standard ether work-up followed by chromatography (light petroleum–ether, 99:1) gave the *title thiophene* (**8a**) (0.082 g, 76%) as a yellow syrup, R_F 0.9 (light petroleum–ether, 3:1) $\nu_{max.}$(film) 3 060, 2 950, 2 920, 2 855, and 1 740 cm^{-1}; $\lambda_{max.}$ 225 (4 260) and 250 nm (3 610); δ_H 6.46 (1 H, s), 3.62 (3 H, s), and 3.00—0.75 (30 H, m); *m/z* 350 (M^+) (Found: C, 72.0; H, 10.0. $C_{21}H_{34}O_2S$ requires C, 72.00; H, 9.78%).

Methyl 5-{5,6-*Dihydro*-4-[(E)-*oct*-1-*enyl*]-4H-*cyclopenta*[b]*thiophen*-2-*yl*}*pentanoate* (**8b**).—The standard procedure for thiophene formation was followed for the cyclopentanone (**21b**) (0.055 g, 0.17 mmol) and saturated solutions of H_2S and HCl (3 ml each). The reaction mixture was stirred at room temperature for 1 h, mercury(II) trifluoroacetate (0.02 g, 0.05 mmol) was added, and the mixture was stirred at room temperature overnight with the exclusion of light. A standard ether work-up followed by chromatography (light petroleum–ether, 99:1) gave the *thiophene* (**8b**) (0.035 g, 61%) as a yellow syrup, R_F 0.9 (light petroleum–ether, 99:1); $\nu_{max.}$(film) 3 060, 3 020, 2 950, 2 920, 2 850, and 1 740 cm^{-1}; $\lambda_{max.}$ 230 (4 890) and 250 nm (4 190); δ_H 6.39 (1 H, s), 5.42 (2 H, m), 3.62 (3 H, s), and 3.00—0.80 (26 H m) (Found: M^+, 348.2117. $C_{21}H_{32}O_2S$ requires *M*, 348.2123).

Attempted Preparation of Methyl 5-{4-[(E)-3-(*Dimethyl-t-butylsiloxy*)*oct*-1-*enyl*]-5,6-*dihydro*-4H-*cyclopenta*[b]*thiophen*-2-*yl*}*pentanoate* (**8c**) *from Keto Alkyne* (**21c**).—(*a*) The standard procedure for thiophene preparation was followed for the cyclopentanone (**21c**) (0.09 g, 0.40 mmol). After 72 h at −25 °C and then 30 min at reflux, the ^1H n.m.r. spectrum of the crude product did not show any thiophene proton or the presence of the dimethyl-t-butylsiloxy function.

(*b*) The standard procedure for thiophene preparation was followed for the cyclopentanone (**21c**) (0.19 g, 0.86 mmol), but mercury(II) acetate (0.17 g, 0.40 mmol) was added. After 5 h at room temperature, the ^1H n.m.r. spectrum of the crude reaction mixture did not show any thiophene proton or the presence of the dimethyl-t-butylsiloxy function.

General Procedure for the Preparation of Bicyclic N-*Phenylpyrroles.*—A solution of the appropriate keto alkyne in chloroform (2 ml) was added to a mixture containing aniline, pyridinium chloride, and mercury(II) trifluoroacetate in chloroform (20 ml). The reaction mixture was refluxed until t.l.c. indicated the complete consumption of starting material (*ca.* 5 h), then was cooled, and filtered through a short column of silica gel (~5 g). Removal of the chloroform under reduced pressure followed by chromatography with light petroleum–ether (9:1) as eluant gave the required pyrrole.

Methyl 5-(4,5,6,7-*Tetrahydro*-1-*phenylindol*-2-*yl*)*pentanoate* (**9a**).—The standard procedure for the preparation of pyrroles was followed for compound (**11a**) (0.18 g, 0.76 mmol), aniline (0.40 g, 4.30 mmol), pyridinium chloride (0.10 g, 0.87 mmol), and mercury(II) trifluoroacetate (0.36, 0.85 mmol). Chromatography gave the *indole* (**9a**) as a pale yellow oil (0.13 g, 55%), R_F 0.5 (light petroleum–ether, 3:1); $\nu_{max.}$(film) 1 740, 1 600, 1 500, and 700 cm^{-1}; $\lambda_{max.}$ 220 (9 340) and 240sh nm (7 110); δ_H 7.72—7.08 (5 H, m), 5.84 (1 H, s), 3.64 (3 H, s), and 2.80—1.40 (16 H, m); δ_C 173.64, 138.67, 132.22, 128.87, 127.93, 127.22, 116.54, and 104.80 (Found: M^+, 311.1885. $C_{20}H_{25}NO_2$ requires M, 311.1885).

Methyl 5-(1,4,5,6-*Tetrahydro*-1-*phenylcyclopenta*[b]*pyrrol*-2-*yl*)*pentanoate* (**9b**).—The standard procedure for the preparation of pyrroles was followed for compound (**11b**) (0.1 g, 0.45 mmol), aniline (0.21 g, 2.26 mmol), pyridinium chloride (0.06 g, 0.52 mmol), and mercury(II) trifluoroacetate (0.21 g, 0.50 mmol). Chromatography gave *pyrrole* (**9b**) as a pale yellow oil (0.031 g, 23%), R_F 0.5 (light petroleum–ether, 3:1); $\nu_{max.}$(film) 1 740, 1 600, 1 500, and 700 cm^{-1}; $\lambda_{max.}$ 235 nm (9 160); δ_H 7.62—7.00 (5 H, m), 5.84 (1 H, s), 3.64 (3 H, s), and 3.00—1.40 (14 H, m); δ_C 173.90, 139.55, 137.85, 136.38, 129.98, 126.70, 126.23, 125.52, and 102.04 (Found: M^+, 297.1729. $C_{19}H_{23}NO_2$ requires M, 297.1729).

Acknowledgements

We thank the S.E.R.C. for studentships (Stuart Cook and Kevan Richardson) and a postdoctoral research assistantship (Douglas Henderson). We are also grateful to Searle Research and Development for financial support.

References

1 For a recent review dealing with the synthesis of prostacyclin analogues see R. F. Newton, S. M. Roberts, and R. J. K. Taylor, *Synthesis*, 1984, 449.
2 (*a*) Pyridazine: K. C. Nicolaou, W. E. Barnette, and R. L. Magolda, *J. Am. Chem. Soc.*, 1979, **101**, 766; (*b*) Pyrazole: M. Suzuki, S. Sugiura, and R. Noyori, *Tetrahedron Lett.*, 1982, **23**, 4817; (*c*) Pyrrole: H. W. Smith, M. K. Bach, A. W. Harrison, H. G. Johnson, N. J. Major, and M. A. Wasserman, *Prostaglandins*, 1982, **24**, 543; (*d*) Furan: R. C. Nickolson and H. Vorbruggen, *Tetrahedron Lett.*, 1983; **24**, 47; (*e*) Thiazole: R. H. Bradbury and K. A. M. Walker, *J. Org. Chem.*, 1983, **48**, 1741; (*f*) For benzo analogues see M. Phialas, P. G. Sammes, P. D. Kennewell, and R. Westwood, *J. Chem. Soc., Perkin Trans. 1*, 1984, 687 and references therein.
3 Preliminary communiction: K. A. Richardson, J. Saunders, and R. J. K. Taylor, *Tetrahedron Lett.*, 1985, **26**, 1171.
4 K. E. Schulte, J. Reisch, and A. Mock, *Arch. Pharm. (Weinheim, Ger.)*, 1962, **295**, 627, 645.
5 K. E. Schulte, J. Reisch, and D. Bergenthal, *Chem. Ber.*, 1968, **101**, 1540.
6 J. Reisch, *Arch. Pharm. (Weinheim, Ger.)*, 1965, **198**, 591.
7 J. Saunders, D. C. Tipney, and P. Robins, *Tetrahedron Lett.*, 1982, **23**, 4147; J. B. Bicking, J. H. Jones, W. J. Holtz, C. M. Robb, F. A. Kuehl, D. H. Minsker, and E. J. Cragoe, *J. Med. Chem.*, 1978, **21**, 1011.
8 D. Henderson, K. A. Richardson, R. J. K. Taylor, and J. Saunders, *Synthesis*, 1983, 996.
9 M. Suzuki, A. Yanagisawa, and R. Noyori, *Tetrahedron Lett.*, 1983, **24**, 1187; M. Riediker and J. Schwartz, *J. Am. Chem. Soc.*, 1982, **104**, 5842.
10 E. J. Nienhouse, R. M. Irwin, and G. R. Finni, *J. Am. Chem. Soc.*, 1967, **89**, 4557; T. Mukaiyama, H. Ishiara, and K. Inomata, *Chem. Lett.*, 1975, 527, 531.
11 Th. Morel and P. E. Verkade, *Recl. Trav. Chem. Pays-Bas*, 1951, **70**, 35; E. Wolters and H. Schaaf, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 682; I. V. Machinskaya, G. P. Smirnova, and V. A. Barkash, *Zh. Obshch, Khim.*, 1962, **32**, 1248 (*Chem. Abstr.*, 1963; **58**, 3377); K. D. Moeller and R. D. Little, *Tetrahedron Lett.*, 1985, **26**, 3417.
12 R. J. K. Taylor, *Synthesis*, 1985, 364.
13 J. Bagli and T. Bogri, *Tetrahedron Lett.*, 1972, 3815.
14 S. G. Levine, *J. Am. Chem. Soc.*, 1958, **80**, 6150.
15 K. C. Nicolaou, R. L. Magolda, and D. A. Claremon, *J. Am. Chem. Soc.*, 1980, **102**, 1404.
16 Z. Kosarych and T. Cohen, *Tetrahedron Lett.*, 1980, **21**, 3959.
17 P. Demerseman, J. P. Lechartier, C. Pene, A. Cheutin, R. Royer, and M. L. Desvoye, *Bull. Soc. Chim. Fr.*, 1965, 1473.
18 J. V. Greenhill, M. A. Moten, and R. Hanke, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1213.
19 G. Buchi and B. Egger, *J. Org. Chem.*, 1971, **36**, 2021.
20 C. E. Castro, E. J. Gaughan, and D. C. Owsley, *J. Org. Chem.*, 1966, **31**, 4071.
21 G. Zweifel and C. C. Whitney, *J. Am. Chem. Soc.*, 1967, **89**, 2753; J. W. Patterson and J. H. Fried, *J. Org. Chem.*, 1974, **39**, 2506.
22 E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, 1972, **94**, 7210.

Received 3rd *September* 1986; *Paper* 6/1777