Synthesis of Thyroid Hormone Analogues. Part 2.[1] Oxidative Coupling Approach to SK&F L-94901

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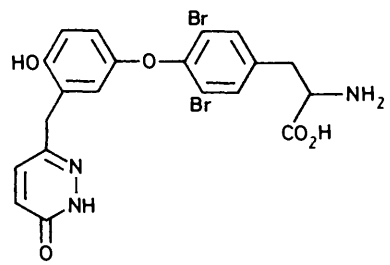
A synthesis of L-3,5-dibromo-3'-[(6-oxo-1,6-dihydropyridazin-3-yl)methyl]thyronine-SK&F L-94901 (**1**), a novel, selective and potent thyromimetic – is described. The key step in this synthesis involves the formation of a hindered diaryl ether moiety. This paper describes an approach *via* oxidative coupling of the hindered phenols (**2**) and (**3**). Some by-products and impurities generated during the synthesis are discussed briefly.

One of the major causes of mortality in the developed world is atherosclerosis. A correlation between circulating cholesterol levels and atherosclerosis has been established for many years. Recently, favourable effects on rates of heart attacks and death due to cardiac disease were demonstrated in patients treated with the hypocholesterolaemic drug cholestyramine.[2] Other hypocholesterolaemic compounds would be useful additions to the armoury of cardiovascular drugs. Naturally occurring thyroid hormones, although effective in lowering plasma cholesterol levels,[3] cannot be used as hypocholesterolaemic drugs because of the undesirable side-effect of increasing heart rate.[4] A study of compounds with structures based on natural thyroid hormones was therefore undertaken with the aim of producing a thyromimetic which mimics the natural hormones in their effect on the liver, but not the cardiac side-effect. From this study SK&F L-94901 (**1**) was identified as a novel, potent, and selective thyromimetic.[5] A viable route for the synthesis of kilogram quantities of SK&F L-94901 (**1**) was therefore required.

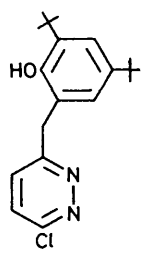
The key step in the synthesis of SK&F L-94901 (**1**) is the formation of the hindered diaryl ether moiety. Several methods are known for the formation of diaryl ethers, such as Ullmann-type coupling,[6,7] nucleophilic displacement,[8] and pyrolysis of carbonates.[9] However, our initial investigations using these approaches revealed a number of problems when applied to the synthesis of SK&F L-94901 (**1**). In particular, the route used to prepare the 3,5-di-iodothyronines from the corresponding dinitro derivatives [1] gave low yields for the dibromo analogues.

We describe here a synthesis of SK&F L-94901 (**1**) *via* oxidative coupling of two phenols. It is well known that oxidative coupling of phenols *via* stable phenoxyl radicals leads to quinol ethers,[10,11] which are precursors to a range of diaryl ethers.[12] This type of approach has been reported in studies on model reactions for the biosynthesis of thyroxine;[13,14] however, low yields were obtained using derivatives of 3,5-dibromotyrosine as one of the phenol components.

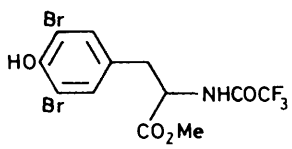
In contrast to these results we have successfully applied this approach to the synthesis of SK&F L-94901 (**1**), as described in detail below. Alternative syntheses of SK&F L-94901 (**1**) and related compounds are discussed in Parts 1[1] and 3.[15]



(**1**)



(**2**)

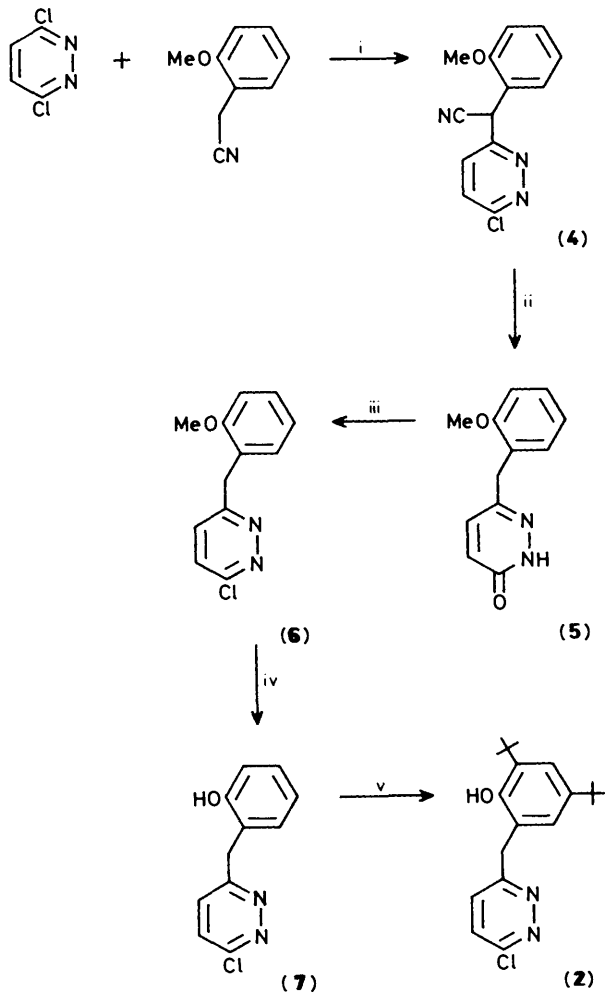


(**3**)

Results and Discussion

A hindered phenol capable of conversion into a stable phenoxyl radical was required for the key step in the synthesis of SK&F L-94901 (**1**). Retrosynthetic analysis gave the hindered phenol (**2**) and the tyrosine derivative (**3**)[16] as the required components. This approach also takes advantage of the fact that the phenol (**3**) is derived from natural tyrosine. In addition the synthesis is equally applicable to the formation of either enantiomer or the racemic mixture.

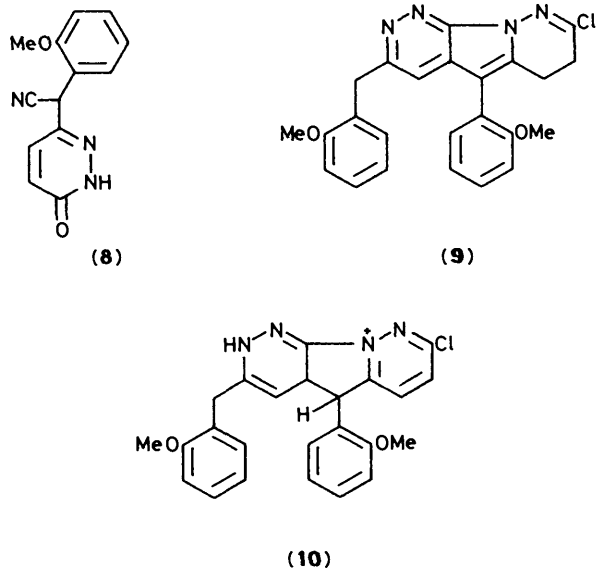
Synthesis of the di-t-butylphenol (**2**) was carried out as shown in Scheme 1. Base-catalysed alkylation of 3,6-dichloropyridazine with 2-methoxybenzyl cyanide to give the coupled product (**4**) was unsuccessful using sodium methoxide or



Scheme 1. *Reagents, conditions and yields:* i, Bu^{t}OK–Bu^{t}OH, 30 °C, 84%; ii, HOAc–HCl–water, heat, 77%; iii, $POCl_3$–CH_2Cl_2, heat, 87%; iv, BBr_3–CH_2Cl_2, −50 °C, 80%; v, Bu^{t}OH–urea–75% aq. H_2SO_4, room temp., 94%

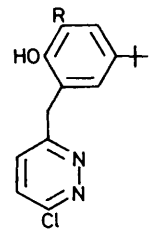
aqueous sodium hydroxide–toluene with a phase-transfer catalyst, and using potassium t-butoxide in tetrahydrofuran gave low yields. Use of sodium hydride in dimethylformamide (DMF) was successful, although unsuitable for large-scale reactions owing to the potential hazards associated with this mixture.[17] The alkylation reaction occurred readily using potassium t-butoxide in t-butyl alcohol. It was found that acid hydrolysis to give the pyridazinone (**5**) occurred smoothly in a mixture of glacial acetic acid and hydrochloric acid. The course of this reaction is best followed by n.m.r. spectroscopy, monitoring for the disappearance of the intermediate cyanopyridazinone (**8**), because of the similar chromatographic characteristics of compounds (**5**) and (**8**). The corresponding acid intermediate was not observed, indicating that the decarboxylation is a rapid reaction under these conditions. The cyanopyridazinone (**8**) could be isolated in high yield by carrying out the hydrolysis in 20% aqueous sulphuric acid under reflux. Under these conditions the cyanopyridazinone (**8**) precipitated from the reaction medium and was not further hydrolysed.

Chlorination of the pyridazinone (**5**) was accomplished using phosphorus oxide trichloride in refluxing dichloromethane to give the chloropyridazine (**6**). Some reactions gave rise to a minor impurity which was visible on t.l.c. as a blue fluorescent spot under u.v. light (254 nm), and in one case this fluorescent compound was the only isolable product. ^{1}H N.m.r., ^{13}C n.m.r., and mass spectra data are consistent with the dimeric pyrrolodipyridazine structure (**9**). This compound could be formed by either an initial acid-catalysed intermolecular quaternisation followed by cyclisation, or as an acid-catalysed loss of one benzylic proton and tautomerism to the enamine form followed by intermolecular alkylation, then cyclisation. In both cases the initial product of cyclisation followed by loss of HCl is the non-aromatic intermediate (**10**). Under the conditions of the reaction a series of tautomeric changes could lead to the presumably thermodynamically more stable heteroaromatic product (**9**). Literature precedent exists for this type of product from chloropyridazines, and the authors postulate 'an oxidation–reduction sequence' to account for the formation of the observed product.[18] In our view a sequence of tautomeric changes offers a more plausible explanation.



Demethylation of the chloropyridazine (**6**) was best accomplished using boron tribromide or boron trichloride at a temperature less than 0 °C in dichloromethane, giving the desired phenol (**7**) in good yield. Monoalkylation of the phenol (**7**) was rapid using conc. H_2SO_4–urea–Bu^{t}OH–H_2O,[19] giving the mono-t-butylphenol (**11**). Although further alkylation occurred to give the desired hindered phenol (**2**), it was found to be very slow, and a large excess of t-butyl alcohol was required. On scale-up one reaction at 5.0 kg scale gave a major (45%) water-soluble by-product. This by-product was removed by slurrying the crude product in dichloromethane followed by filtration. The insoluble material was analysed by ^{1}H n.m.r. spectroscopy and gave a spectrum virtually identical with that of the phenol (**2**), except that the resonance at δ 1.42 due to the *ortho*-t-butyl group was absent, and the aromatic resonances were shifted downfield to δ 7.25 and 7.38 from δ 7.09 and 7.26. M.s., i.r., and n.m.r. data are consistent with the structure being formulated as the sulphonic acid (**12**). No hydrolysis of the chloropyridazine moiety was observed under the butylation conditions. Other alkylation conditions were tried, such as isobutene–conc. H_2SO_4–H_2O, t-butyl acetate–conc. H_2SO_4–H_2O, t-butyl bromide–conc. H_2SO_4–H_2O, t-butyl alcohol–conc. H_2SO_4–H_2O; these however did not offer any advantages over the t-butyl alcohol–urea system.

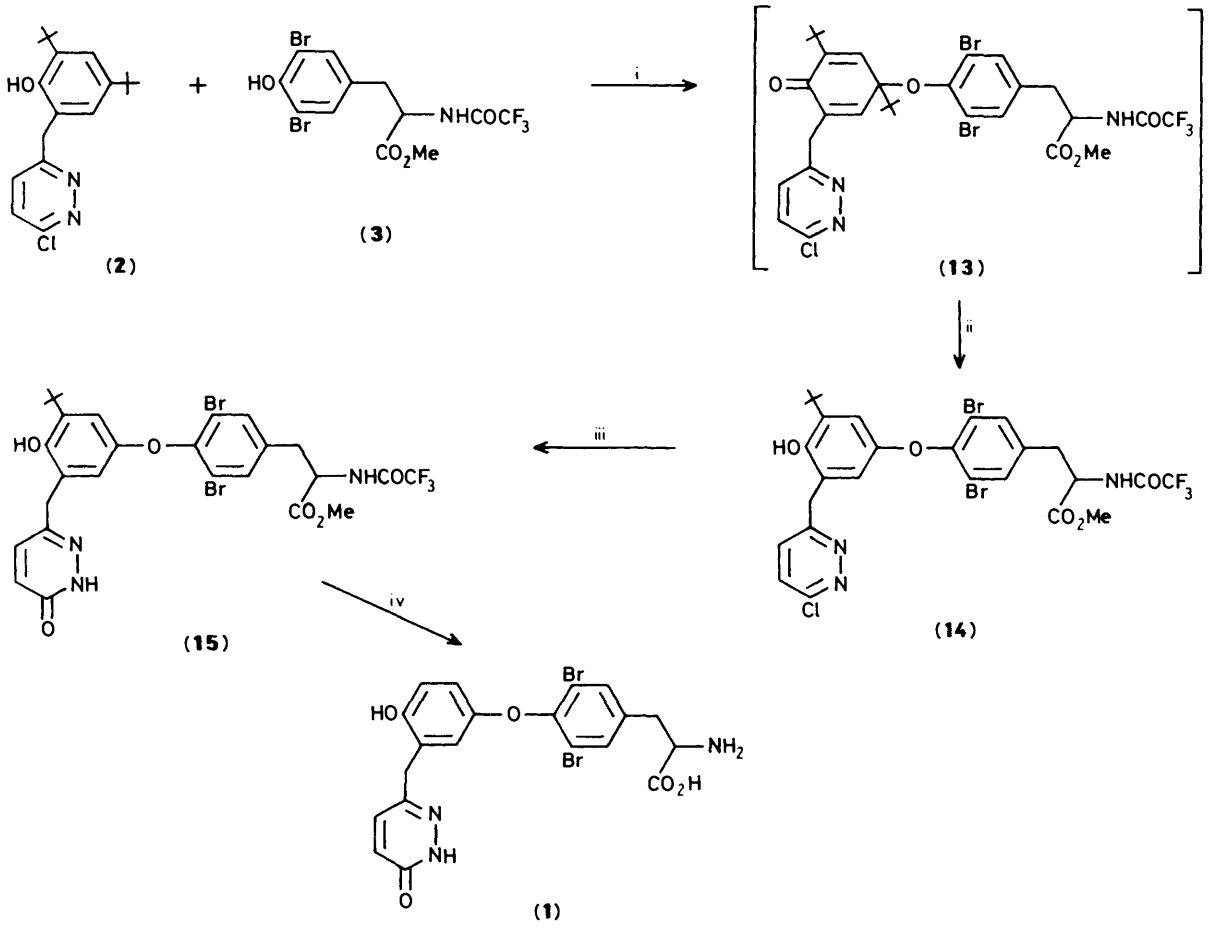
Synthesis of the phenol (**3**) from L-tyrosine was straightforward. L-Tyrosine was successively brominated using bromine



(11) R = H
(12) R = SO_3H

in glacial acetic acid, esterified using hydrogen chloride gas in methanol, then *N*-trifluoroacetylated with trifluoroacetic anhydride to give the desired phenol (**3**) in 72% overall yield.[16]

Synthesis of the thyromimetic SK&F L-94901 as accomplished by oxidative coupling of phenols (**2**) and (**3**) followed by a deprotection sequence, and this is shown in Scheme 2. Several oxidants have been used in the formation of quinol ethers.[10,11] However, a survey of oxidants such as 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), alkaline potassium ferricyanide [$K_3Fe(CN)_6$], iron(III) chloride–DMF complex, iron(III) chloride, manganese(III) trisacetylacetonate, and potassium manganate (K_2MnO_4) indicated that activated manganese dioxide was superior to any other tried. It was noted, however, that the quality of manganese dioxide was very important, and best results were obtained using activated manganese dioxide prepared by the method of Attenburrow *et al.*[20] Commercially available manganese dioxide could also be used, and material available from Fisons, Sci-Lab, and BDH gave the highest yields on the oxidative coupling step. The oxidative coupling could be carried out in a variety of solvents such as diethyl ether, ethyl acetate, and toluene. The latter solvent was found to be the most appropriate since the quinol ether (**13**) was shown to be unstable in solution and to isolation, and hence the formation of the diaryl ether (**14**) was carried out at once by *trans*-t-butylation using an excess of toluene in the presence of a Lewis acid catalyst. Of the several Lewis acid catalysts investigated for the *trans*-butylation reaction, only titanium tetrachloride, tin tetrachloride, or aluminium chloride–nitromethane[12] gave the desired product. All attempts to remove both t-butyl groups at this stage failed. The success of the oxidative coupling sequence from (**2**) and (**3**) to (**14**) was found to be very dependent on conditions employed. Good results were obtained when the starting phenols (**2**) and (**3**) were recrystallised before use, four separate treatments of manganese dioxide were used, with the 'spent' reagent filtered off between each treatment, and the total reaction time was kept below 5 h. The diaryl ether (**14**) was produced as a straw-coloured glass which we were unable to crystallise. The crude product obtained from the oxidative coupling sequence was sufficiently pure to use in subsequent steps. However, the quality of SK&F L-94901 (**1**) produced was significantly better when the diaryl ether (**14**) was purified by column chromatography prior to the deprotection sequence

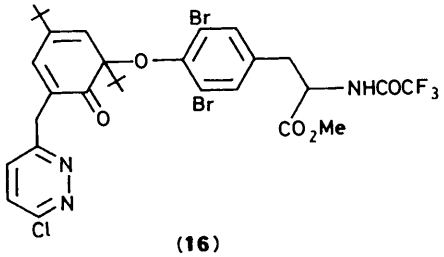


Scheme 2. *Reagents, conditions and yields:* i, MnO_2–toluene, room temp.; ii, $TiCl_4$–toluene, room temp., 42% overall; iii, NaOAc–HOAc, 92%; iv, 48% HBr–HOAc, heat; then recrystallisation, 66% overall

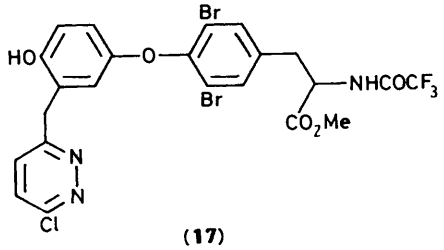
(**14**) ⟶ (**15**) ⟶ (**1**). In principle the oxidative coupling could give the corresponding *ortho*-quinol ether (**16**), though literature precedent[10,11] favours the formation of the *para*-quinol ether (**13**). After *trans*-butylation the product diaryl ether shows by ^{1}H n.m.r. spectroscopy a t-butyl resonance at δ 1.40 which is consistent with a t-butyl group *ortho* to the phenol, therefore confirming the structure of the diaryl ether as (**14**).

In principle the synthesis of SK&F L-94901 (**1**) could be shortened by omitting the difficult t-butylation and de-t-butylation steps. However, treatment of the mono-t-butylphenol (**11**) and the dibromotyrosine derivative (**3**) with manganese dioxide in ether, followed by titanium tetrachloride in toluene, did not give any of the desired thyronine derivative (**17**).

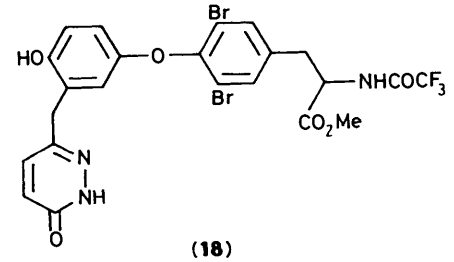
Treatment of the diaryl ether (**14**) with anhydrous sodium acetate in refluxing glacial acetic acid gave the corresponding pyridazinone (**15**). Trifluoroacetic acid has been reported[21] to be useful for *ortho*- and *para*-debutylation of phenols; however, clean debutylation of compound (**15**) was not observed. Use of hydrobromic acid in glacial acetic acid (1:1) at reflux for 5 h gave the desired product (**1**) as the hydrobromide salt, which on recrystallisation from aqueous alcohol gave SK&F L-94901 (**1**) as the free amino acid. SK&F L-94901 (**1**) could be prepared from the diaryl ether (**14**) in a one-pot reaction, but a cleaner product was obtained when the two-step procedure *via* the pyridazinone (**15**) was employed. Debutylation of quinol ethers using aluminium chloride–toluene–nitromethane is well documented,[12] but this method was found not to work rapidly on the diaryl ether (**15**), the reaction being incomplete after 24 h. In the presence of stronger acceptors such as anisole or *N*,*N*-dimethylaniline the de-t-butylation reaction was slightly faster. Unexpectedly, ^{1}H n.m.r. evidence suggested that the *ortho*-t-butyl group in compound (**15**) was removed using aluminium chloride in dichloromethane in the *absence* of a t-butyl acceptor, giving the protected amino acid (**18**).



(**16**)



(**17**)



(**18**)

Extended reflux times in acid solution during debutylation led to partial recemisation, and when the sequence described above was used the SK&F L-94901 (**1**) produced contained 6.7% of the D-isomer, as determined by high-pressure liquid chromatography (h.p.l.c.) using a chiral column[22] [the tyrosine derivative (**3**) contains 0.5% of the D-isomer[16]]. The synthesis of SK&F L-94901 (**1**) thus described gave an overall yield of 11% from 2-methoxybenzyl cyanide and forms the basis of a route suitable for kilogram preparations of this thyromimetic.

Experimental

Materials and Equipment.—M.p.s were determined on a Buchi 510 apparatus and are uncorrected. Unless otherwise stated, i.r. spectra were obtained for Nujol mulls on a Perkin-Elmer 781 instrument, and n.m.r. spectra for deuteriochloroform solutions with tetramethylsilane as internal standard on a JEOL GX270 or Bruker AM250 instrument. Mass spectra were recorded on a VG 7070F spectrometer. Light petroleum refers to the fraction with b.p. 60—80 °C. Silica gel (70—200 mesh) was used for column chromatography. The protected L-dibromotyrosine (**3**) was prepared by known chemistry.[16] Chiral h.p.l.c. analysis indicated the presence of 0.5% of the D-enantiomer in the dibromotyrosine derivative (**3**).[16]

Preparation of (6-*Chloropyridazin*-3-*yl*)-(2-*methoxyphenyl*)-*acetonitrile* (**4**).—A solution of 3,6-dichloropyridazine (100.2 g, 0.67 mol) and 2-methoxybenzyl cyanide (98.7 g, 0.67 mol) in t-butyl alcohol (300 ml) at 40—45 °C was added to a solution of potassium t-butoxide (150.0 g, 1.34 mol) in t-butyl alcohol (1 l) while the internal temperature was kept at 30—35 °C. After being stirred at 30—35 °C for 1.5 h the reaction mixture was quenched with 25% aqueous NH_4Cl (500 ml). The resultant slurry was diluted with water (500 ml) then filtered, and the residue was washed with water and dried *in vacuo* at 50 °C to give (6-*chloropyridazin*-3-*yl*)-(2-*methoxyphenyl*)*acetonitrile* (**4**) (147 g, 84%) as a white solid, m.p. 91—92 °C (from CH_2Cl_2–light petroleum) (Found: C, 59.7; H, 3.8; N, 16.2; Cl, 13.4. $C_{13}H_{10}ClN_3O$ requires C, 60.1; H, 3.9; N, 16.2; Cl, 13.7%); $\nu_{max.}$ 2 250 (CN), 1 255, 1 030, and 755 cm^{-1}; δ 3.82 (s, 3 H, OMe), 5.86 (s, 1 H, Ar_2CHCN), 6.93 (d, *J* 7.8 Hz, 1 H, ArH), 7.04 (t, *J* 7.8 Hz, 1 H, ArH), 7.39 (t, *J* 7.8 Hz, 1 H, ArH), 7.51 (s, 2 H, pyridazine-H), and 7.53 (d, *J* 7.8 Hz, 1 H, ArH).

Preparation of 6-(2-*Methoxybenzyl*)*pyridazin*-3(2H)-*one* (**5**).—The chloropyridazine (**4**) (33.5 g, 0.13 mol) was dissolved in a mixture of conc. HCl (200 ml), glacial acetic acid (100 ml), and water (100 ml). The resultant solution was refluxed and the reaction was followed by n.m.r. analysis for the disappearance of the signal at δ 5.86. Typical reaction time was 6 h. The solvents were evaporated off and the residue was crystallised from ethyl acetate–light petroleum to give 6-(2-*methoxybenzyl*)-*pyridazin*-3(2H)-*one* (**5**) (21.4 g, 77%) as a white solid, m.p. 142—143 °C (Found: C, 66.6; H, 5.6; N, 12.9. $C_{12}H_{12}N_2O_2$ requires C, 66.7; H, 5.6; N, 13.0%); $\nu_{max.}$ 3 320—2 400 (NH, CH), 1 675 (C=O), 1 660, 1 250, 1 013, and 757 cm^{-1}; δ 3.84 (s, 3 H, OMe), 3.96 (s, 2 H, Ar_2CH_2), 6.83—6.96 (m, 3 H, ArH), and 7.13—7.31 (m, 3 H, ArH).

Preparation of 3-*Chloro*-6-(2-*methoxybenzyl*)*pyridazine* (**6**).—The pyridazinone (**5**) (15.7 g, 73 mmol) was dissolved in dichloromethane (50 ml) and treated with phosphorus oxide trichloride (16 ml) and the mixture was stirred at reflux for 1 h. The resultant mixture was cooled and slowly poured onto crushed ice (100 g), and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 100 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (100 ml), dried ($MgSO_4$), and evaporated.

The residue was extracted several times with boiling light petroleum. The combined extracts were treated with activated charcoal and evaporated to give 3-*chloro*-6-(2-*methoxybenzyl*)-*pyridazine* (**6**) (14.8 g, 87%) as an off-white solid, m.p. 63 °C (Found: C, 61.4; H, 4.8; N, 12.0; Cl, 15.0. $C_{12}H_{11}ClN_2O$ requires C, 61.4; H, 4.7; N, 11.9; Cl, 15.1%); $\nu_{max.}$ 3 000—2 780 (CH), 1 250, 1 050, 1 034, and 762 cm^{-1}; δ 3.81 (s, 3 H, OMe), 4.35 (s, 2 H, Ar_2CH_2), 6.85—6.97 (m, 2 H, ArH), and 7.20—7.37 (m, 4 H, ArH).

One experiment gave an orange product which fluoresced blue under u.v. light of 254 nm. This product was crystallised from isopropyl alcohol to give 8-*chloro*-6,7-*dihydro*-3-(2-*methoxybenzyl*)-5-(2-*methoxyphenyl*)*pyrrolo*[1,5-b:2,3-c′]*dipyridazine* (**9**) as dark yellow crystals, m.p. >200 °C (decomp.) [Found: *m/z* 401.1145 ($M^+ - OCH_3$). $C_{23}H_{18}ClN_4O$ requires *m/z* 401.1169]; $\nu_{max.}$ 1 610, 1 580, and 1 450 cm^{-1} (C=C); δ 2.93 (t, *J* 7.8 Hz, 2 H, CH_2CH_2), 3.25 (t, *J* 7.8 Hz, 2 H, CH_2CH_2), 3.70 (s, 3 H, OMe), 3.80 (s, 3 H, OMe), 4.50 (s, 2 H, $ArCH_2$), and 6.80—7.40 (m, 9 H, ArH); δ_C 19.1, 28.9, 36.0, 55.0, 55.3, 106.6, 110.1, 111.1, 117.1, 119.7, 120.6, 120.7, 122.4, 127.7, 128.0, 129.0, 130.53, 130.80, 130.85, 148.0, 150.3, 156.0, 156.7, and 157.3; *m/z* (%), 432 (M^+, 2), 401 (100), 312 (15), 91 (25), and 77 (20).

Preparation of 2-[(6-*Chloropyridazin*-3-*yl*)*methyl*]*phenol* (**7**).—The pyridazine (**6**) (2.35 g, 10 mmol) was dissolved in dry dichloromethane (20 ml) and the solution was cooled and stirred to −50 °C. Boron tribromide (3 ml, 32 mmol) was added dropwise, and then the resultant solution was allowed to warm to room temperature. After 30 min the orange reaction mixture was added to ice–water (200 ml) and acetone was added to dissolve the precipitated solid. The resultant mixture was extracted with dichloromethane (3 × 100 ml). The combined extracts were washed with water (200 ml), dried ($MgSO_4$), and evaporated. The residue was crystallised from ethyl acetate–light petroleum to give 2-[(6-*chloropyridazin*-3-*yl*)*methyl*]-*phenol* (**7**) (1.75 g, 80%), m.p. 132—132.5 °C (Found: C, 59.6; H, 4.1; N, 12.5; Cl, 16.1. $C_{11}H_9ClN_2O$ requires C, 59.9; H, 4.1; N, 12.7; Cl, 16.1%); $\nu_{max.}$ 1 603, 1 593, 1 459 (C=C), 1 415, and 748 cm^{-1}; δ [$CDCl_3$ + $(CD_3)_2SO$] 4.30 (s, 2 H, Ar_2CH_2), 6.78 (t, *J* 7.6 Hz, 1 H, ArH), 6.90 (d, *J* 7.6 Hz, 1 H, ArH), 7.03—7.17 (m, 2 H, ArH), 7.42 (d, *J* 9.5 Hz, 1 H, pyridazine-H), and 7.46 (d, *J* 9.5 Hz, 1 H, pyridazine-H).

Preparation of 2-[(6-*Chloropyridazin*-3-*yl*)*methyl*]-4,6-*di*-*t*-*butylphenol* (**2**).—A solution of the phenol (**7**) (2.4 g, 11 mmol) and urea (14.0 g, 233 mmol) in 75% aqueous sulphuric acid (100 ml) was treated slowly with t-butyl alcohol (17.0 ml, 180 mmol). The mixture was stirred well at ambient temperature, and further quantities of t-butyl alcohol were added after 4 h (18.0 ml, 191 mmol), 24 h (5.0 ml, 53 mmol), and 28 h (20.0 ml, 212 mmol). After 120 h the reaction mixture was poured into water. The mixture was thoroughly extracted with diethyl ether, and the combined extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and evaporated. The residue was recrystallised from diethyl ether–light petroleum to give 2-[(6-*chloropyridazin*-3-*yl*)*methyl*]-4,6-*di*-*t*-*butylphenol* (**2**) (3.43 g, 94%), m.p. 143—143.5 °C (Found: C, 68.3; H, 7.5; N, 8.4; Cl, 10.9. $C_{19}H_{25}ClN_2O$ requires C, 68.6; H, 7.6; N, 8.4; Cl, 10.7%); $\nu_{max.}$ 1 233, 885, and 826 cm^{-1}; δ 1.29 (s, 9 H, Bu^t), 1.41 (s, 9 H, Bu^t), 4.30 (s, 2 H, Ar_2CH_2), 7.09 (s, 1 H, ArH), 7.26 (s, 1 H, ArH), 7.61 (d, *J* 9.8 Hz, 1 H, pyridazine-H), 7.6 (d, *J* 9.8 Hz, 1 H, pyridazine-H), and 8.45 (br s, 1 H, OH).

Isolation of By-product (**12**).—A portion (2.5 g) of the crude product obtained from the reaction described above carried out on the phenol (**7**) (5.0 kg) was stirred with dichloromethane (50 ml) at ambient temperature for 30 min. The resulting mixture was filtered under reduced pressure and the isolated precipitate was washed thoroughly with dichloromethane. The off-white solid was dried *in vacuo* at ambient temperature and gave the following analytical data: m.p. 267—270 °C; $\nu_{max.}$ 3 160, 3 080, 2 480 (SO_2OH), 2 060, 1 640, 1 540, 1 490, 1 465 (C=C), 1 380 (SO_2), 1 150 (SO_2), 860 (S–O), 650, and 625 cm^{-1}; δ [$(CD_3)_2SO$] 1.23 (s, 9 H, Bu^t), 4.23 (s, 2 H, Ar_2CH_2), 7.25 (d, *J* 3.3. Hz, 1 H, ArH), 7.38 (d, *J* 3.3. Hz, 1 H, ArH), 7.55 (d, *J* 8.7 Hz, 1 H, pyridazine-H), and 7.77 (d, *J* 8.7 Hz, 1 H, pyridazine-H); δ_C 32.4, 34.9, 36.9, 123.3, 125.4, 130.0, 130.3, 131.0, 131.4, 141.6, 150.3, 155.7, 162.6, and 163.4; *m/z* 357/9 (M^+ + H, 12%), 277 (28), 117 (100), 79 (41), 61 (83), and 57 (63).

Oxidative Coupling of the Phenols (**2**) *and* (**3**).—Toluene (225 ml) was placed in a round-bottomed flask and a small quantity (13 ml) was distilled out. Protected dibromotyrosine (**3**) (8.98 g, 20 mmol) was added to the hot toluene. When the substrate had dissolved the toluene was cooled to ambient temperature, and the solution was treated with the phenol (**2**) (5.88 g, 20 mmol). The resulting solution was cooled to 7 °C and placed under a nitrogen blanket. The cooled solution was treated with activated manganese dioxide (Fisons) (13.91 g, 160 mmol) and the mixture was stirred at 0—8 °C for 1 h. After this time the mixture was filtered under reduced pressure through Celite, and the filtrate was treated with activated manganese dioxide (Fisons) (13.91 g, 160 mmol). The resultant mixture was stirred at 0—8 °C under nitrogen for 1 h. Four successive treatments with fresh manganese dioxide were carried out. The filtrate obtained from the last reaction was treated with titanium tetrachloride (6.6 ml, 60 mmol) under nitrogen. After 5 min the reaction mixture was cautiously quenched with distilled water (60 ml), in an ice–water-bath. The resultant two-phase mixture was stirred overnight. The toluene layer was separated, and washed successively with saturated aqueous $NaHCO_3$ (60 ml) and saturated aqueous NaCl (2 × 60 ml), and dried over anhydrous $MgSO_4$. The dried toluene layer was evaporated to give the crude dibromothyronine (**14**) (10.8 g, 55%), which was purified for analysis by chromatography over silica gel with EtOAc–light petroleum (1:1) as eluant to give L-3,5-dibromo-3′-[(6-chloropyridazin-3-yl)methyl]-5′-t-butyl-*N*-trifluoroacetylthyronine methyl ester (**14**) (8.25 g, 42%) as a straw-coloured glass; $\nu_{max.}$ 1 745, 1 720 (C=O), 1 600, 1 545, and 1 450 cm^{-1} (C=C); δ 1.40 (s, 9 H, Bu^t), 2.99 (dd, *J* 15.5 and 7.8 Hz, 1 H, β-H), 3.30 (dd, *J* 15.5 and 5.8 Hz, 1 H, β-H), 3.88 (s, 3 H, CO_2Me), 4.11 (s, 2 H, Ar_2CH_2), 4.86 (ddd, *J* 7.8, 7.8, and 5.8 Hz, 1 H, α-H), 6.27 (d, *J* 3.9 Hz, 1 H, ArH), 6.80 (d, *J* 3.9 Hz, 1 H, ArH), 7.00 (d, *J* 7.8 Hz, 1 H, NH), 7.37 (s, 2 H, 2- and 6-H), 7.46 (d, *J* 9.7 Hz, 1 H, pyridazine-H), 7.50 (d, *J* 9.7 Hz, 1 H, pyridazine-H), and 9.10 (br s, 1 H, OH). The spectrum also indicated that *ca.* 3% ethyl acetate and ~0.7% light petroleum had been occluded; *m/z* 721/3/5 (M^+, 1%), 706 (1), 334/6/8 (3), 263/5/7 (4), 57 (80), and 43 (100).

Reaction of the Diaryl Ether (**14**) *with Sodium Acetate*.—The diaryl ether (**14**) (1.45 g, 2 mmol) was dissolved in glacial acetic acid (12 ml) and treated with anhydrous sodium acetate (0.49 g, 6 mmol). The resultant solution was refluxed for 3 h, then cooled and poured into distilled water (100 ml). The mixture was neutralised with saturated aqueous $NaHCO_3$, and the product was filtered off, washed with water, and dried *in vacuo* to give L-3,5-*dibromo*-3′-[(6-*oxo*-1,6-*dihydropyridazin*-3-*yl*)*methyl*]-5′-*t*-*butyl*-N-*trifluoroacetylthyronine methyl ester* (**15**) (1.30 g, 92%), m.p. 120 °C (decomp.) (Found: C, 46.0; H, 4.0; N, 6.0. $C_{27}H_{26}Br_2F_3N_3O_6$ requires C, 46.0; H, 3.7; N, 6.0%); $\nu_{max.}$ 3 300 (NH), 1 745 and 1 723 (C=O), 1 680 and 1 660 (CONH), 1 600 and 1 550 cm^{-1} (C=C); δ 1.35 (s, 9 H, Bu^t), 3.00 (dd, *J* 15.1 and 7.6 Hz, 1 H) and 3.30 (dd, *J* 15.1 and 6.0 Hz, 1 H) (together β-H_2), 3.75 (s, 2 H, $ArCH_2Ar$), 3.85 (s, 3 H, CO_2Me), 4.90 (ddd, *J* 7.6, 7.6, and 6.0 Hz, 1 H, α-H), 6.30 (d, *J* 3.8 Hz, 1 H,

ArH), 6.75 (br s, 1 H, OH), 6.80 (d, *J* 3.8 Hz, 1 H, ArH), 6.95 (d, *J* 9.4 Hz, 1 H, pyridazine-H), 7.22 (d, *J* 9.4 Hz, 1 H, pyridazine-H), 7.25 (br d, *J* 7.6 Hz, 1 H, NH), and 7.40 (s, 2 H, 2- and 6-H).

Formation of SK&F L-94901 (**1**).—The diaryl ether (**15**) (0.71 g, 1 mmol) was dissolved in glacial acetic acid (4 ml) and the solution was treated with 48% aqueous HBr (4 ml). The resulting mixture was refluxed for 5 h. After this time distilled water (15 ml) was slowly added to the refluxing solution. After addition of the water was complete the solution was allowed to cool. The product was filtered off and washed with water, then dried at 50 °C *in vacuo* to give SK&F L-94901 (**1**) as the hydrobromide salt (0.50 g, 80%). This salt (0.31 g) was dissolved in methanol (0.25 ml), and water (2 ml) was added at reflux. The mixture was cooled and filtered, and the insoluble product was washed with water, and dried *in vacuo* at 50 °C to give L-*3,5-dibromo-3′-[(6-oxo-1,6-dihydropyridazin-3-yl)methyl]thyronine* (**1**) (0.22 g, 82%) as off-white solid, m.p. 283 °C (decomp.); chiral h.p.l.c. analysis[21] gave a 6.7% D-enantiomer (Found: C, 44.4; H, 3.3; N, 7.8; Br, 29.6. $C_{20}H_{17}Br_2N_3O_5$ requires C, 44.6; H, 3.2; N, 7.8; Br, 29.6%); $\nu_{max.}$ 3 500—2 800 (NH, OH, CH), 1 670, 1 655 (C=O), 1 595, 1 550, and 1 505 cm^{-1} (C=C); δ[$(CD_3)_2SO$] 3.19 (dd, *J* 14.6 and 6.9 Hz, 1 H, β-H), 3.25 (dd, *J* 14.6 and 6.9 Hz, 1 H, β-H), 3.80 (s, 2 H, Ar_2CH_2), 4.48 (t, *J* 6.9 Hz, 1 H, α-H), 4.97 (br s, 5 H, NH_2, OH, CO_2H, NH), 6.44 (dd, *J* 9.6 and 3.8 Hz, 1 H, ArH), 6.64 (d, *J* 3.8 Hz, 1 H, ArH), 6.81 (d, *J* 9.6 Hz, 1 H, ArH), 6.84 (d, *J* 9.9 Hz, 1 H, pyridazine-H), 7.30 (d, *J* 9.9 Hz, 1 H, pyridazine-H), and 7.73 (s, 2 H, 2- and 6-H).

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References

1 Part 1, P. D. Leeson and J. C. Emmett, preceding paper.
2 Lipid Research Clinics Coronary Primary Prevention Trial Team, *JAMA, J. Am. Med. Assoc.*, 1984, **251**, 351, 365.
3 J. S. Boyd and M. F. Oliver, *J. Endocrinol.*, 1960, **21**, 25; P. Hansson, S. Valdemarsson, and P. Nilsson-Ehle, *Horm. Metab. Res.*, 1983, **15**, 449.
4 G. S. Boyd and M. F. Oliver, *J. Endocrinol.*, 1960, **21**, 33; The Coronary Drug Project Research Group, *JAMA, J. Am. Med. Assoc.*, 1972, **220**, 996.
5 A. H. Underwood, J. C. Emmett, D. Ellis, S. B. Flynn, P. D. Leeson, G. M. Benson, R. Novelli, N. J. Pearce, and V. P. Shah, *Nature*, 1986, **324**, 425.
6 J. Wright and E. C. Jorgensen, *J. Org. Chem.*, 1968, **33**, 1245.
7 A. Afzali, H. Firouzabadi, and A. Khalafi-nejad, *Synth. Commun.*, 1983, **13**, 335.
8 G. A. Neville and R. Y. Moir, *Can. J. Chem.*, 1969, **47**, 2787.
9 H. Witt, H. Holtschmidt, and E. Muller, *Angew. Chem., Int. Ed. Engl.*, 1970, **9**, 67.
10 E. R. Altwicker, *Chem. Rev.*, 1967, **67**, 475.
11 E. L. Dreher, in 'Houben Weyl, Methoden der Organische Chemie,' eds. E. Muller and O. Bayer, Georg Thieme Verlag, Stuttgart, 1970, vol. II/3b, p. 580.
12 M. Tashiro, H. Yoshiya, and T. Yamamoto, *Synthesis*, 1978, 399.
13 T. Matsuura and H. J. Cahnmann, *J. Am. Chem. Soc.*, 1960, **82**, 2055.
14 T. Matsuura and A. Nishinaga, *J. Org. Chem.*, 1962, **27**, 3072.
15 Part 3, following paper.
16 N. Lewis and P. Wallbank, *Synthesis*, 1987, 1103.
17 T. Laird, *Chem. Ind. (London)*, 1986, 134.
18 H. Lund and S. Gruhn, *Acta Chem. Scand.*, 1966, **20**, 2637.
19 N. B. Nevrekar, S. R. Sawardekar, T. S. Pandit, and N. A. Kudav, *Chem. Ind. (London)*, 1983, 206.
20 J. Attenburrow, A. F. B. Cameron, J. A. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1952, 1094.
21 J. McOmie and S. Saleh, *Tetrahedron*, 1973, **29**, 4003.
22 A. N. Carter and D. W. Darkin, unpublished results.

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