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Process Development of Voriconazole: A Novel Broad-Spectrum Triazole Antifungal Agent

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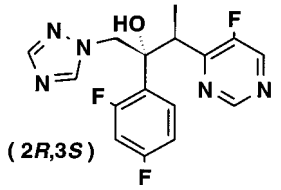
Abstract:

In the synthesis of (2*R*,3*S*)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (voriconazole), the relative stereochemistry is set in the addition of a 4-(1-metalloethyl)-5-fluoropyrimidine derivative to 1-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)-1-ethanone. The diastereocontrol of this reaction has been examined by variation of pyrimidine substitution pattern and by changes in the metalation and reaction conditions. Excellent diastereoselection (12:1) is obtained using an organozinc derivative of 6-(1-bromoethyl)-4-chloro-5-fluoropyrimidine. After removal of the chlorine from the pyrimidine ring, the absolute stereochemistry of voriconazole is established via a diastereomeric salt resolution process using (1*R*)-10-camphorsulfonic acid. Synthetic routes to the pyrimidine partner have also been evaluated. The initial six-step development route from 5-fluorouracil has been superseded by a four-step synthesis involving fluorination of methyl 3-oxopentanoate and cyclisation with formamidine acetate.

Introduction

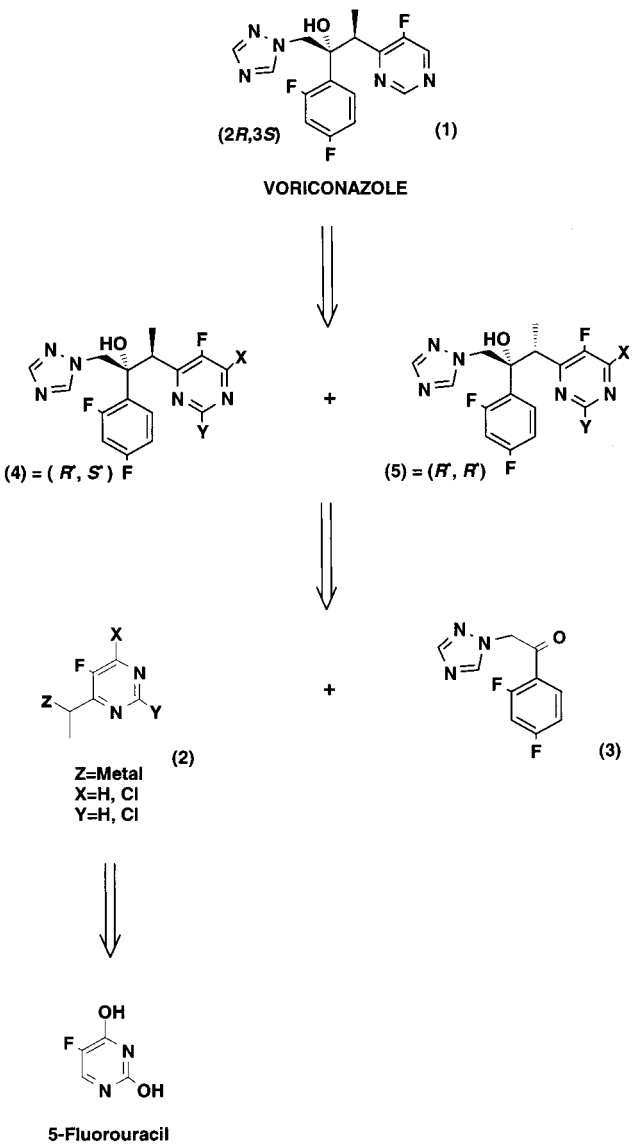
Voriconazole (**1**) is currently undergoing phase III, comparative clinical trials to establish its full potential as a broad-spectrum antifungal agent.[1] A number of synthetic



VORICONAZOLE (1)

approaches to voriconazole have been evaluated in our laboratories. This report focuses on the selection and development of the preferred commercial route. The strategy for enantioselective synthesis of voriconazole (**1**) is outlined in the form of a retrosynthetic analysis in Scheme 1. The single enantiomer (2*R*,3*S*) of voriconazole is obtained from the racemate **4** via a resolution process. The racemic intermediate **4** is assembled by a diastereoselective addition of a substituted ethylpyrimidine-organometallic derivative **2** to the arylketone[1] **3**, which is an intermediate in the commercial synthesis of Diflucan. Because chlorine substituents are compatible with organometallics, and easily removed, chloropyrimidines were chosen for study. These in turn could be accessed from readily available 5-fluorouracil through functionalization[2,3] of the dichlorinated derivative.

Scheme 1



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(3) (a) Sing, Y. L.; Len F. *J. Heterocycl. Chem*. **1989**, *26*, 7. (b) Hamamichi, N.; Miyasaka, T. *J. Org. Chem*. **1994**, *59*, 1525.

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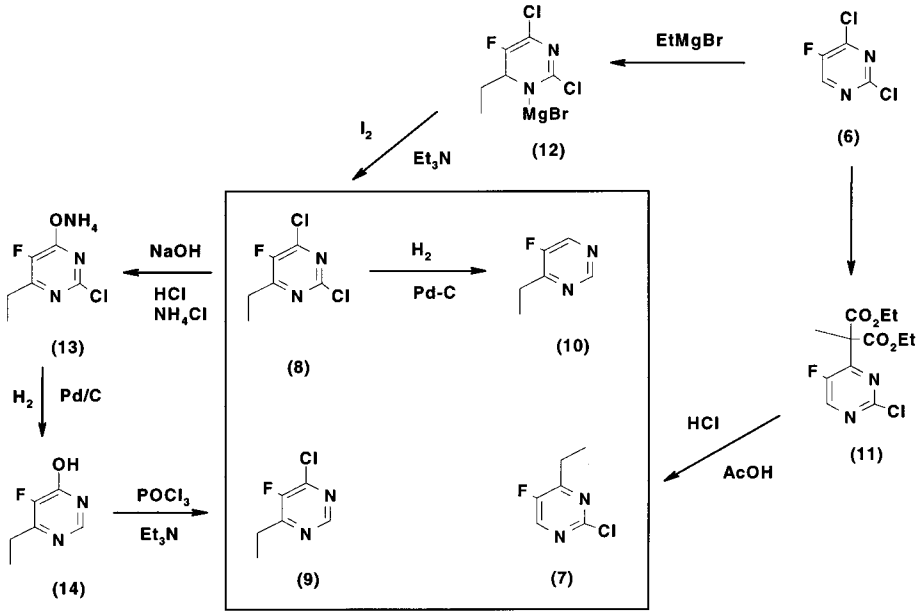
Scheme 2



In the development of this synthesis there are three key issues to be addressed:

- to find an expedient synthesis of the preferred ethylpyrimidine intermediate.
- development of a high-yielding diastereoselective process to form **4** as a racemic (*R**,*S**) mixture with minimal formation of the diastereomer **5**.
- identification of a process to resolve **4**; the racemic precursor of voriconazole.

In Scheme 1, our proposal involves adding a metalated ethylpyrimidine to a ketone partner to give the (*R**,*S**) diastereoisomer. The addition of carbanions[4,5] to carbonyls possessing an α-hetereoatom[6] substituent often proceed with good diastereoselectivity. Indeed, acetophenones substituted with α-halogen[7] and α-dialkylamino[8] groups have been reacted with organometallic reagents to give predominantly the same relative stereochemistry as that of compound **4**. While the metalation of alkylheterocycles and subsequent reaction with electrophiles have been reported in the literature, there are very few examples of ketone[9] reaction partners and little information about diastereocontrol. In our work to establish diastereocontrol we therefore investigated two factors:

(i) evaluation of different methodologies for preparing metalated ethylpyrimidines **2** and the reaction of these derivatives with the ketone partner **3**,

(ii) evaluation of a series of differently substituted ethylpyrimidines as partners in the addition reaction.

(4) Masamune. S.; Choy. W.; Kerdesky, F. A. J.; Imperiali. B. *J. Am. Chem. Soc*. **1981**, *103*, 1566.
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Results and Discussion

The first synthetic challenge was to identify a versatile synthesis of the ethyl 5-fluoropyrimidine reaction partners for addition to ketone **3**. The readily commercially available compound 5-fluorouracil possesses a 5-fluoro substituent on a pyrimidine framework. We therefore investigated potential methods to introduce an ethyl group and provide optional substituents on the 2- and 6-positions.

Synthesis of Pyrimidine Substrates (**Scheme 2).** By using a literature[10] method, 5-fluorouracil was chlorinated in both the 2- and 4-positions using a mixture of phosphorus oxychloride and *N*,*N*-dimethylaniline at 95 °C. In an improved procedure, we found that quenching of the reaction mixture into 3 N HCl (at 10 °C) raised the yield from 50% to 95% by limiting the hydrolysis of chloro groups (back to 5-fluorouracil). Selective displacement of the 4-chloro group in 2,4-dichloro-5-fluoropyrimidine (**6**) was achieved with the sodium anion of diethyl methylmalonate in THF. Refluxing the product **11** in AcOH/HCl mixture resulted in complete decarboxylation and the formation of 2-chloro-4-ethyl-5-fluoropyrimidine (**7**) albeit in low isolated yield (20%), from **6**.

In a complementary sequence, **6** was reacted with ethyl magnesium bromide to give the dihydropyrimidine adduct **12**. Such adducts have been studied in the literature[2] and typically exhibit poor stability in the N−H form. The oxidation of dihydropyrimidines is usually achieved using mild reagents such as DDQ, and yields of the pyrimidine products are often very low. Using a variety of oxidation methods we found that conversion of **12** to **8** gave yields up to 25% accompanied by significant degradation of starting material. In an improved procedure, we have found that adduct **12** can be oxidised prior to quenching (presumably as the N−MgBr salt form) using a mixture of iodine and triethylamine in THF to give 2,4-dichloro-6-ethyl-5-fluoropyrimidine (**8**) in 75% yield. Reaction of **8** with 2 equiv of

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Table 1. **Reaction of Lithium and Sodium Anions of Ethylpyrimidines with (3)**

	LDA, THF, −60 °C		NaHMDS, THF, −60 °C	
pyrimidine	yield of **4** + **5** (%)	ratio **4**:**5**	yield of **4** + **5** (%)	ratio **4**:**5**
7 (X = H, Y = Cl)	0		30	1:2
8 (X = Cl, Y = Cl)	0		0	
9 (X = Cl, Y = H)	50	1.2:1	25	1:3
10 (X = H, Y = H)	0		8	1:1

aqueous NaOH at reflux gave selective displacement of the 4-chloro group. Acidification of the reaction and extraction with dichloromethane gave 2-chloro-6-ethyl-5-fluoro-4(3*H*)-pyrimidinone which was conveniently isolated as its ammonium salt, **13**. Dechlorination of **13** was achieved using catalytic hydrogenation ($Pd-C/H_2$, 50 psi, 50 °C) to provide 6-ethyl-5-fluoropyrimidin-4-one (**14**) in 80% yield. The ammonium counterion conveniently served as a stoichiometric base to neutralise the HCl formed in the hydrogenolysis. Reaction of **14** with phosphorus oxychloride and triethylamine afforded 4-chloro-6-ethyl-5-fluoropyrimidine (**9**) (90% yield).

Palladium-catalysed hydrogenation of **8** in the presence of sodium acetate base gave a 35% yield of the highly volatile oil; 4-ethyl-5-fluoropyrimidine (**10**).

Route Selection. To identify the best combination of metal and 4-ethyl-5-fluoropyrimidine, the following objectives were addressed in order:

(i) to study the effect of pyrimidine substitution pattern on diastereoselectivity using LDA or sodium hexamethyldisilazide (NaHMDS) to form the carbanions,

(ii) to apply a variety of metalation conditions with the optimum pyrimidine substrate and evaluate differences in diastereoselectivity,

(iii) to retest the effect of pyrimidine substitution pattern on diastereoselectivity using the optimum method of metalation.

(a) Selection of Optimum Pyrimidine. With all possible chlorinated 4-ethyl-5-fluoropyrimidine derivatives in hand we investigated their deprotonation with LDA (or NaHMDS) in THF and the aldol with ketone **3** (see Table 1). The dichloropyrimidine **8** was deprotonated (Scheme 3), but dimerisation to **15** occurred by displacement of the reactive 4-chloro-group[3] in preference to addition to the ketone **3**. Monochloro derivative **9** was deprotonated with LDA and gave a 50% yield of the alcohol adducts **4** and **5** as a nearly equal mixture of diastereoisomers. The 2-chloro derivative **7**, was similarly deprotonated using NaHMDS to give a 30% yield of aldol products **4** and **5**, but with an inferior isomer ratio of 1:2. Finally, 4-ethyl-5-fluoropyrimidine itself (**10**) was deprotonated using NaHMDS and reacted with ketone **3**. Although a small amount of alcohol product was formed, the main reaction observed involved addition of the carbanion across the azine bond of the ring to give a dihydropyrimidine **16** which was isolated in 75% yield.

From the survey of ethylfluoropyrimidine derivatives, it was clear that the lithium anion of the 4-chloro-substituted compound **9** gave the best yield of the desired diastereoisomer **4** (~25%). No clear explanation is available for the differences in reaction seen for the sodium and lithium anions of 4- and 2-chloro derivatives.

The following observations were made from a further study of the reaction of **9** with **3** using LDA as a base:

(1) The lithium anion of **9** has poor stability at temperatures above −40 °C and tends to dimerize through self-addition (cf. compound **16**).

(2) Maximum conversion of the ketone **3** appears to be ~50%. Such ketones are known[11a] to undergo facile enolisation in the presence of lithium-carbanions or -alkoxides, and this is expected to be partly responsible for the modest yield.

(3) Small levels of diastereoelectivity can be obtained by decreasing the polarity of the solvent (e.g., toluene/THF mixtures), but scope for using neat toluene is limited by the solubility of the reactants.

(b) Selection Of Optimum Base/Metal. The limitations associated with lithium anions of **9** coupled with the challenges of running cryogenic reactions on a large scale drew us to screen a variety of alternative anion forming methodologies. Table 2 (Schemes 3 and 4), summarizes the findings of this work.

Generation of alternative alkali metal anions (e.g., Na, K) did not improve yield or diastereoselectivity. The fact that we were unable to improve the yield beyond 50% might be due to the relative basic character of lithium, sodium, and potassium anions which may be causing competitive enolisation of the ketone **3**. It is well-known that such problems can often be overcome by switching to more covalently bound metal anions[11] which can act as potent nucleophiles without deprotonating enolisable ketones. Unfortunately, attempts to transmetalate the lithium anion and with titanium, cerium, or zirconium counterparts failed to give any desired product.

The work of Chollet[12] describes reaction of α-bromoesters with triazolyl-ketones such as **3** under Reformatsky conditions to give *β*-hydroxyesters containing a single chiral centre. The only report of Reformatsky-type reagents involving bromoalkyl heterocycles[13] involves the reaction of 2-(bromomethyl)-4-carbethoxy-1,3-oxazole with zinc dust to form an organozinc derivative which undergoes nucleophilic addition to aldehydes and ketones. Again, only one chiral centre is formed, and it is not easy therefore to predict the outcome for a diastereotopic process such as that depicted in Scheme 5. To apply this methodology to the ethyl 5-fluoropyrimidines we first reacted **9** with NBS in the presence of AIBN initiator to obtain **17**. Reaction of **17** with magnesium, zinc, or manganese all provided the corresponding organometals and gave modest yields of the products **4** and **5**. Furthermore, the zinc reaction (activated zinc in refluxing THF) gave an improvement in diastereoselectivity

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Scheme 3

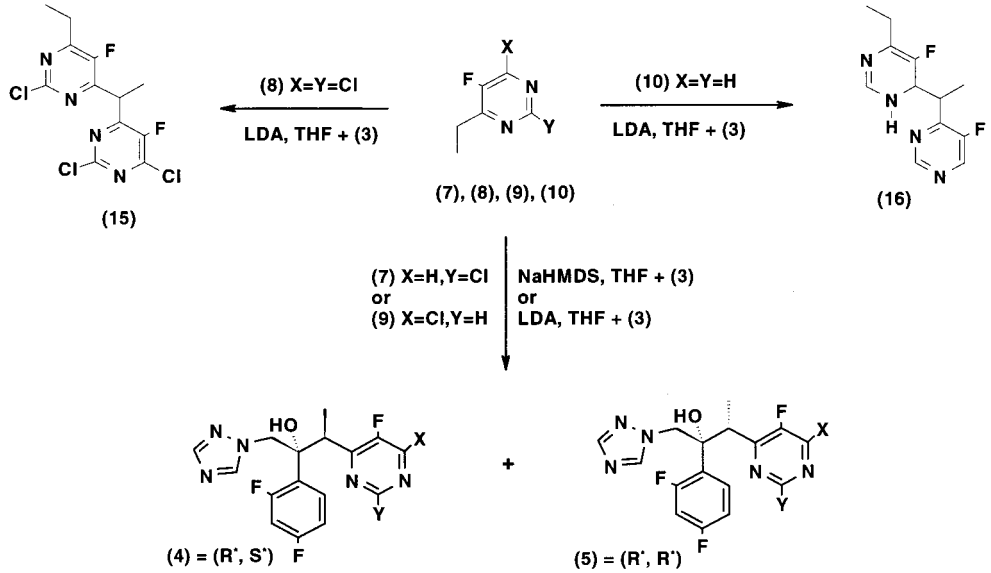


Table 2. **Evaluation of Various Metalation Procedures**

pyrimidine	methodology	yield (%)	ratio of **4**:**5**[a]
9	LDA, toluene/THF, −60 °C	50	55:45
9	LDA, $ClTi(OPr)_3$, THF, −60 °C	0	
9	NaHMDS, THF, −60 °C	25	25:75
9	LDA, $ZnCl_2$, THF, 0 °C	44	40:60
9	KHMDS, THF, −60 °C	25	25:75
9	LDA, $CeCl_3$, THF, 0 °C	0	
9	LDA, $Zr(OBu)_4$, THF, 0 °C	0	
9	Et_3N, $TfOB(Bu)_2$, THF, 0 °C	0	
17	Zn, THF, reflux	50	64:36
17	Mg (cat. iodine), THF, 25 °C	12	50:50
17	Mn (cat. iodine), THF, reflux	34	48:52

[a] The ratio of **4** to **5** was estimated by HPLC relative peak area calculations.

(ratio of **4**:**5** = 2:1) without the need for cryogenic conditions.

(c) Confirmation Of Optimum Pyrimidine. Following the successful application of the Reformatsky reaction of **17** with ketone **3**, we next prepared the bromo-derivatives of ethyl pyrimidines **7**, **8**, and **10**. All of these were accessed in the same way as **17** via radical bromination with NBS in the presence of AIBN to give **18**, **19**, and **20**, respectively. These, together with **17**, were then individually reacted with ketone **3** in refluxing THF in the presence of zinc metal, in an attempt to identify the preferred coupling partner with which to access voriconazole. The end of reaction profiles are compared in Table 3. For simplicity, only pyrimidine-containing compounds are presented, and these are normalized to percentage values assuming equivalent HPLC response factors. As well as the two product diastereomers, the starting materials, and the product of debromination, two other products were also observed in the reaction mixture, the Wurtz-coupled **21** and the dipyrimidine **22** depicted in Scheme 4.

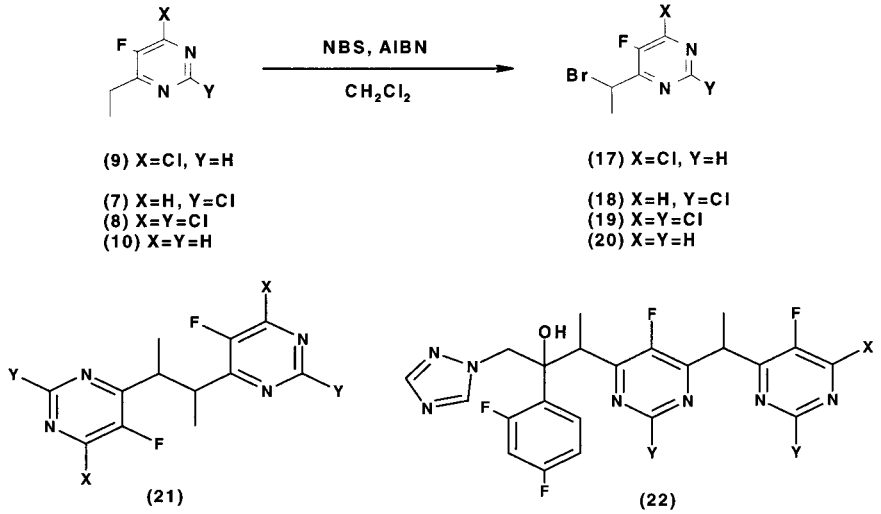
It can be seen from these results that the bromoethyl pyrimidines **17** and **20** gave the highest yields (∼70%) of the desired aldol products. It could be concluded that the zinc carbanions of **17** and **20** are more nucleophilic in character[9] than the anion of **18** which gives a poor yield of aldol products. The presence of a neighbouring chlorine in the 2-position of **18** may be providing a relative increased stabilization of the anion, making it less reactive[9] towards the ketone partner. At the end of reaction, only 12−15% of unreacted carbanion remains for **17** and **20** compared with 64% for **18**.

Pyrimidine **19** on the other hand, presents an exception to the proposed trend of nucleophilic behaviour. The presence of two chlorines in the ring (including the 2-position) would be expected to further increase stabilization of the anion relative to **18**. While a similar yield (∼10%) of simple aldol products is found for both **18** and **19**, compound **19** also forms a 51% yield of bis-ethylpyrimidine aldol products **22**. A possible mechanistic rationale for this unusual result is that the aldol step might be taking place *after* bis-pyrimidine (**15**) formation. Indeed, unreacted **15** was found in the crude reaction mixture at a level of 2%. Compound **15** possess an acidic proton on the bridging methine between the pyrimidine rings. Thus, the aldol step to form **22** might be taking place via a dianion derivative of **15** with enhanced nucleophilicity.

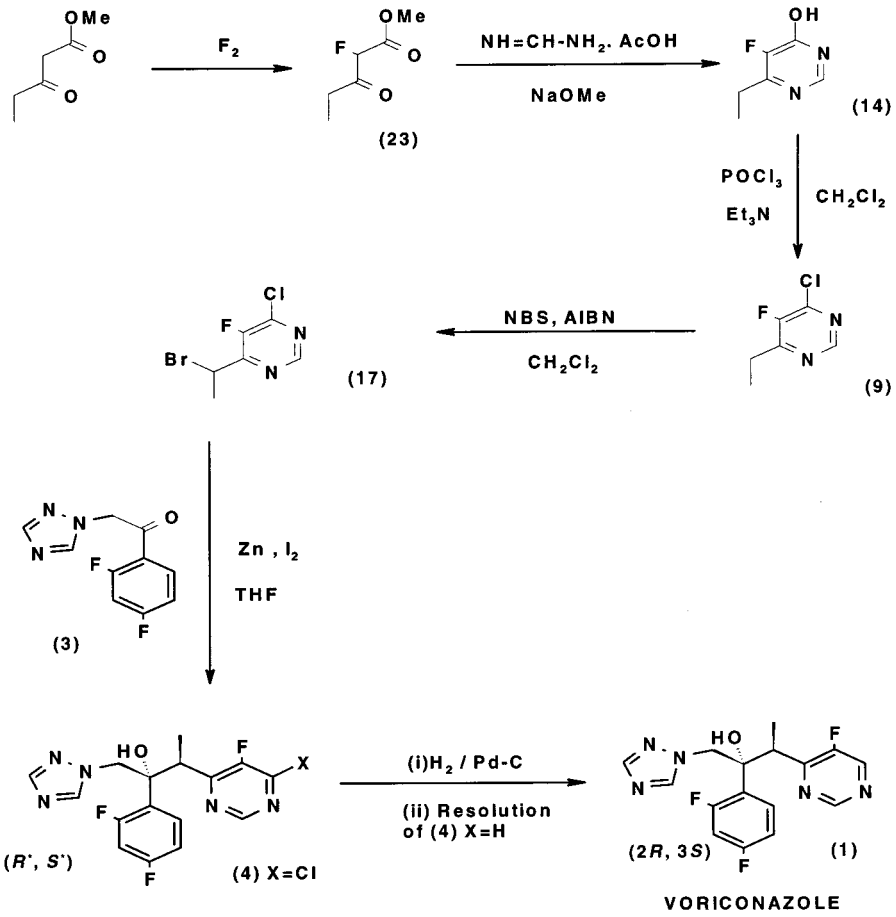
A comparison of the diastereoselectivities of the four substrates shows a range of 2:1 in favour **17** to 3:1 against **20**. Subsequent work has shown that the diastereoselectivity of this Reformatsky-type reaction is temperature-sensitive, with lower-temperature reactions with **17** giving better diastereoselectivity. Suggesting a kinetically controlled reaction one can only speculate that the transition states for each diastereomer product are very similar in energy and that the presence or absence of chlorines on the pyrimidine ring may subtly alter the geometry and energy of this to favour one diastereomer or the other. The four experiments in Table 3 confirmed that the best yield and diastereoselectivity for intermediate **4** was obtained via a Reformatsky reaction of pyrimidine **17** with ketone **3**.

Process Development of the Selected Route. Although all four pyrimidines are capable of generating voriconazole, we demonstrated that the mono-4-chloropyrimidine gives the

Scheme 4



Scheme 5



most favourable yield of the desired diastereomer and that Reformatsky-type chemistry provided the best metalation methodology. The program to develop the selected route included establishing an efficient bulk route to compound **9**, optimisation of the new organozinc methodology, and selection of the best resolution point to complete the synthesis of voriconazole.

(a) Development of an Efficient Route to 4-Ethyl-5-fluoro-4(3*H*)-pyrimidinone (14). Although 100 kg quantities of 4-chloro-6-ethyl-5-fluoropyrimidine (**9**) were readily prepared via the 5-fluorouracil chemistry, we sought a more efficient route to this compound. In partnership with F-Tech (Japan) and F2-Chemicals (UK) a highly efficient synthesis (Scheme 5) was developed in which methyl 3-oxopentanoate was fluorinated[14] with fluorine gas in a solvent to give primarily methyl 2-fluoro-3-oxopentanoate (**23**). This ester

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Table 3. **Reaction of Brominated Ethylpyrimidines[a] with 3 at Reflux**

pyrimidine	**4**[b]	**5**	unreacted pyrimidine	desbromo-pyrimidine	**21**	**22**
17 (X = Cl, Y = H)	47.5	24.0	0.0	15	4.3	9.2
18 (X = H, Y = Cl)	6.0	5.0	25	64	0.0	0.0
19 (X = Cl, Y = Cl)	5.3	4.6	8.5	28	0.0	51.6
20 (X = H, Y = H)	17.8	53.2	14.2	12.8	2.0	0.0

[a] All reactions were performed according to Experimental Section part (xv) except that addition and reaction of ketone and pyrimidine were carried out at reflux. [b] For simplicity, only pyrimidine-containing compounds are presented, and these are normalized to percentage values assuming equivalent HPLC response factors.

was then cyclised[15] with formamidine acetate in the presence of NaOMe to give 6-ethyl-5-fluoro-4(3*H*)-pyrimidinone (**14**) directly. This chemistry has now been successfully scaled to provide 100 kg quantities of the pyrimidinone **14**.

(b) Development of the Reformatsky Process. The activation of zinc metal for improved reactivity towards alkyl halides has been a subject of much interest in the literature.[16] A number of methods were tried for the formation of organozinc derivative of compound **17** with limited success. Significant variability in yield was experienced on account of factors such as zinc surface oxidation or the presence of moisture. Better results were obtained using zinc dust and treating with iodine/THF mixture before adding the reactants **17** and **3**. However, reactions were often incomplete, and results varied, depending upon the commercial grade of zinc metal. Elemental analysis of a series of zinc metals showed that those grades with high levels of lead (natural impurity) gave more reproducible results. Alternatively, addition of lead powder (5 wt %) to any grade of zinc gave a degree of consistency. The extent of conversion in these reactions critically depended upon a continuous feed of **17**/**3** mixture; after a prolonged interlude reactions would often shut-down such that further addition of reactants would not form any more product. Further work showed that the lead could be omitted if iodine is continuously added along with the supply of **17** and **3**. These observations are consistent with a need to maintain a clean/reactive zinc surface throughout the consumption of **17**. Furthermore, there is a clear trend of increased diastereoselectivity when supplying up to 2 mole equivalents of iodine together with 3 mol equiv of zinc. This effect can also be achieved by adding 2 mol equiv of other Lewis acids (e.g., $ZnCl_2$) although ZnI_2 gave best results. Running the reaction at 10 °C also improves the diastereoselectivity of the process giving diastereoselectivities in the region of 12:1. Isolation as a hydrochloride salt then gave **4** (X = Cl) of high diastereomeric purity. The addition of carbanions to carbonyl compounds is well-known, and a variety of examples have been published where diastereocontrol can be influenced via closed or open transition states. Diastereocontrol in closed transition states[4] often requires fixed enolate geometry, whilst in open transition states the stereochemistry may arranged via Felkin Anh or chelation -controlled mechanisms.[5] We believe that the experimental observations for our process are consistent with a chelation-controlled mechanism.

(c) Dechlorination of 4 and Resolution to Provide Voriconazole. Although, it would be more synthetically efficient to resolve at the earlier stage of compound **4** (X = Cl), our attempts to find a viable process were not successful, and therefore we developed the previously known resolution of racemic voriconazole. Thus, compound **4** (X = Cl, Y = H) can be dechlorinated using standard hydrogenation conditions (5% w/w palladium-on-carbon/15 psi hydrogen/25 °C) to give the racemate of voriconazole. The racemate **4** (X = H) of voriconazole can be resolved using (1*R*)-10-camphorsulfonic acid and crystallization of the required diastereomeric salt (see Scheme 5). Both of these steps have previously been described in the literature,[1] although improved yields (from 20 to 80% of theoretical maximum) in the resolution step were obtained using acetone/methanol solvent mixture. Attempts to epimerize the unwanted enantiomer have not been successful.

Conclusions

The versatile chemistry of 5-fluorouracil has enabled access to a series of substituted 4-ethyl-5-fluoropyrimidines. A variety of methods for metalation of these ethylpyrimidines have been tested with the aim of performing a diastereoselective aldol reaction with an arylketone partner. A number of 2-aryl-3-pyrimidinyl-1-triazolyl-2-butanols were prepared using Reformatsky-type methodology in which 4-(1-bromoethyl) pyrimidines were converted to their organozinc derivatives by using zinc dust in the presence of iodine before reaction with the ketone partner. This methodology offers a convenient way of generating carbanions of ethyl pyrimidines and similar heterocycles without resorting to cryogenic processes, and its scope is being explored.

From the series of pyrimidines under investigation, 4-chloro-6-ethyl-5-fluoropyrimidine gave the best diastereoselectivity favouring the (*R**,*S**) over the (*R**,*R**) isomers in a 12:1 ratio and 70% isolated yield. The (*R**,*S**) product **4** was readily converted to voriconazole following dechlorination and resolution. The possibility of an asymmetric version of this Reformatsky methodology continues to be an area of interest in our laboratories.

Experimental Section

Proton NMR data were recorded on a Varian Unity 300 spectrometer operating at 300 MHz. Mass spectra were recorded using a Finnigan Navigator running in electrospray mode. Melting points were determined on a Buchi melting point apparatus.

(i) 2,4-Dichloro-5-fluoropyrimidine (6). A stirred mixture of 5-fluorouracil (111.5 g) and phosphorus oxychloride (394.6 g) was heated to 95 °C and *N*,*N*-dimethylaniline (207 g) added over 1 h during which time an exotherm was noted. The mixture was maintained at 95 °C for 15 h, then cooled to room temperature, and cautiously quenched into 3 N aqueous hydrochloric acid solution (450 mL) at 10 °C over 4 h, maintaining the temperature below 30 °C during this

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(16) (a) Erdik, E. *Tetrahedron.* **1987**, *43*, 2203. (b) Rieke, R. D. *Science* **1989**, *246*, 1260.

operation. The mixture was extracted with dichloromethane (2 × 390 mL), and the combined extracts were washed with water (280 mL) until the aqueous washings reached pH 7 and were concentrated under reduced pressure. The residue was taken up in dimethoxyethane (190 mL) and the solution of the product used directly in the next step. Analysis of the solution by GLC indicated a yield of 95%. A sample was chromatographed on silica gel using ethyl acetate/heptane as an eluent and crystallized from heptane: mp 37.5 °C (cf. literature[10] mp 37−38 °C)

^{1}H NMR ($CDCl_3$) δ 8.5 (d, 1H) ppm.

(ii) 2-Methyl-2-(2-chloro-5-fluoropyrimidinyl-4-yl)-1,3-propanedioic Acid, Diethyl Ester (11). Sodium hydride (60% oil dispersion, 2.8 g) and diethyl methylmalonate (6 g) were reacted at −10 °C in THF (200 mL). After 30 min a solution of 2,4-dichloro-5-fluoropyrimidine (**6**) (5 g) in THF (25 mL) was added over 30 min at −10 °C. The reaction was partitioned between dichloromethane (200 mL) and water (200 mL) and acidified with acetic acid, and the layers were separated. The organic layer was concentrated under reduced pressure to an oil and chromatographed on silica gel using dichloromethane as the eluent. This gave, after combination and evaporation of the appropriate fractions, the title compound (9 g, 98% yield) which was characterised using ^{1}H NMR and mass spectrometry.

^{1}H NMR ($CDCl_3$) δ 1.3 (t, 6H), 1.9 (s, 3H), 4.6 (m, 4H), 8.5 (d, 1H) ppm.

MS (Thermospray), m/e = 304.

(iii) 2-Chloro-4-ethyl-5-fluoropyrimidine (7). Compound **11** (3.2 g) was dissolved in acetic acid (25 mL) and diluted with 5 N HCl (10 mL). After the mixture was heated at 100 °C for 16 h, it was cooled and partitioned between water (30 mL) and dichloromethane (45 mL). The dichloromethane layer was separated, dried, and concentrated under reduced pressure to give an oil. The title compound (yield = 350 mg, 21% yield) was isolated by chromatography on silica gel using dichloromethane as the eluent. The product was characterised by ^{1}H NMR and mass spectrometry.

^{1}H NMR ($CDCl_3$) δ 1.3 (t, 3H), 2.9 (m, 2H), 8.4 (s, 1H) ppm.

MS (Thermospray) m/e = 160.

(iv) 2,4-Dichloro-6-ethyl-5-fluoropyrimidine (8). To a stirred mixture of magnesium turnings (12.1 g) in tetrahydrofuran (161 mL) was added a solution of bromoethane (54.3 g) in tetrahydrofuran (53 mL), maintaining the reaction temperature below 50 °C during the addition. The solution of the Grignard reagent was cooled to 0 °C and a solution of compound **6** (56 g) in dimethoxyethane (170 mL) added, maintaining the reaction temperature below 15 °C during the addition. The reaction was stirred for 1 h at 15 °C and cooled to 0 °C. A solution of triethylamine (34 g) in tetrahydrofuran (70 mL) was added, maintaining the reaction temperature at about 5 °C, followed by a solution of iodine (85 g) in tetrahydrofuran (256 mL), maintaining the reaction temperature below 15 °C. The reaction was then quenched with water (840 mL), maintaining the reaction temperature below 25 °C. The pH was adjusted to 1 using 5 N aqueous hydrochloric acid solution (50 mL) and the mixture extracted with toluene (1 × 490 mL followed by 1 × 210 mL). The combined organic layers were washed with 2% w/w aqueous sodium metabisulfite solution (700 mL); water (700 mL) was then added, and the remaining tetrahydrofuran was removed by distillation under reduced pressure. The mixture was cooled, and the organic layer was separated, washed with water (425 mL), and then concentrated under reduced pressure to provide the product as an oil (50 g). Analysis by GLC gave an estimated yield of 75% (∼49 g activity).

^{1}H NMR ($CDCl_3$) δ 1.30 (t,3H), 2.90 (dq, 2H) ppm.

(v) 2-Chloro-6-ethyl-5-fluoro-4-hydroxypyrimidine, Ammonium Salt (13). A mixture of compound **8** (40 g) and water (10 g) was heated to 90 °C and 4 N aqueous sodium hydroxide solution (127 mL) added. Heating was continued at 80 °C for 30 min, and then the mixture was cooled to 25 °C. The mixture was washed with toluene (124 mL), the aqueous layer was separated, and dichloromethane (162 mL) was added thereto. To this mixture was added concentrated hydrochloric acid until pH 1 was achieved. The organic layer was separated and the aqueous layer extracted with dichloromethane (162 mL). The combined organic layers were treated with activated carbon (8.8 g). The solution was filtered and the filtrate treated with concentrated aqueous ammonia solution until pH 9 was achieved. The product precipitated as a solid and was collected by filtration (34 g, 92% yield), mp 125−131 °C.

^{1}H NMR ($CDCl_3$) δ 1.08 (t, 3H), 2.39 (dq, 2H), 7.38 (bs, 4H) ppm.

(vi) 6-Ethyl-5-fluoro-4-hydroxypyrimidine (14). To a mixture of the compound **13** (34 g), ethanol (170 mL), and water (5 g) was added 5% w/w palladium-on-carbon (50% w/w water content) (3.4 g) and the mixture hydrogenated at 50 °C and (50 psi) until completion of the reaction. Water (10.5 mL) was added and the catalyst removed by filtration. The filtrate was concentrated under reduced pressure to a small volume and extracted with dichloromethane (2 × 58 mL). The combined organic extracts were concentrated under reduced pressure and toluene (150 mL) was added. The mixture was concentrated under reduced pressure to 50 mL in volume, and toluene (50 mL) was added and cooled to 4 °C for 4 h. The precipitated product was collected by filtration, washed with toluene (10 mL), and dried (20 g, 80% yield), mp 112−114 °C.

^{1}H NMR ($CDCl_3$) δ 1.25 (m, 3H), 2.73 (m, 2H), 8.00 (s, 1H) ppm.

(vii) 4-Chloro-6-ethyl-5-fluoropyrimidine (9). To a mixture of compound (**14**) (40 g), dichloromethane (120 mL), and triethylamine (28.4 g) was slowly added phosphorus oxychloride (47.2 g) over 3 h, maintaining the reaction temperature below 40 °C during the addition. The mixture was heated under reflux for 5 h, cooled to 25 °C, and cautiously quenched into 3 N aqueous hydrochloric acid solution (176 mL), maintaining the temperature below 20 °C during this operation. The layers were separated, the aqueous phase was extracted with dichloromethane (50 mL), and the combined organic layers were washed with water (50 mL). The organic layer was concentrated under reduced pressure to provide the product as an oil (40.69 g, 90% yield).

^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H), 2.87 (q, 2H), 8.65 (s, 1H) ppm.

(viii) 4-Ethyl-5-fluoropyrimidine (10). A mixture of compound **8** (10 g), sodium acetate (8.83 g), 5% palladium-on-carbon (50% water wet, 2 g), and methanol (30 mL) was hydrogenated at 50 °C and 50 psi for 5 h. The resulting slurry was filtered through a cellulose-based filter aid, the pad was washed with further methanol (5 mL), and the resulting orange filtrate was distilled at 64 °C and atmospheric pressure to provide a colourless distillate. This was partitioned between water (300 mL) and ether (40 mL), and the two phases were separated. The organic phase was washed with water (4 × 500 mL) and dried over $MgSO_4$, and the solvent was removed at room temperature under reduced pressure to provide the title compound as a pale yellow liquid (2.2 g, 35% yield).

^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H), 2.89 (dq, 2H), 8.43 (s, 1H), 8.92 (d,1H) ppm.

(ix) 6-(1-Bromoethyl)-4-chloro-5-fluoropyrimidine (17). A stirred mixture of compound **9** (38.5 g), azoisobutyronitrile (AIBN) (1.92 g), NBS (49 g), and dichloromethane (198 mL) was heated under reflux under nitrogen for 12 h. The mixture was cooled to 25 °C and water (239 mL) added. The layers were separated, and the aqueous layer was extracted with dichloromethane (120 mL). The combined organic layers were washed with a solution of sodium metabisulfite (22.8 g) in water (239 mL), followed by water (239 mL). The organic layer was concentrated under reduced pressure, toluene (240 mL) was added, and the resulting solution was concentrated under reduced pressure to give the product as an oil (54.5 g activity by ^{1}H NMR, 95% yield).

^{1}H NMR ($CDCl_3$) δ 2.08 (d, 3H), 5.35 (q, 1H), 8.80 (s, 1H) ppm.

(x) 4-(1-Bromoethyl)-2-chloro-5-fluoropyrimidine (18). A stirred mixture of compound **7** (3.60 g), AIBN (180 mg), and NBS (5.30 g) in 1,1,1-trichloroethane (50 mL) was heated to reflux for 30 h. The reaction mixture was cooled and washed with a solution of sodium metabisulfite (2.5 g) in water (25 mL) and then with water (25 mL). The organic layer was concentrated at reduced pressure to give the product oil (5.0 g activity by ^{1}H NMR, 93% yield).

^{1}H NMR ($CDCl_3$) δ 2.07 (d, 3H), 5.28 (q, 1H), 8.47 (s, 1H) ppm.

(xi) 4-(1-Bromoethyl)-2,4-dichloro-5-fluoropyrimidine (19). A stirred solution of compound **8** (14.0 g), AIBN (700 mg), NBS (14.2 g), and bromine (5.75 g) in dichloromethane (70 mL) and water (21 mL) was heated to reflux for 96 h. The reaction mixture was cooled and separated, and the organic phase was subsequently washed with a solution of sodium metabisulfite (9 g) in water (90 mL) and then with water (90 mL). The organic layer was concentrated at reduced pressure to give the product oil (19 g activity by ^{1}H NMR, 96% yield).

^{1}H NMR ($CDCl_3$) δ 2.06 (d, 3H), 5.29 (q, 1H) ppm.

(xii) 4-(1-Bromoethyl)-5-fluoropyrimidine (20). A stirred mixture of compound **10** (6.0 g), AIBN (300 mg), and NBS (9.32 g) in dichloromethane (100 mL) was heated to reflux for 6 h. The reaction mixture was cooled and washed with a solution of sodium metabisulfite (5 g) in water (50 mL) and then with water (50 mL). The organic layer was concentrated at reduced pressure to give the product oil (9.40 g activity by ^{1}H NMR, 96% yield).

^{1}H NMR ($CDCl_3$) δ 2.08 (d, 3H), 5.38 (q, 1H), 8.58 (1H), 9.03 (1H) ppm.

(xiii) General Procedure for Reformatsky Reactions of 4-(1-Bromoethyl)-5-fluoropyrimidines (17), (18), (19), and (20) with Ketone (3). A stirred mixture of zinc powder (2.40 g), lead (0.12 g), and tetrahydrofuran (10 mL) was heated to reflux under a nitrogen atmosphere for 3 h. A solution of iodine (2.29 g) in tetrahydrofuran (10 mL) was added at reflux. After 30 min a combined solution of the 4-(1-bromoethyl)-5-fluoropyrimidine (11 mmol), 1-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)-1-ethanone (**3**) (2.23 g) and iodine (0.25 g) in tetrahydrofuran (30 mL) was finally added to the mixture at reflux over 30 min. After a further 30 min at reflux the mixture was cooled and a sample taken and subjected to HPLC analysis according to the conditions set out in (xiv).

(xiv) (*R,*S**)-3-(6-Chloro-5-fluoro-4-pyrimidinyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol hydrochloride (4) (X = Cl, Y = H) [Method with Lead].** A stirred mixture of zinc powder (9.35 g), lead (0.47 g), and tetrahydrofuran (53 mL) was heated under reflux under a nitrogen atmosphere for 3 h. The mixture was then cooled to 25 °C and stirring continued for 16 h. A solution of iodine (7.42 g) in tetrahydrofuran (21 mL) was added over 80 min, and the reaction temperature was allowed to rise to 45 °C during the addition. The mixture was then cooled to between 0 and −5 °C. A solution of 1-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)-1-ethanone (**3**) (6.53 g) and 4-(1-bromoethyl)-6-chloro-5-fluoropyrimidine (**17**) (7.01 g) in tetrahydrofuran (53 mL) was then added, maintaining the reaction temperature below +5 °C during the addition. The mixture was warmed to 25 °C, and glacial acetic acid (8.84 g) and water (84 mL) were added. The solid metal residues were separated by decantation, and 60 mL of tetrahydrofuran was removed by distillation under reduced pressure. Ethyl acetate (76 g) was added, and the distillation was continued to remove 165 mL of solvent. The mixture was cooled and extracted with ethyl acetate (2 × 84 mL), and the combined extracts were washed with a solution of disodium ethylenediaminetetraacetate dihydrate (3.22 g) in water (161 mL), followed by saturated brine (30 mL).

The ratio of the diastereomer pairs contained in the organic layer was determined by HPLC analysis using a 25 cm C18 Dynamax 60 Å reverse phase column, a mobile phase consisting of 65:35, by volume, acetonitrile:water and a flow rate of 1 mL/min. The detector was set at 254 nm. This analysis showed a 9:1 molar ratio of the (*R**,*S**) (t_R = 5.53 min) to the (*R**,*R**) (t_R = 4.47 min) enantiomeric pair of the free base of the title compound.

The organic layer was concentrated to a volume of 56 mL and a solution of hydrogen chloride (1.2 g) in 2-propanol (6 mL) added at 25 °C. The title compound precipitated as a solid. This was collected by filtration, washed with ethyl acetate (5 mL), and dried (7.89 g, 65%), mp 126−130 °C.

Analysis by HPLC confirmed that the hydrochloride salt crystallisation had further improved the diastereomer ratio to 99:1.

^{1}H NMR (DMSO-d_6) δ 1.14 (d, 3H), 3.93 (q, 1H), 4.54 (d, 1H), 4.82 (d, 1H), 6.91 (ddd, 1H), 7.20 (ddd, 1H), 7.28 (ddd, 1H), 7.93 (s, 1H), 8.73 (s, 1H), 8.84 (s, 1H) ppm.

(xv) (*R,*S**/*R**,*R**)-3-(6-Chloro-5-fluoro-4-pyrimidinyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (4) (X = Cl, Y = H) ["Split Iodine" Method].** A solution of iodine (2.25 g) in tetrahydrofuran (6 mL) was added dropwise to a stirred slurry of zinc (3.00 g) and lead (0.15 g) in tetrahydrofuran (19 mL) under a nitrogen atmosphere at 25 °C. The reaction temperature was allowed to rise during the addition. The mixture was then cooled to 2 °C. A solution of 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone (**3**) (2.00 g), 6-(1-bromoethyl)-4-chloro-5-fluoropyrimidine (**17**) (2.84 g), and iodine (0.02 g) in tetrahydrofuran (16 mL) was added dropwise over 10 min. The reaction temperature was limited to a maximum of 16 °C during the addition by cooling. Further cooling was then applied to obtain a temperature below +5 °C. The reaction was stirred below +5 °C for 30 min. A sample of the reaction mixture was taken and subjected to HPLC analysis, according to the conditions set out in (xiv). The analysis showed a 10.3:1 molar ratio of the (*R**,*S**) to the (*R**,*R**) enantiomeric pair of the title compound. The yield of the diastereomer pair was calculated to be 90% using an internal standard.

(xvi) (*R,*S**)-2-(2,4-Difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (4) (X = Y = H).** A stirred mixture of the compound **4** (X = Cl, Y = H) as its hydrochloride salt (26.5 g), dichloromethane (400 mL), and water (184 mL) was adjusted to pH 11 using 40% w/w aqueous sodium hydroxide solution (10 mL). The organic layer was separated, washed with a solution of disodium ethylenediaminetetracetate dihydrate (8.74 g) in water (183.5 mL) followed by water (184 mL), and then concentrated under reduced pressure to an oil. This was dissolved in ethanol (134 mL), sodium acetate (8 g), and 5% w/w palladium-on-carbon (50% w/w water content) (3.34 g) were added, and the mixture was hydrogenated at 15 psi and 25 °C until completion of the reaction. The catalyst was removed by filtration and the filtrate concentrated to a volume of 51 mL. Dichloromethane (152 mL) and water (152 mL) were added, and the pH was adjusted to 11 using 40% w/w aqueous sodium hydroxide solution. The layers were separated, and the aqueous layer was extracted with dichloromethane (61 mL). The combined organic extracts were washed with water (61 mL) and concentrated under reduced pressure; 2-propanol (70 mL) was added, and the mixture was concentrated to a volume of 62 mL. The mixture was stirred for 3 h at 20 °C, and the solid was collected by filtration, washed with 2-propanol (2 × 5 mL), and dried to provide the title compound (19 g, 85% yield), mp 127 °C.

^{1}H NMR (DMSO-d_6) δ 1.1 (d, 3H), 3.93 (q, 1H), 4.34 (d, 1H), 4.80(d, 1H), 5.97 (bs, 1H), 6.91 (ddd, 1H), 7.17 (ddd, 1H), 7.28 (ddd, 1H), 7.61 (s, 1H), 8.23 (s, 1H), 8.84 (s, 1H), 9.04 (s, 1H) ppm.

(xvii) (2*R*,3*S*)-2-(2,4-Difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (1). To a solution of the racemic compound **4**, (X = Y = H) (18.93 g) in acetone (426 mL) was added a solution of (1*R*)-10-camphorsulfonic acid (12.57 g) in methanol (142 mL) and the mixture heated under reflux until a solution was obtained. The solution was cooled to 20 °C and granulated overnight. The solid was collected by filtration, washed with acetone (9.35 g), and dried to provide (2*R*,3*S*)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (1*R*)-10-camphorsulfonate as a white solid (12.3 g). The above camphorsulfonate salt (12.3 g) was taken up in dichloromethane (61.5 mL) and water (61.5 mL) and the pH adjusted to 11 by adding 40% w/w aqueous sodium hydroxide solution (2.5 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (14 mL). The combined organic extracts were washed with water (3 × 45 mL), filtered, and the solvent was removed by distillation under reduced pressure. 2-Propanol (30 mL) was added, and the distillation was continued until a volume of 22 mL was achieved. The mixture was cooled to 0 °C and stirred for 2 h. The product was collected by filtration and washed with 2-propanol (2 × 4 mL) to provide the title compound as a white solid (7.6 g, 40% mass yield or 80% of available enantiomer), mp 134 °C

^{1}H NMR (DMSO-d_6) δ 1.1 (d, 3H), 3.93 (q, 1H), 4.34 (d, 1H), 4.80 (d, 1H), 5.97 (bs, 1H), 6.91 (ddd, 1H), 7.17 (ddd, 1H), 7.28 (ddd, 1H), 7.61 (s, 1H), 8.23 (s, 1H), 8.84 (s, 1H), 9.04 (s, 1H) ppm.

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