Synthesis of Thyroid Hormone Analogues. Part 3.[1] Iodonium Salt Approaches to SK&F L-94901

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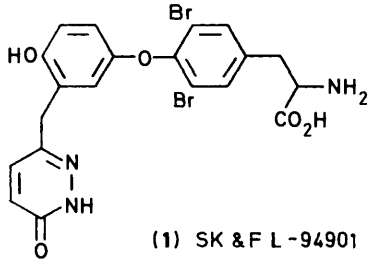
The key step in the synthesis of L-3,5-dibromo-3'-[6-oxo-1,6-dihydropyridazin-3-yl)methyl]-thyronine, SK&F L-94901 (**1**), a novel, selective, and potent thyromimetic, is the formation of the hindered diaryl ether moiety. This paper describes an investigation into the formation of the required diaryl ether by copper-catalysed reaction both of symmetrical iodonium salts (**2a**) and (**10**) and mixed iodonium salts (**2b**—**e**) with protected dibromotyrosine (**5**). The importance of the counter-ion of the iodonium salt is discussed. This work is extended to a large-scale synthesis of SK&F L-94901 (**1**).

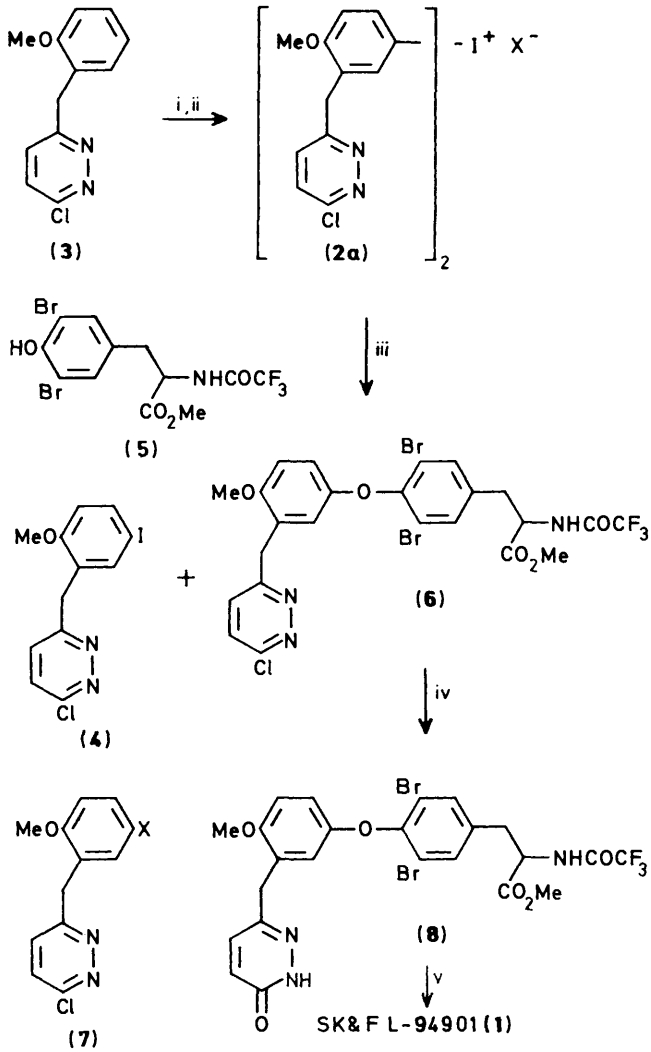
High plasma cholesterol levels are associated with an increased incidence of a number of cardiovascular diseases, including coronary heart disease, estimated to be the greatest cause of death in the western world. A cholesterol-lowering drug has been shown to reduce the incidence of both heart attacks and resulting deaths.[2] Thyroid hormones reduce circulating cholesterol levels in animal models and in man,[3] but adverse cardiac effects have precluded their therapeutic use.[4] A programme of research designed to identify a thyroid hormone mimetic which had cholesterol-lowering activity but no cardiac side-effects yielded the novel, potent, and selective thyromimetic SK&F L-94901.[5] In the preceding paper in this series a viable synthetic route to this compound was described. We here detail alternative approaches including the route used for large-scale preparation of SK&F L-94901 (**1**).



(**1**) SK & F L-94901

Results and Discussion

(a) *Symmetrical Iodonium Salts.*—The key synthetic problem in the synthesis of SK&F L-94901 (**1**) is the formation of the hindered diaryl ether moiety. A number of methods for the formation of diaryl ethers exist,[6,7] but the one which has proved most versatile in our hands for the preparation of SK&F L-94901 (**1**) and a number of other dibromothyronines utilises the reaction of an iodonium salt with a protected dibromophenol to give a protected thyronine derivative. Subsequent deprotection yields the required thyromimetic. For SK&F L-94901 (**1**) the iodonium salt initially investigated, and also used on a large scale, was the symmetrical bis-{3-[(6-chloropyridazin-3-yl)methyl]-4-methoxyphenyl}iodonium salt (**2a**) (Scheme 1).



Scheme 1. *Reagents:* i, $I(OCOCF_3)_3$–CF_3CO_2H–$(CF_3CO)_2O$; ii. aq. NaX; iii, Cu bronze–NEt_3–CH_2Cl_2; iv, NaOAc–AcOH; v. HBr–HOAc; then recrystallisation to give free base (**1**)

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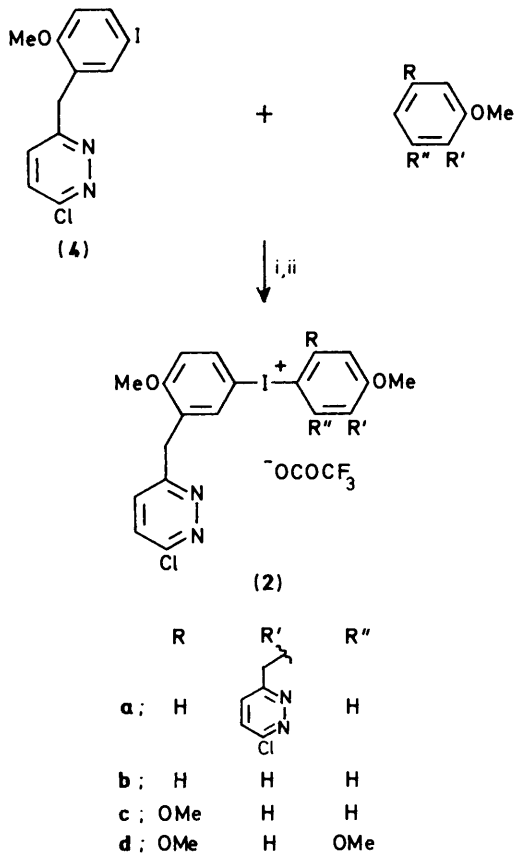
The iodonium salt was prepared from the corresponding anisole (**3**)[1] by reaction with iodine tristrifluoroacetate. This in turn was prepared by the oxidation of iodine in trifluoroacetic anhydride (TFAA) with fuming nitric acid. We have developed a modified procedure for preparing iodine tristrifluoroacetate, since in most literature procedures[8,9] a considerable exotherm occurs, acceptable on a small scale but totally unsuitable for the preparation of large amounts. We have repeatedly used our modified procedure for the preparation of iodine tristrifluoroacetate on a one mol scale without problems.

The iodonium salt was prepared by reaction of the anisole (**3**) with the iodine tristrifluoroacetate in a mixture of trifluoroacetic acid (TFA) and TFAA at room temperature for 16 h. After the reaction mixture had been quenched into an aqueous salt solution, the iodonium salt was extracted into dichloromethane. The best way to obtain the iodonium salt as a solid was found to be by slow addition of this dichloromethane extract to diethyl ether.

This salt could also be prepared by treatment of the anisole (**3**) and the iodoanisole (**4**)[10] with ammonium persulphate in glacial acetic acid containing 5% conc. sulphuric acid (Scheme 2).



Scheme 2. *Reagents and conditions:* i, ammonium persulphate–HOAc–5% conc. H_2SO_4, room temp.; ii, $NaOCOCF_3$

The concentration of sulphuric acid was critical,[11] as more than 5% led to rapid decomposition of the reactants and products. Work-up with aqueous sodium trifluoroacetate, followed by precipitation as described above, gave the salt (**2a**) as the trifluoroacetate. Although this method requires the preparation of the iodoanisole (**4**), it avoids the preparation and handling of the moisture-sensitive iodine tristrifluoroacetate and, in addition, the iodonium salt obtained has fewer highly coloured impurities. ^1H N.m.r. analysis of the products formed by both methods showed that the iodonium substitution was *para* to the methoxy group, confirming structure (**2a**).

Table 1.

Experiment	Iodonium salt (**2a**) counter-ion	Yield of the thyronine (**6**) (%)
(i)	0.8 Cl^-/0.2 $CF_3CO_2^-$	13
(ii)	0.3 AcO^-/0.7 $CF_3CO_3^-$	30
(iii)	0.95 $CF_3CO_2^-$	50—60
(iv)	0.87 ClO_4^- [a,b]	51
(v)	0.23 AcO^-/0.08 Cl^-/ 0.21 $CF_3CO_2^-$/0.48 ClO_4^- [a]	26

[a] ClO_4^- assumed when all other possible anions have been measured. [b] Microanalysis supports ClO_4^- counter-ion.

The coupling of the iodonium salt (**2a**) with protected dibromotyrosine (**5**)[12] was carried out in the presence of triethylamine and copper bronze in dichloromethane (Scheme 1). The expected products are the thyronine (**6**) and the iodoanisole (**4**). Initial experiments on the coupling reaction gave poor yields of coupled product (**6**). Monitoring of the reaction by high-pressure liquid chromatography (h.p.l.c.) showed the consumption of the iodonium salt (**2a**) without complete utilisation of the dibromotyrosine (**5**). This suggested that nucleophiles other than the dibromotyrosine (**5**) were competing effectively for the iodonium salt. This, in turn, implicated the iodonium salt counter-ion. We subsequently found that the counter-ion was in fact crucial in obtaining good yields.

Depending on the work-up procedure used, iodonium salt (**2a**) could be obtained with either chloride, acetate, or trifluoroacetate as the major counter-ion (Table 1). In other instances, attempts to prepare the perchlorate salt using aqueous sodium perchlorate and sodium acetate gave variable quantities of acetate and trifluoroacetate in the product, the remainder presumed to be perchlorate. The perchlorate counter-ion could not be detected by ion-exchange chromatographic analysis.[13] The use of the tetrafluoroborate was discounted in the light of a literature report on the explosive nature of diphenyliodonium tetrafluoroborate.[14]

The above salts gave different yields of the coupled product (**6**) (Table 1). In experiment (i), as well as iodoanisole (**4**) another compound was formed in comparable amounts, as observed by h.p.l.c. Although it could not be separated from the iodoanisole (**4**) by preparative chromatography, available spectroscopic evidence is consistent with it being the chloroanisole (**7**; X = Cl). In experiment (ii) although the yield of the required product (**6**) was higher, another by-product was clearly observed, presumed to be the acetate derivative (**7**; X = OAc). With trifluoroacetate as the only anion present [experiment (iii)] clean conversion of the salt (**2a**) and phenol (**5**) into the thyronine derivative (**6**) and the iodoanisole (**4**) was observed, only trace impurities being observed by h.p.l.c. Good yields were also obtained with some batches of iodonium salt (**2a**) as the non-nucleophilic perchlorate salt.

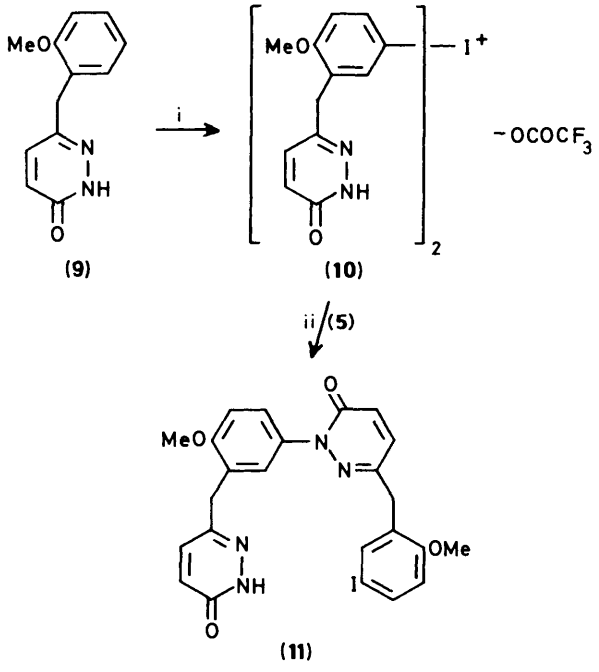
The crude reaction mixture from the coupling step was purified in two stages. Filtration through silica removed the copper and most of the highly coloured impurities. Further chromatography separated the required product (**6**) from the iodoanisole (**4**), small amounts of dibromotyrosine (**5**), and other minor impurities. In this way reproducible yields of (50—60%) of the pure isolated coupled product were obtained, using the trifluoroacetate salt.

While the mechanism by which the copper-catalysed coupling occurs is not clearly understood, we have established that the copper and triethylamine are required for reactions of

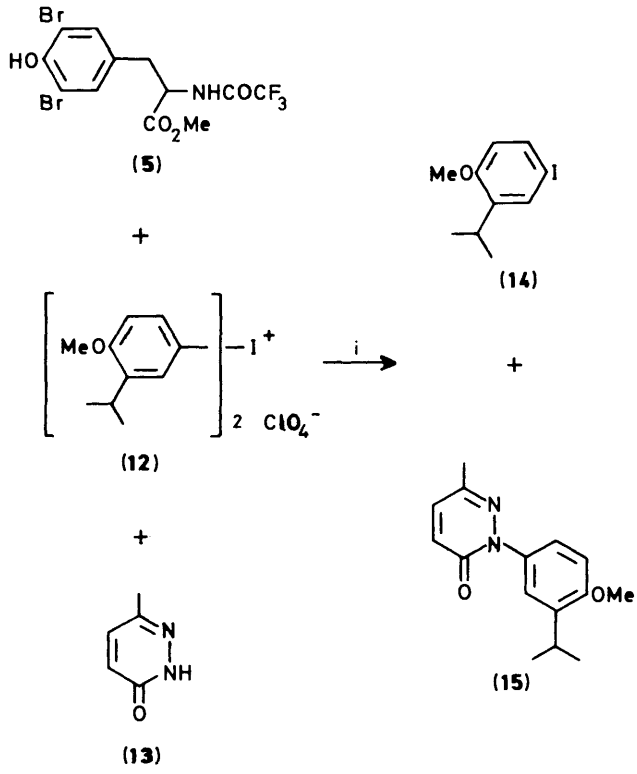
iodonium salts of this type with the dibromophenol (**5**). Dichloromethane appears to be a particularly good solvent for this reaction, although tetrahydrofuran and chloroform have also been used. In earlier work using methanol as solvent considerable quantities of methoxy-substituted products were obtained. This has also been observed by Lockhart.[15] We have used copper bronze in these reactions, but Lockhart[15] has recently presented some strong evidence that a copper(I) species is in fact the active species in this reaction, and argues that the reaction involves an intermediate arylcopper(III) species which, after co-ordination of an appropriate nucleophile, undergoes reductive elimination to give the product and regenerate a copper(I) species. Stable copper(III) complexes have recently been prepared.[16] Of interest in this respect is the fact that in this particular reaction there appears to be a time lag before the reaction starts. Thus, the h.p.l.c. profile of the reaction revealed essentially no reaction after 30 min, but the reaction was virtually complete after 2 h. In the light of the above this could conceivably be due to generation of a copper(I) species from the copper bronze. Paine has recently provided evidence that in the Ullmann condensation of diarylamines with iodobenzenes, a single copper(I) species is formed from the three oxidation states of copper.[17] We investigated the use of catalytic quantities of copper(I) iodide and, although it proved to be an effective catalyst, it offered no advantages over copper bronze. One obvious problem in the use of copper(I) salts is the introduction of other potential nucleophiles to compete with the dibromotyrosine (**5**).

It was initially surprising to us that the chloride and acetate counter-ions would compete effectively as nucleophiles with the anion of the dibromophenol (**5**). However, related work on the reaction of the anion of the dibromophenol (**5**) with 4-nitrohalogenobenzenes has shown this phenoxide to be a particularly poor nucleophile.[18] We ascribe the low reactivity of this phenoxide to be due to both steric factors and the inductive electron-withdrawing nature of the two bromine atoms.

The preparation of the starting anisole (**3**) has been described in the preceding paper in this series.[1] This compound was derived from the corresponding pyridazinone (**9**), and, in the



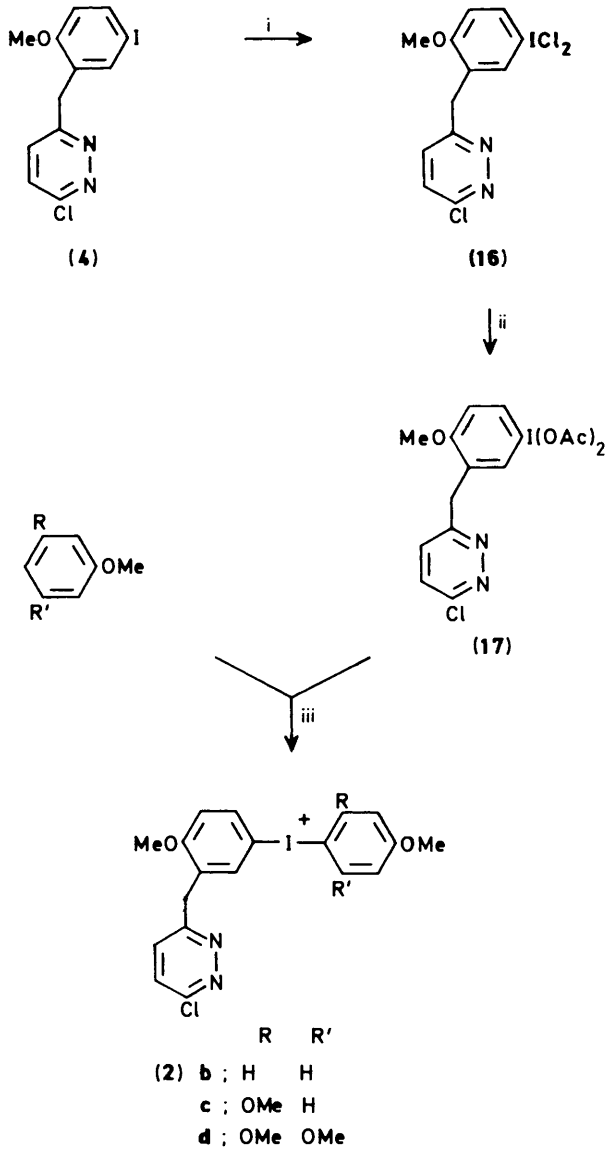
Scheme 3. *Reagents and conditions:* i, $I(OCOCF_3)_3$; ii, Cu bronze–NEt_3–CH_2Cl_2, room temp.



Scheme 4. *Reagents and conditions:* i, Cu bronze–Et_3N–CH_2Cl_2, room temp.

early stages of this work, conversion of the this pyridazinone into the chloropyridazine (**3**) proved particularly troublesome on a large scale. To avoid these difficulties, and to shorten the route, we attempted to use the iodonium salt prepared from the pyridazinone (**9**) in the coupling reaction. This salt was prepared (presumably as the trifluoroacetate) in low yield in an unoptimised reaction from compound (**9**) (Scheme 3). On reaction of the salt (**10**) with dibromotyrosine derivative (**5**), triethylamine, and copper bronze in dichloromethane only a trace of the expected coupled product (**8**) was formed, and the major isolable product was the *N*-arylated pyridazinone (**11**). This indicates that the pyridazinone group is competing effectively with the dibromotyrosine (**5**) as a nucleophile. To study this reaction the simple diaryliodonium salt (**12**) was treated with 6-methylpyridazinone (**13**) and the dibromotyrosine derivative (**5**) in the proportions 1:1:1 under standard coupling conditions. The major product isolated, in addition to the iodoanisole (**14**) was the *N*-arylated pyridazinone (**15**) (Scheme 4). This again demonstrates the poor nucleophilicity of the dibromotyrosine, and makes the iodonium salt (**10**) useless for the production of SK&F L-94901 (**1**). The above reaction is analogous to that of 1,2,3-benzotriazin-4(3*H*)-one with di-*p*-tolyliodonium chloride.[19]

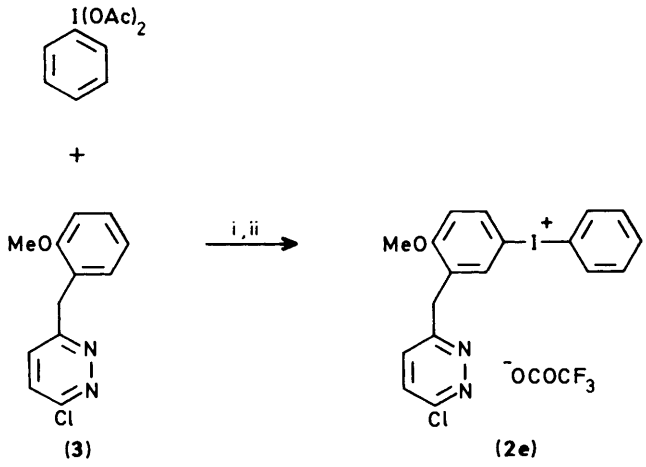
(b) *Unsymmetrical Iodonium Salts.*—While the above method using the symmetrical iodonium salt (**2**) gave good and reproducible yields of the desired diaryl ether (**6**), one half of an expensive substrate was not utilised. We therefore undertook a study of migratory aptitudes of a series of mixed iodoinium salts with copper catalysis. It has been reported that unsymmetrical diaryliodonium salts react with nucleophiles such as alkoxides,[20–22] water,[20] halides,[23] nitrite,[20,24,25] and cyanide[20,24] in solution, in the *absence* of copper, at the most electron-deficient aryl ring, although selectivity was not high (up to a *maximum* of 12:1 in almost all cases). Competition between



Scheme 5. *Reagents and conditions:* i, Cl_2–CH_2Cl_2, room temp.; ii, AgOAc or NaOAc; iii, CF_3CO_2H

nucleophilic displacement and electron-transfer mechanisms has been proposed for these reactions.[21-24] In the presence of copper, although rates were enhanced, in two cases unsymmetrical iodonium salts reacted with water to give an unchanged product distribution,[26,27] and, in another, selectivity was dramatically reduced.[24] In view of the limited data for the copper-catalysed reaction of mixed iodonium salts with nucleophiles, we studied a series where we varied the substitution on one aryl group. No single method[8] was appropriate for the preparation of the iodonium salts (**2b**—**e**), and the successful methods are shown in Schemes 2, 5, and 6.

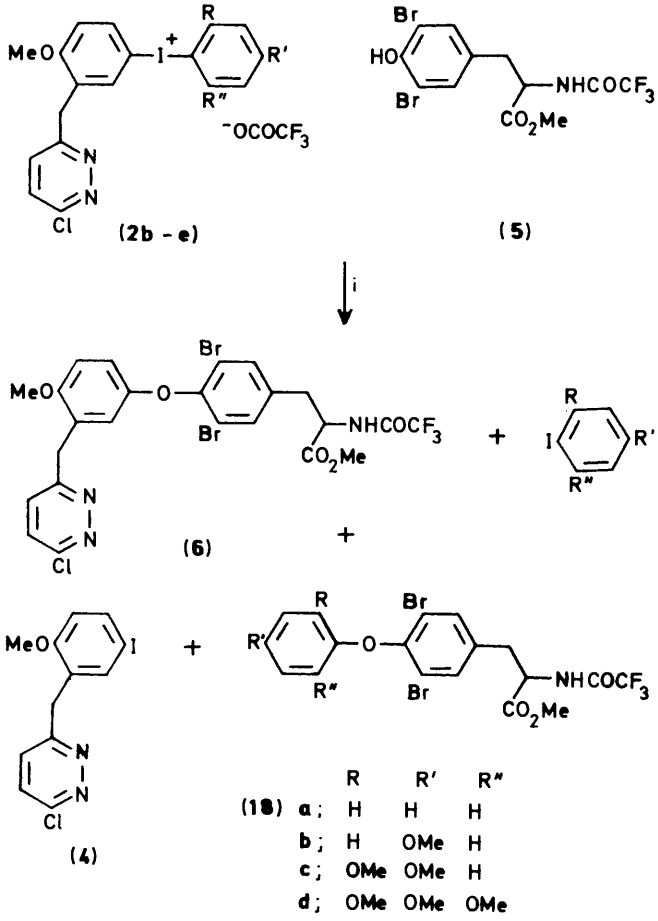
The mixed iodonium salt (**2b**) was prepared from the iodoanisole (**4**) and anisole using ammonium persulphate in acid as described above for the salt (**2a**) (Scheme 2). However, for mixed iodonium salts (**2c** and **d**) only low yields were obtained, possibly due to the formation of radical cations of the methoxybenzenes by oxidation by ammonium persulphate, which then undergo side-reactions.[28] It was found that the mixed iodonium salts (**2b**—**d**) could be prepared by the route shown in Scheme 5. Treatment of the iodoanisole (**4**) in dichloromethane with chlorine gave the iododichloride (**16**) as a reasonably stable bright yellow solid. Treatment of the iododichloride (**16**) with silver acetate, or sodium acetate, gave the corresponding iododiacetate (**17**). The iododiacetate (**17**) was found to be very unstable, and had to be freshly prepared and used immediately. Coupling with polymethoxybenzenes occurred in good yield only at −30 °C to give the iodonium salts (**2c** and **d**) though reaction with anisole could be carried out at 10 °C to give the iodonium salt (**2b**). The mixed iodonium salt (**2e**) could be prepared in high yields from commercially available (diacetoxyiodo)benzene and the pyridazine (**3**) in a mixture of TFA and TFAA (Scheme 6).



Scheme 6. *Reagents and conditions:* i. CF_3COH; ii, $NaOCOCF_3$

With the required iodonium salts (**2b**—**e**) in hand, coupling reactions with the protected dibromotyrosine (**5**) were carried out at room temperature in dichloromethane in the presence of copper bronze and triethylamine. In each case all expected products were obtained (Scheme 7). As stated previously, the symmetrical iodonium salt (**2a**) gave only products (**4**) and (**6**). The product mixtures from reaction of iodonium salts (**2b**—**e**) were subjected to chromatography over silica gel and analysed by n.m.r. spectroscopy. The ratio of desired diaryl ether (**6**) to alternative diaryl ether (**18a**—**d**), and the isolated yields of (**6**), are shown in Table 2. The results show that in this system increasing the number of electron-donating substituents on one aryl ring resulted in the preferential transfer of the other aryl substitutent. However the selectivity is small, and disappointingly low for our purposes. This reaction is clearly relatively insensitive to substituent effects. This is highlighted by the result with iodonium salt (**2d**), in which the opposite selectivity was observed, probably due to steric factors. It has been noted[29] that with sterically hindered mixed iodonium salts, bromide ion preferentially attacks at the more hindered position to relieve steric strain. This factor may have been of more importance than the electronic one in determining the overall selectivity of the mixed iodonium salt (**2d**).

Thus, the above work with the series of mixed iodonium salts shows the preferential transfer of the electron-deficient aromatic substituent to the incoming nucleophile. The overall yield of the diaryl ether (**6**) from the anisole (**3**) *via* iodonium salt (**2c**) is 30.5%, compared with 26% *via* the symmetrical iodonium salt (**2a**). However, with the selectivity only reaching 3:1, the product mixture from (**2c**) was considerably more complex than that obtained in the case of the symmetrical iodonium salt (**2a**). For this and other reasons, the route *via* symmetrical iodonium salt (**2a**) was used for the large-scale preparation of SK&F



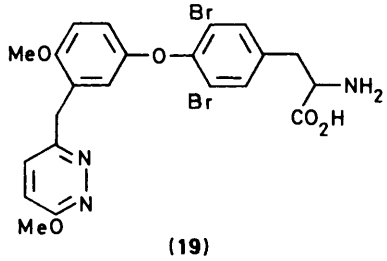
Scheme 7. *Reagents and conditions:* i, Cu bronze–Et_3N–CH_2Cl_2, room temp.

Table 2.

Iodonium salt	R	R	R	Ratio (6):(18)	Yield of (6) (%)
(2e)	H	H	H	1:1	37
(2b)	H	OMe	H	2:1	47
(2c)	OMe	OMe	H	3:1	58
(2d)	OMe	OMe	OMe	0.8:1	34

L-94901 (**1**). A total of 1.5 kg of the coupled product **6**) was prepared in three batches.

(c) *Preparation of* SK&F L-94901 (**1**).—The required SK&F L-94901 (**1**) was obtained by removal of the protecting groups (Scheme 1). The first deprotection step involved conversion of the chloropyridazine group of (**6**) into the pyridazinone (**8**). This was achieved by refluxing a solution of compound (**6**) in sodium acetate–acetic acid. Subsequent addition of water is sufficient to hydrolyse the presumed acetoxypyridazinone intermediate to the pyridazinone (**8**), which is separated by filtration. Initially the remaining protecting groups were removed in two steps; treatment with boron tribromide to remove the ether and ester methyl groups. followed by aqueous sodium hydroxide to remove the trifluoroacetyl group. However, this procedure failed to give complete cleavage of the methyl ether, and the residual ether contaminant (**19**) (*ca.* 2%) in the final product (**1**)



proved very difficult to remove. It was subsequently found that all three groups could be removed by refluxing the pyridazinone (**8**) in aqueous hydrobromic acid–acetic acid. Quenching with water gave the required product (**1**) as the hydrobromide salt. Recrystallisation (aq. ethanol) of this salt gave the product (**1**) as the free base. The overall yield for the deprotection of the coupled product (**6**) to give SK&F L-94901 (**1**) free base was 54%. Attempts to remove all four protecting groups from compound (**6**) in one step using aqueous hydrobromic acid–acetic acid gave a mixture of products which was difficult to purify.

Chiral h.p.l.c. analysis[30] of the various batches of SK&F L-94901 produced indicated that they contained 4—8% of the D-enantiomer. The dibromotyrosine derivative (**5**) used contained only 0.5% of its D-enantiomer.

The 7-step synthesis of SK&F L-94901 (**1**) *via* the symmetrical iodonium salt (**2a**) is shorter than the oxidative coupling approach,[1] and an overall yield of 8% from 2-methoxybenzyl cyanide was obtained. This route has been used to prepare 500 g of SK&F L-94901. The route *via* the unsymmetrical iodonium salt (**2d**), though one step longer, gives an overall yield of 9% from 2-methoxybenzyl cyanide.

Experimental

Materials and Equipment.—M.p.s were determined on a Buchi 510 apparatus or Electrothermal 1A6304 m.p. apparatus and are uncorrected. Unless otherwise stated, i.r. spectra were obtained as Nujol mulls on a Perkin-Elmer 781 instrument, and n.m.r. spectra as deuteriochloroform solutions with tetramethylsilane as internal standard on a JEOL GX270 or Bruker AM250 instrument. Mass spectra were recorded by a VG 7070F spectrometer. Light petroleum refers to the fraction with b.p. 60—80 °C. IMS refers to 94% industrial methylated spirits. Silica gel (70—200 mesh) was used for column chromatography. Synthesis of the anisole (**3**),[1] iodoanisole (**4**),[10] and the L-dibromotyrosine derivative (**5**)[12] have been described. Chiral h.p.l.c. analysis showed the L-dibromotyrosine derivative (**5**) to contain 0.5% of the D-enantiomer.[30] Counter-ion analysis of the iodonium salts (**2a—e**) was carried out using a Dionex Ion chromatograph.[13] (Diacetoxyiodo)benzene was purchased from Aldrich. L.c.-m.s. analysis was carried out using a Finnigan TSQ46 instrument and a thermospray interface, with aq. ammonium acetate–acetonitrile mobile phase and a positive ionisation mode.

Preparation of Iodonium Salts.—(a) *Bis{3-[(6-chloropyridazin-3-yl)methyl]-4-methoxyphenyl}iodonium trifluoroacetate* (**2a**). 1. *From the anisole* (**3**). Iodine (159 g, 0.63 mol) was suspended in TFA (1 l) and the mixture was stirred mechanically under nitrogen and heated to 36 °C. Fuming nitric acid (350 ml, 7.9 mol) was added dropwise during 90 min. During this addition a white solid was initially precipitated which, after addition of *ca.* 100—150 ml of the fuming nitric acid, redissolved in an exothermic process. The addition of further fuming nitric acid was stopped until this exotherm subsided (cooling of the reaction vessel was sometimes necessary). The addition of the

remaining fuming nitric acid proceeded smoothly. The resulting solution was held at 40 °C for 1 h. and then allowed to cool. Most of the residual dinitrogen tetraoxide fumes were removed under a stream of nitrogen, and the solvent was gently removed by distillation (water-bath at 40 °C) under reduced pressure (1 mmHg) to leave a yellow solid. TFA (300 ml) was added and the distillation was repeated. This process was repeated once more to give iodine(III) tristrifluoroacetate as a pale yellow solid. This was suspended in TFAA (1.2 l) and the mixture was cooled to −20 °C under nitrogen. A solution of 3-chloro-6-(2-methoxybenzyl)pyridazine (**3**) (600 g, 2.55 mol) in TFA (1.2 l) was added dropwise, while the temperature was maintained at between −10 and −20 °C. The reaction mixture was stirred at −10 °C for a further 1 h and left to warm to room temperature overnight.

The reaction mixture was evaporated to dryness to give a dark oil, which was poured into a stirred solution of sodium sulphate (3.5 g) in water (20 l). The pH was adjusted to 2 with 50% aqueous sodium hydroxide and the mixture was extracted with dichloromethane (2 × 3 l, 1 × 2 l). The combined extracts were dried ($MgSO_4$), filtered, and reduced to a volume of *ca.* 2 l by rotary evaporation under reduced pressure. This solution was added slowly to vigorously stirred diethyl ether (12 l) whereupon a grey-coloured solid precipitated. After the mixture had been stirred overnight the product was filtered off, washed with ether, and dried (40 °C, 50 mmHg, 6 h) to give the title *iodonium trifluoroacetate* (**2a**) (845 g, 95%), m.p. 145—147 °C (Found: C, 44.0; H, 3.0; N, 8.0; Cl, 10.0. $C_{26}H_{20}Cl_2F_3IN_4O_4$ requires C, 44.15; H, 2.85; N, 7.9; Cl, 10.0%); anion analysis, molar ratios: trifluoroacetate 0.94; acetate 0.04; chloride 0.02; $\nu_{max.}$ 1 675 (CO), 1 630, 1 590, 1 570, 1 540 (4 × aryl C=C), 1 250, 1 200, 1 170, 1 125 (3 × CF_3), and 1 020 cm^{-1}; δ[$(CD_3)_2SO$] 3.81 (3 H, s, OMe), 4.25 (2 H, s, CH_2), 7.12 (1 H, m, ArH), 7.58 (1 H, d, *J* 9 Hz, pyridazine-H), 7.80 (1 H, d, *J* 9 Hz, pyridazine-H), 8.02 (1 H, m, ArH), and 8.06 (1 H, m, ArH).

The dichloromethane solution of the iodonium salt was washed with aqueous sodium chloride and the salt (**2a**) subsequently isolated had both chloride and trifluoroacetate counter-ions in the ratio 8:2. This could not be reconverted into the trifluoroacetate by shaking with aqueous trifluoroacetate. Quenching of the crude iodonium salt preparation into aqueous sodium acetate–sodium sulphate gave iodonium salt (**2a**) with a 7:3 mixture of acetate and trifluoroacetate counter-ions, whereas treatment with aqueous sodium sulphate or distilled water gave the stoicheiometric trifluoroacetate salt. In other instances, attempts to prepare the perchlorate salt using aqueous sodium perchlorate and sodium acetate gave variable quantities of acetate and trifluoroacetate in the product, the remainder presumed to be perchlorate. The perchlorate counter-ions could not be detected by ion-exchange chromatographic analysis.

2. *From the iodoanisole* (**4**). A solution of the anisole (**3**) (7.0 g, 30 mmol), the iodoanisole (**4**) (10.8 g, 30 mmol), and ammonium persulphate (13.7 g, 60 mmol) in glacial acetic acid (200 ml) was treated with a solution of conc. sulphuric acid (12 ml) in glacial acetic acid (28 ml) during 15 min. The resultant mixture was stirred at ambient temperature for 22 h, then was treated with a solution of sodium trifluoroacetate (16.3 g, 120 mmol) in *demineralised* water (120 ml). After 45 min the pH of the solution was carefully adjusted to 4 with 40% w/v aqueous sodium hydroxide (~75 ml), with the temperature kept below 25 °C. The reaction mixture was diluted with demineralised water (300 ml). The aqueous mixture was extracted with dichloromethane (2 × 300 ml) and the combined extracts were washed successively and thoroughly with demineralised water (3 × 110 ml) and 0.5M aqueous sodium trifluoroacetate (2 × 100 ml). The extracts were dried ($MgSO_4$), and reduced to 100 ml under reduced pressure. The concentrated dichloromethane solution was added dropwise during 45 min to rapidly stirred and cooled diethyl ether (800 ml). The light brown solid that crystallised was filtered off after 30 min, and washed with cold diethyl ether (30 ml) to give bis{3-[(6-chloropyridazin-3-yl)methyl]-4-methoxyphenyl}iodonium trifluoroacetate (**2a**) (15.8 g, 75%), m.p. 144—149 °C (decomp.); this material was spectroscopically identical with the sample prepared above (method 1).

(b) {3-[(6-*Chloropyridazin*-3-*yl*)*methyl*]-4-*methoxyphenyl*}-(4-*methoxyphenyl*)*iodonium trifluoroacetate* (**2b**). Repetition of the above procedure (method a.2) using the iodoanisole (**4**) (5.4 g, 15 mmol), anisole (1.65 g, 15 mmol), and ammonium persulphate (6.6 g, 30 mmol) in glacial acetic acid (114 ml) containing conc. sulphuric acid (6 ml) gave the title compound (**2b**) (5.2 g, 60%) as a light brown solid, m.p. 126—128 °C; anion analysis, molar ratios: trifluoroacetate 0.73; chloride 0.27; $\nu_{max.}$ 1 670 (C=O), 1 585, 1 570, 1 460, and 1 405 cm^{-1} (C=C); δ[$(CD_3)_2SO$] 3.78 (3 H, s, OMe), 3.81 (3 H, s, OMe), 4.27 (2 H, s, Ar_2CH_2), 6.82—6.91 (3 H, m, ArH), 7.29 (1 H, d, *J* 9.8 Hz, pyridazine-H), 7.38 (1 H, d, *J* 9.8 Hz, pyridazine-H), and 7.80—7.92 (4 H, m, ArH); *m/z* (positive ion FAB) 466/8 ($M^+ - 1$, 100/40%), 360/2 (45/15), 235(87), and 91(45).

(c) *Preparation of the mixed iodonium salts* (**2b—d**) via *the iododichloride* (**16**). 1. *Formation of the iododichloride* (**16**). A solution of the iodoanisole (**4**) (40 g, 110 mmol) in chloroform (500 ml) was treated with chlorine gas generated by addition of conc. hydrochloric acid (90 ml) dropwise to potassium permanganate (14.4 g). A bright yellow precipitate appeared which was filtered off under reduced pressure and thoroughly washed with chloroform (200 ml), then dried *in vacuo* at ambient temperature to give 3-*chloro*-6-[5-(*dichloroiodo*)-2-*methoxybenzyl*]*pyridazine* (**16**) (43. 7 g, 92%), m.p. 110—114 °C (Found: C, 32.7; H, 2.3; N, 6.3. $C_{12}H_{10}Cl_3IN_2O$ requires C, 33.4; H, 2.3; N, 6.5%); $\nu_{max.}$ 1 595, 1 570, 1 490, 1 460, and 1 405 cm^{-1} (C=C); δ[$(CD_3)_2SO$] 3.73 (3 H, s, OMe), 4.22 (2 H, s, Ar_2CH_2), 6.85 (1 H, d, *J* 9.2 Hz, ArH), 7.74 (3 H, m, 2 × ArH + pyridazine-H), and 7.80 (1 H, d, *J* 9.8 Hz, pyridazine-H).

2. *Mixed iodonium salts* (**2b—d**). The iododichloride (**16**) (3.4 g, 8 mmol) was suspended in acetonitrile (40 ml) and treated with sodium acetate (2.6 g, 32 mmol). After being stirred for 4 h the pale cream mixture was filtered under reduced pressure. The filtrate was cooled to −30 °C and treated with anisole (0.88 g, 8 mmol) followed by the dropwise addition of TFA (10 ml, 130 mmol) during 1 h. The resulting mixture was stirred under a blanket of nitrogen at −30 °C for 1 h then allowed to warm to ambient overnight. The reaction mixture was treated with dichloromethane (50 ml) then basified, with cooling, to pH 4 with 40% w/v aqueous sodium hydroxide. The dichloromethane layer was separated and washed with water (30 ml). The organic phase was then dried ($MgSO_4$), and evaporated under reduced pressure to low volume. The resulting extract was slowly added to cooled, rapidly stirred diethyl ether (50 ml), and the light brown precipitate was filtered off under reduced pressure, washed with diethyl ether, and dried *in vacuo* at ambient temperature to give {3-[(6-chloropyridazin-3-yl)methyl]-4-methoxyphenyl}-(4-methoxyphenyl)iodonium trifluoroacetate (**2b**) (2.5 g, 54%), m.p. 126—128 °C. This material was spectroscopically identical with that prepared above (method b).

The reaction described above was repeated using the following quantities of reagents: iododichloride (**16**) (13.7 g, 32 mmol), sodium acetate (10.5 g, 128 mmol), acetonitrile (200 ml), 1,3-dimethoxybenzene (4.4 g, 32 mmol), and TFA (40 ml, 520 mmol) to give {3-[(6-chloropyridazin-3-yl)methyl]-4-methoxyphenyl}-(2,4-dimethoxyphenyl)iodonium trifluoroacetate (**2c**) (11.8 g, 60%) as an off-white solid, m.p. 113—115 °C; anion analysis, molar ratio: trifluoroacetate (0.92; sulphate 0.05; chloride 0.02; $\nu_{max.}$ 1 665 (C=O), 1 585, 1 495, 1 460, and 1 410 cm^{-1} (C=C); δ 3.81 (3 H, s, OMe), 3.85 (3 H, s, OMe), 3.89 (3 H, s,

OMe), 4.28 (2 H, s, Ar_2CH_2), 6.47—6.55 (2 H, m, ArH), 6.86 (1 H, d, *J* 8.5 Hz, ArH), 7.32 (1 H, d, *J* 9.7 Hz, pyridazine-H), 7.40 (1 H, d, *J* 9.7 Hz, pyridazine-H), 7.73 (1 H, d, *J* 8.5 Hz, ArH), 7.81 (1 H, d, *J* 2.3 Hz, ArH), and 7.86 (1 H, dd, *J* 8.5 and 2.3 Hz, ArH); *m/z* (positive ion FAB) 497 (M^+, 16%), 361 (27), 277 (50), 235 (72), 185 (100), and 93 (100).

Repetition of the reaction described for the preparation of compound (**2b**) but with the following quantities of reagents: iododichloride (**16**) (3.4 g, 8 mmol), silver acetate (2.7 g, 16 mmol), acetonitrile (50 ml), 1,3,5-trimethoxybenzene (1.34 g, 8 mmol), and TFA (10 ml, 130 mmol) gave {3-[(6-chloropyridazin-3-yl)methyl]-4-methoxyphenyl}-(2,4,6-trimethoxyphenyl)-iodonium trifluoroacetate (**2d**) (3.5 g, 68%) as an off-white solid, m.p. 158—160 °C; anion analysis, molar ratio: trifluoroacetate 0.91; sulphate 0.05; chloride 0.04; $\nu_{max.}$ 1 665 (C=O), 1 585, 1 460, and 1 415 cm^{-1} (C=C); δ 3.80 (3 H, s, OMe) 3.86 (3 H, s, OMe), 3.89 (6 H, s, 2 × OMe), 2.47 (2 H, s, Ar_2CH_2), 6.15 (2 H, s, 2 × ArH), 6.81 (1 H, d, *J* 8.6 Hz, ArH), 7.34 (1 H, d, *J* 9.4 Hz, pyridazine-H), 7.42 (1 H, d, *J* 9.4 Hz, pyridazine-H), 7.74 (1 H, d, *J* 3.9 Hz, ArH), and 7.85 (1 H, dd, *J* 8.6 and 3.9 Hz, ArH); *m/z* (positive ion FAB) 528 (M^+ + 1, 34%), 294 (16), 181 (15), 121 (67), and 91 (67).

(d) {3-[(6-*Chloropyridazin*-3-*yl*)*methyl*]-4-*methoxyphenyl*}-*phenyliodonium trifluoroacetate* (**2e**). (Diacetoxyiodo)benzene (64.4 g, 200 mmol) was suspended in TFA (80 ml, 1.04 mol). The resultant mixture was stirred, and cooled with an ice–water-bath. The cooled mixture was treated with a solution of the anisole (**3**) (46.9 g, 200 mmol) in TFA (80 ml, 1.04 mol). The resultant mixture was stirred at 0—10 °C for 4 h, and was then allowed to warm to ambient temperature overnight. The reaction mixture was cooled to 10 °C after a total reaction time of 20 h, then treated with dichloromethane (200 ml) followed by demineralised water (400 ml). The mixture was basified to pH 2 using 40% w/v aqueous sodium hydroxide, with the internal temperature kept below 30 °C. The resulting mixture was filtered under reduced pressure and the insoluble product was dried *in vacuo* to give the title compound (**2e**) (85.03 g, 77%) as a pale pink solid. Extraction of the filtrate with dichloromethane (200 ml) and concentration to low volume, followed by precipitation from cooled diethyl ether (500 ml), afforded a further crop (21 g, 19%) of the desired product (**2e**), m.p. 148—151 °C: anion analysis, molar ratio: trifluoroacetate 0.91; chloride 0.06; sulphate 0.03; $\nu_{max.}$ 1 660 (C=O), 1 580, and 1 560 cm^{-1} (C=C); δ[$(CD_3)_2SO$] 3.80 (3 H, s, OMe), 4.25 (2 H, s, Ar_2CH_2), 7.15 (1 H, d, *J* 8.8 Hz, ArH), 7.51 (2 H, t, *J* 8.8 Hz, 2 × ArH), 7.58—7.69 (1 H, m, ArH), 7.63 (1 H, d, *J* 9.8 Hz, pyridazine-H), 7.86 (1 H, d, *J* 9.8 Hz, pyridazine-H), 8.11 (1 H, d, *J* 3.5 Hz, ArH), 8.14—8.25 (3 H, m, 3 × ArH); *m/z* (positive ion FAB) 436/438 (M^+ − 1, 23/10%), 360 (18), 348 (12), 305 (12), 217 (15), 141 (23), 107 (12), 81 (20), 78 (11), and 39 (100).

L-3,5-*Dibromo*-3′-[(6-*chloropyridazin*-3-*yl*)*methyl*]-4′-O-*methyl*-N-*trifluoroacetylthyronine Methyl Ester* (**6**) *from the Symmetrical Iodonium Salt* (**2a**).—The iodonium trifluoroacetate (**2a**) (814 g, 1.15 mol) was dissolved in dichloromethane (5.7 l) and the protected dibromotyrosine (**5**) (516 g, 1.15 mol) was added, followed by copper bronze (75 g) and triethylamine (190 g, 1.85 mol). The mixture was stirred at room temperature for 18 h, ether (1 425 ml) was added, and the mixture was poured onto a silica column (8 kg) packed in dichloromethane–ether (80:20 v/v). Elution with dichloromethane–ether (70:30) as solvent gave, after a forerun of 10 l, the partially purified product (**6**) contaminated with the iodoanisole (**4**) and a small amount of the starting dibromotyrosine (**5**). The total weight recovered after evaporation of the fractions was 1.06 kg. This was absorbed onto silica (4 kg) and the mixture was added to a column of silica (10 kg) packed in dichloromethane. Elution with 4—6% butan-2-one in dichloromethane gave the iodoanisole (**4**) followed by the required compound. Evaporation of the appropriate fractions yielded the *title compound* (**6**) (394 g, 50%) as a glass. A mixed fraction (80 g) was also obtained. Chromatography of this mixture gave a further sample of the *title compound* (**6**) (40 g, 5%) (Found: M^+, 678.933 ± 0.014. $C_{24}H_{19}Br_2ClF_3N_3O_5$ requires *M*, 678.932); $\nu_{max.}$(liq. film) 3 300 (NH), 3 050 (ArC*H*), 2 950 (CH), 1 745, 1 720, 1 545 (C=O), 1 500, 1 450, and 1 405 cm^{-1}; δ 3.10 (1 H, dd, *J* 14.1 and 6.7 Hz, β-H), 3.26 (1 H, dd, *J* 14.1 and 6.7 Hz, β-H), 3.77 (3 H, s, CO_2Me), 3.83 (3 H, s, OMe), 4.29 (2 H, s, Ar_2CH_2), 4.86 (1 H, ddd, *J* 8.4, 6.7, and 6.7 Hz, α-H), 6.63 (1 H, dd, *J* 8.4 and 3.4 Hz, ArH), 6.72 (1 H, d, *J* 3.4 Hz, ArH), 6.81 (1 H, d, *J* 8.4 Hz, ArH), 7.17 (1 H, d, *J* 8.4 Hz, NH), 7.24 (1 H, d, *J* 9.8 Hz, pyridazine-H), 7.37 (2 H, s, 2 × ArH), and 7.38 (1 H, d, *J* 9.8 Hz, pyridazine-H); *m/z* (very weak FAB spectrum) 680/2/4/6 (M^+ + 1, very weak).

3-*Chloro*-6-(5-*chloro*-2-*methoxybenzyl*)*pyridazine* (**7**; X = Cl).—Repetition of the above reaction with the iodonium salt (**2a**) in which the counter-ion was Cl^-:$CF_3CO_2^-$, 0.8:0.2, mol/mol, gave the coupled product (**6**), isolated in 12% yield. The iodoanisole (**4**) fraction contained an additional component. Subtracting the peaks due to the iodoanisole (**4**) from the ^1H n.m.r. spectrum of the mixture gave the following spectrum: δ 3.79 (3 H, s, OMe), 4.29 (2 H, s, CH_2), 6.81 (1 H, d, *J* 9 Hz, ArH), 7.2 (2 H, m, ArH), 7.24 (1 H, d, *J* 9 Hz, pyridazine-H), and 7.37 (1 H, d, *J* 9 Hz, pyridazine-H). The chemical-shift differences of the protons of the anisole ring for this compound, when compared with the iodo anisole (**4**), are entirely consistent with a chloro- in place of an iodo-substituent [Δδ (**4**) − δ(**7**; X = Cl): *ortho* to methoxy, −0.16; *meta* to methoxy, +0.35]. L.c.—m.s. analysis of the mixture gave a clear separation of the two components and confirmed the unknown component to be the chloroanisole (**7**; X = Cl). Thus, protonated molecular ions at *m/z* 269/271/273 in the proportions 9:6:1 were produced, consistent with the isotope pattern expected of a compound containing 2 chlorine atoms. The molecular weight of 268 agrees with the empirical formula $C_{12}H_{10}Cl_2N_2O$.

The molar ratio of iodoanisole (**4**) to chloroanisole (**7**; X = Cl) recovered was 1:0.72 by ^1H n.m.r. spectroscopy. The estimated recovery of the iodoanisole (**4**) was essentially quantitative, whilst the chloroanisole was obtained in *ca.* 75% yield.

Preparation of Diaryl Ether (**6**) *from Mixed Iodonium Salts* (**2b—e**).—Following the general procedure described above for the preparation of the diaryl ether (**6**) the mixed iodonium salts (**2b—e**) were treated with the dibromotyrosine derivative (**5**). Purification of the crude products by chromatography gave the required diaryl ether (**6**) and the alternative diaryl ethers (**18a—d**). The ratios of the two products, and the yields of the required diaryl ether (**6**), are given in Table 2.

L-3,5-*Dibromo*-4′-O-*methyl*-3-[(6-*oxo*-1,6-*dihydropyridazin*-3-*yl*)*methyl*]-N-*trifluoroacetylthyronine methyl ester* (**8**).—The fully protected thyronine (**6**) (470 g, 0.69 mol) was dissolved in hot acetic acid (2.35 l), anhydrous sodium acetate (117.5 g, 1.43 mol) was added, and the solution was refluxed for 1.5 h. Water (2.35 l) was added and the reaction mixture was left to cool overnight. The solid was filtered off, washed with water, dissolved in dichloromethane (1.5 l), and this solution was washed successively with aqueous sodium carbonate and water, dried ($MgSO_4$), and filtered. The filtrate was brought to reflux temperature and light petroleum (2 l) was added. The solution was left to cool overnight, and the solid was filtered off and washed with light petroleum–dichloromethane (3:1) and dried (hot-air drier, 60 °C, 18 h) to give the *title compound* (**8**) (314 g, 69%), m.p. 179—80 °C (Found: C, 43.4; H, 2.9; N, 6.2; Br, 24.2. $C_{24}H_{20}Br_2F_3N_3O_6$ requires C, 43.5; H, 3.0; N, 6.3; Br, 24.1%);

$\nu_{max.}$ 3 260 (NH), 1 740, 1 700, 1 675, 1 650 (C=O), 1 600, 1 560, and 1 550 cm^{-1} (C=C); δ 3.08 (1 H, dd, *J* 13.6 and 7.0 Hz, β-H), 3.26 (1 H, dd, *J* 13.6 and 7.0 Hz, β-H), 3.79 (3 H, s, CO_2Me), 3.84 (3 H, s, OMe), 3.87 (2 H, s, Ar_2CH_2), 4.86 (1 H, ddd, *J* 8.5, 7.0, and 7.0 Hz, α-H), 6.57 (1 H, d, *J* 3.9 Hz, ArH), 6.65 (1 H, dd, *J* 8.5 and 3.9 Hz, ArH), 6.79 (1 H, d, *J* 8.5 Hz, ArH), 6.86 (1 H, d, *J* 9.7 Hz, pyridazine-H), 7.16 (1 H, d, *J* 9.7 Hz, pyridazine-H), 7.35 (2 H, s, 2 × ArH), and 7.42 (1 H, d, *J* 8.5 Hz, NH).

L-3,5-*Dibromo*-3′-[(6-*oxo*-1,6-*dihydropyridazin*-3-*yl*)*methyl*]-*thyronine* (**1**).—A solution of conc. hydrobromic acid (48%; 1.55 l) and glacial acetic acid (1.55 l) was purged with nitrogen for 10 min, the protected pyridazinone (**8**) (314 g, 0.47 mol) was added, and the solution was refluxed under nitrogen for 19 h. Hot water (10.7 l) was added to the reaction mixture and the solution was left to cool. The solid was filtered off, washed with water, and dried (hot-air drier, 60 °C, 5 h) to give the *title compound* (**1**) as the *hydrated hydrobromide salt* (2.81 g, 95%), m.p. 226 °C (Found: C, 37.7; H, 3.2; N, 6.6; Br, 36.7. $C_{20}H_{17}Br_2N_3O_5$·HBr·1.5H_2O requires C, 37.1; H, 3.3; N, 6.5; Br, 37.0%). This material was combined with another batch of hydrobromide salt and recrystallised as follows: A mixture of 94% industrial methylated spirits (13 l) and water (19 l) was heated to reflux (solution temperature 78 °C) and the thyronine hydrobromide (500 g, 0.81 mol) was added to give a clear solution. The solution temperature was maintained at 78 °C for 1 h and left to cool. The solid was separated by filtration, washed thoroughly, and dried (fluid-bed drier, 100 °C, 4 h; convection oven, 160 °C, 2.5 h) to give the title compound (**1**) (360 g, 83%), m.p. 251—253 °C; $[\alpha]_D^{25}$ −11.34° [*c* 1.00 in EtOH–5M-NaOH (5:3 v/v)] (Found: C, 44.0; H, 3.3; N, 7.6; Br, 29.45. Calc. for $C_{20}H_{17}Br_2N_3O_5$·0.3H_2O: C, 44.1; H, 3.25; N, 7.7; Br, 29.3%); $\nu_{max.}$ 3 500—2 800 (NH, OH, CH), 1 670, 1 660 (CO), 1 590, 1 550, and 1 510 cm^{-1} (C=C); δ(NaOD–D_2O) 2.76 (1 H, dd, *J* 14 and 7 Hz, β-H), 2.96 (1 H, dd, *J* 14 and 5 Hz, β-H), 3.49 (1 H, dd, *J* 7 and 5 Hz, α-H), 3.91 (2 H, s, CH_2Ar_2), 6.21 (1 H, s, ArH), 6.60 (2 H, s, ArH), 6.67 (1 H, d, *J* 9 Hz, pyridazine-H), 7.09 (1 H, d, *J* 9 Hz, pyridazine-H), and 7.51 (2 H, s, ArH).

Derivatisation using (*R*)(+)-1-phenylethyl isocyanate followed by h.p.l.c. analysis of the diastereoisomeric ureas formed showed the sample to contain 6.1% of the D-enantiomer.

Preparation of Bis{4-*methoxy*-3-[(6-*oxo*-1,6-*dihydropyridazin*-3-*yl*)*methyl*]*phenyl*}*iodonium Trifluoroacetate* (**10**).—To a solution of iodine tristrifluoroacetate [prepared from iodine (6.35 g)] in acetic anhydride (50 ml) cooled to −20 °C was added dropwise a solution of 6-(2-methoxybenzyl)pyridazin-3(2*H*)-one (**9**) (21.7 g) in TFA, with the temperature of the reaction mixture kept between −10 and −5 °C. The reaction mixture was then allowed to warm gradually to room temperature and was stirred at this temperature for 65 h. The solvents were then removed under reduced pressure and the residue was dissolved in a methanolic solution of sodium sulphate (50 g) and sodium acetate (50 g). The precipitate was collected, washed briefly with dichloromethane, then triturated under ethyl acetate–diethyl ether (1:1) to give a yellow solid, which was filtered off and dried to give bis{4-methoxy-3-[(6-oxo-1,6-dihydropyridazin-3-yl)methyl]phenyl}iodonium trifluoroacetate (**10**) (5.0 g, 11%), m.p. 146—151 °C; δ[$(CD_3)_2SO$] 3.82 (3 H, s, OMe), 3.85 (2 H, s, CH_2), 6.77 (1 H, d, *J* 9.3 Hz, Pyrid-H), 7.11 (1 H, d, *J* 9.3 Hz, Pyrid-H), 7.25 (1 H, d, *J* 9.5 Hz, ArH), 7.92 (1 H, d, *J* 1.5 Hz, ArH), 8.03 (1 H, dd, *J* 1.5 and 9.5 Hz, ArH), and 12.55 (1 H, br s, NH).

Attempted Reaction of Bis{4-*methoxy*-3-[(6-*oxo*-1,6-*dihydropyridazin*-3-*yl*)*methyl*]*phenyl*}*iodonium Trifluoroacetate* (**10**) *with the Tyrosine* (**5**).—To a solution of the iodonium salt (**10**) (5.0 g), 3,5-dibromo-*N*-trifluoroacetyltyrosine methyl ester (**5**) (3.75 g), and triethylamine (3.0 g) in dichloromethane (50 ml) was added copper bronze (1.0 g) and the mixture was stirred at room temperature for 8 days, then filtered, and the filtrate was washed successively with aqueous acetic acid and aqueous sodium chloride, dried, and evaporated. The residue was chromatographed on silica gel [toluene–acetic acid (5:1)] to give 4-iodo-2-[(6-oxo-1,6-dihydropyridazine-3-yl)methyl]-anisole (1.25 g, 50%), m.p. 167—170 °C; δ 3.80 (3 H, s, OMe), 3.87 (2 H, s, CH_2), 6.65 (1 H, d, *J* 9.3 Hz, ArH), 6.88 (1 H, d, *J* 10.4 Hz, Pyrid-H), 7.17 (1 H, d, *J* 10.4 Hz, Pyrid-H), 7.45 (1 H, d, *J* 1.5 Hz, ArH), and 7.53 (1 H, dd, *J* 1.5 and 9.3 Hz, ArH); and 6-{3-[6-(3-*iodo*-6-*methoxybenzyl*)-3-*oxo*-2,3-*dihydropyridazin*-2-*yl*]-6-*methoxybenzyl*}*pyridazin*-3(2H)-*one* (**11**) (0.39 g, 9.8%), m.p. 126—128 °C (Found: C, 51.5; H, 3.8; N, 10.0; I, 22.6. $C_{24}H_{21}IN_4O_4$ requires C, 51.8; H, 3.8; N, 10.1; I, 22.8%); $\nu_{max.}$(Nujol) 1 675 cm^{-1}; δ[$(CD_3)_2SO$] 3.76 (3 H, s, OMe), 3.81 (3 H, s, OMe), 3.86 (4 H, 2 × CH_2), 6.80 (1 H, d, *J* 9.5 Hz, Pyrid-H), 6.85 (1 H, d, *J* 8.7 Hz, ArH), 6.95 (1 H, d, *J* 9.5 Hz, Pyrid-H), 7.07 (1 H, d, *J* 8.7 Hz, ArH), 7.30—7.40 (4 H, m, ArH and Pyrid-H), and 7.55 (2 H, m, ArH).

Reaction of Bis(3-*isopropyl*-4-*methoxyphenyl*)*iodonium Perchlorate* (**12**) *with the Tyrosine* (**5**) *and the Pyridazinone* (**13**).—Iodine tristrifluoroacetate [prepared as above from iodine (80 g)] in acetic anhydride (500 ml) was treated at 5 °C with a solution of 2-isopropylanisole (200 g) in TFA (180 ml). The reaction mixture was then allowed to warm slowly to room temperature. After 10 h the solvents were removed under reduced pressure and the residue was treated with aqueous sodium acetate–sodium perchlorate. The compound was then extracted into dichloromethane, and the extracts were dried and diluted with light petroleum to precipitate *bis*(3-*isopropyl*-4-*methoxyphenyl*)*iodonium perchlorate* (**12**) as a brown solid (135 g, 38%), m.p. 157—159 °C (Found: C, 45.9; H, 5.0; Cl, 6.5; I, 24.1. $C_{20}H_{26}ClIO_6$ requires C, 45.8; H, 5.0; Cl, 6.8; I, 24.2%).

A solution of the above iodonium salt (**12**) (5.25 g, 0.01 mol), 3,5-dibromo-*N*-trifluoroacetyltyrosine methyl ester (**5**) (4.49 g, 0.01 mol), and 6-methylpyridazin-3(2*H*)-one (**13**) (1.10 g, 0.01 mol) in dichloromethane (20 ml) was treated with triethylamine (2.0 g) and copper bronze (0.5 g) and the mixture was stirred at room temperature overnight. The mixture was filtered, washed successively with aqueous sodium hydroxide and aqueous sodium chloride, dried, and evaporated. The residue was chromatographed on silica gel to give 2-(3-*isopropyl*-4-*methoxyphenyl*)-6-*methylpyridazin*-3(2H)-*one* (**15**) as the major product (1.13 g, 44%), m.p. 47—49 °C (Found: C, 69.8; H, 7.1; N, 10.8. $C_{15}H_{18}N_2O_2$ requires C, 69.7; H, 7.0; N, 10.8%); $\nu_{max.}$ 1 664, 1 597, 1 498, and 1 464 cm^{-1}; δ 1.15 (6 H, d, *J* 6.9 Hz, $ChMe_2$), 2.30 (3 H, s, ArMe), 3.29 (1 H, sextet, *J* 6.9 Hz, $CHMe_2$), 3.84 (3 H, s, OMe), 6.94 (1 H, d, *J* 9.5 Hz, Pyrid 4-H), 7.02 (1 H, m, Ar 5-H), 7.28 (2 H, m, Ar 2- and 6-H), and 7.39 (1 H, d, *J* 9.5 Hz, Pyrid 5-H); *m/z* 258 (M^+, 100%) and 243 ($M^+ - CH_3$, 80). In addition to unchanged 3,5-dibromo-*N*-trifluoroacetyltyrosine methyl ester (**5**) and 4-iodo-2-isopropylanisole (**14**), a trace amount of 3,5-dibromo-3′-isopropyl-4′-*O*-methyl-N-trifluoroacetylthyronine methyl ester was observed in the crude reaction mixture, by t.l.c.

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