General Method for the Synthesis of Enantiomerically Pure β-Hydroxy-α-amino Acids, containing Fluorine Atoms in the Side Chains. Case of Stereochemical Distinction between Methyl and Trifluoromethyl Groups. X-Ray Crystal and Molecular Structure of the Nickel(II) Complex of (2*S*,3*S*)-2-(Trifluoromethyl)threonine

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The chiral Ni[II] complex **1** of a Schiff's base derived from (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone (BPB) and glycine was treated with fluoro-substituted aldehydes (aliphatic and aromatic) in MeOH or $CHCl_3$. The addition proceeds with high diastereoselectivity to give, if catalysed by MeONa in MeOH, the corresponding complexes of *syn*-(2*R*)-3-fluorophenylserines (84–100% d.e.) and *syn*-(2*S*)-fluoroalkylserines (90% d.e.), and, if catalysed by NEt_3 or DABCO (MeOH or $CHCl_3$), the corresponding complexes of *syn*-(2*S*)-, and *anti*-(2*S*)-3-fluorophenylserines and fluoroalkylserines. The second-order asymmetric transformation may be successfully employed to obtain diastereoisomerically pure complexes of *anti*-(2*R*)-3-fluorophenylserines. Condensation of trifluoroacetone with complex **1**, catalysed by MeONa, gave predominantly (at least >95% d.e.) the diastereoisomeric complex, containing (2*S*,3*S*)-β-(trifluoromethyl)threonine, as shown by an X-ray diffraction structural study. Diastereoisomerically and enantiomerically pure fluorine-containing 3-phenyl- and 3-alkyl-serines were obtained from the corresponding diastereoisomerically pure complexes, separated by chromatography or crystallization. The initial chiral auxiliary BPB was recovered (80–98%). The influence of the reaction's conditions and the nature of the corresponding fluoro-substituted aldehydes on the diastereoselectivity of the reactions is discussed.

The synthesis of non-proteinogenic amino acids is an important and fast growing field of research.[1,2] The significance of organoelement analogues of amino aicds in general and fluorine-containing ones in particular has recently been recognized in connection with the design and synthesis of enzyme inhibitors as potential pharmaceuticals and also for the study of enzymic reaction mechanisms.[3] Moreover, recently there has been an increasing interest in the incorporation of fluoro-substituted amino acids into peptides.[4] The burgeoning activity in the field of fluoro-containing analogues of natural products prompted Seebach to coin a new term: flustrates (= fluorine-containing substrates).[1a]

Recently we employed a Ni[II] complex **1** of a Schiff's base derived from (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone BPB† and glycine for the asymmetric synthesis of *o*-, *m*-, *p*-fluorine-containing phenylalanines and their α-methyl-substituted analogues,[5] as well as phosphorus analogues of dicarboxylic α-amino acids.[6]

The present study was undertaken for the following reasons:

1. In spite of achievements in the field of asymmetric synthesis of fluorine-containing amino acids[7] only (2*S*,3*S*)-4,4,4-trifluorothreonine[8] and (2*S*,3*R*)-3-(2-fluorophenyl)- and (2*S*,3*R*)-3-[4-(trifluoromethyl)phenyl]-serine[9] were prepared *via* asymmetric synthesis by Prof. Seebach's group.

2. Biological tests showed that racemic *threo*(*syn*)-β-(4-fluorophenyl)serine prolonged the life of rats transplanted with *Erhlich Ascites*[10] and inhibited the growth of *E. coli*.[11] (2*S*,3*S*)-4,4,4-Trifluorothreonine[12] and (2*S*,3*S*)-4,4-difluorothreonine,[13] prepared *via* enzyme-catalysed resolution of racemic mixtures, were found to possess antitumour and antifungal activity. General and convenient synthetic routes to optically active fluoro-substituted β-phenyl- and β-alkyl-serines might be useful for the synthesis of chiral substrates to study under the conditions.

3. Moreover, chiral fluoro-phenylserines or fluoro-alkylserines may be useful for the modification of natural glycopeptide antibiotics which are known to incorporate substituted serines, as their building blocks.[14] In addition, the amino acids may serve as building blocks, containing two chiral centres for the synthesis of different biologically active compounds; for example, analogues of chloramphenicol.[15]

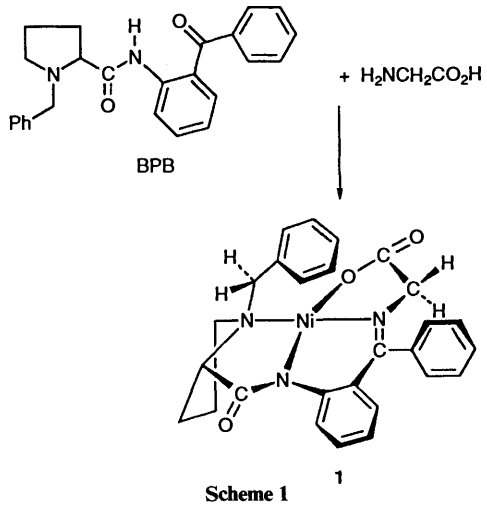
4. The availability of various fluoro-substituted aldehydes might make it possible to investigate the influence of fluorine-containing substituents on the stereochemical course of the aldehyde condensation with complex **1**. The reaction had some interesting features, including the dependence of its thermodynamic diastereoselectivity on the pH of the solution.[16] Introduction of fluorine substituents into the aldehyde molecule would greatly influence the reaction, stabilizing the forming C–C bond, increasing the acidity of the OH group and thus helping to outline the frontiers of the phenomena.

We report here a general procedure for the asymmetric synthesis of enantiomerically pure fluorine-containing β-phenylserines and β-alkylserines *via* condensation of the corresponding fluoro-substituted aldehydes with complex **1**. An unusual influence of fluorine substituents on the diastereoselectivity of the reaction was found and will be discussed.

Results

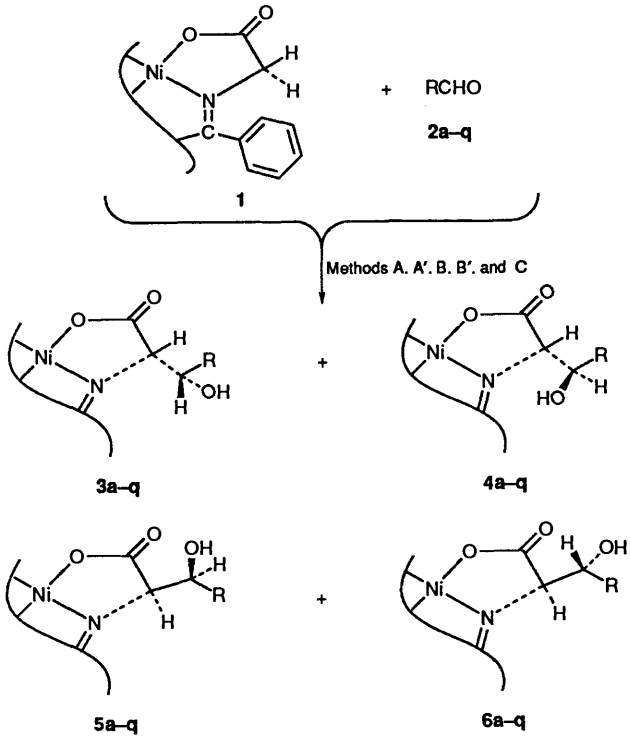
Synthesis of the Ni[II] Complex of the Schiff's Base prepared from (S)-*BPB and Glycine.*—The chiral auxiliary (*S*)-BPB reacted with nickel(II) ions and glycine (see Scheme 1) to give complex **1**, [Ni[II]-(*S*)-BPB-Gly], as described earlier.[16b]

† Available from Merck (cat. no. 814473) and Jansen (cat. no. 2691950).



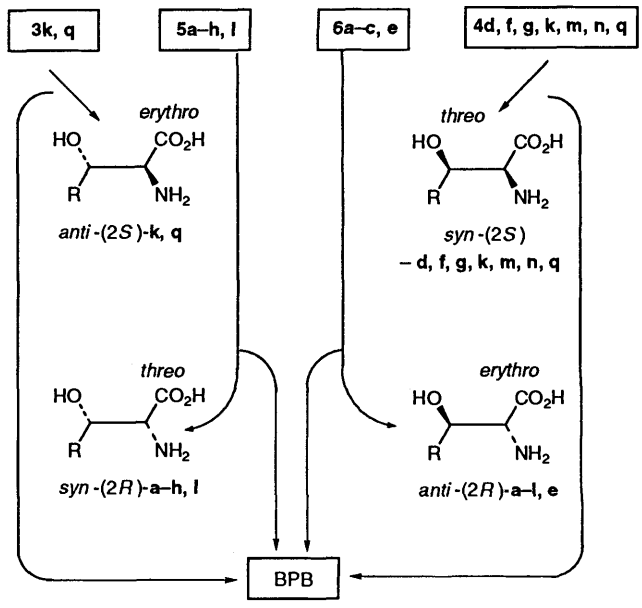
Scheme 1

General Approach to the Condensation of Complex **1** *with Fluoro-substituted Aldehydes* **2a–q** (Scheme 2).—The reactivity of the aldehydes varied in the series under study and, in order to achieve the best possible chemical yields of the condensation products, five different methods of conducting the reaction were selected.



Scheme 2 R = Ph (**a**), 2-FC_6H_4 (**b**), 4-FC_6H_4 (**c**), 2-$(CHF_2O)C_6H_4$ (**d**), 4-$(CHF_2O)C_6H_4$ (**e**), 2-$CF_3C_6H_4$ (**f**), 4-$(CF_3O)C_6H_4$ (**g**), 3-F,4-$MeOC_6H_3$ (**h**), 3,4,5-$(MeO)_3C_6H_2$ (**i**), 4-$NO_2C_6H_4$ (**j**), C_6F_5 (**k**), 4-$(MeO)C_6F_4$ (**l**), CF_3 (**m**), C_4F_9 (**n**), $H[CF_2]_6$ (**o**), C_6F_{13} (**p**), $H[CF_2]_4$ (**q**).

Method A. The reaction of complex **1** with the aldehyde was effected by MeONa in MeOH (the mole ratio of **1** to MeONa in the reaction mixture was kept greater than 1:2) at ambient temperature. After completion of the reaction the diastereoisomeric complexes were separated by flash chromatography on SiO_2 or by crystallization. Enantiopure β-hydroxy-α-amino acids were recovered from the diastereoisomerically pure complexes after their decomposition with aq. HCl and extraction of BPB (Scheme 3).



Scheme 3

Method A'. The same as method A, but the temperature of the mixture was kept at 50 °C.

Method B. A mixture of complex **1** and the aldehyde was kept in a solution of NEt_3 in MeOH (ratio 1:2 by volume) at ambient temperature for a period of several days to ensure equilibration of the resulting diastereoisomeric complex.

Method B'. The same as method B, the only difference was the ratio of NEt_3:MeOH (1:1) by volume).

Method C. A mixture of complex **1** and the aldehyde was kept in a solution of 1,4-diazabicyclo[2.2.2]octane (DABCO) in $CHCl_3$ for 2 h. Other details of the procedure were the same as in method B.

Determination of the Absolute Configuration of Fluoro-substituted β-*Hydroxy-*α-*amino Acids obtained in the Condensation of Complex* **1** *with Aldehydes.*—The absolute configuration of the α-carbon atom of the amino acid moiety was established, using the optical rotatory dispersion (ORD) curves of the corresponding diastereoisomerically pure complexes of the amino acids in neutral solutions. The sign of the Cotton effect in the 500–700 nm region was always positive for (*S*)-α-amino acids and negative for their enantiomers, as illustrated by the corresponding curves of the diastereoisomeric complexes of (*R*)-Ser and other (*S*)-amino acids (see Fig. 1) in a neutral MeOH solution. As was shown earlier, this general trend was not influenced by the structure of the α-amino acid side chain, and the configuration of the β-carbon atoms of the side chains.[2,6,16]

In the case of fluoro-substituted aliphatic aldehydes, single-crystal X-ray analysis data were used to assign the absolute configuration of the amino acid side chain of the major diastereoisomer **4** [*syn*-(2*S*)] furnished by method A', as previously reported for the condensation of aldehyde **2o** with complex **1**.[17]

For a more detailed description of the determination of the *syn*- and *anti*-configuration of the isomers see the Experimental section.

The absolute configuration of the amino acid side chain of the major diastereoisomer, obtained by the condensation of complex **1** with trifluoroacetone (Method A'), was established as (2*S*,3*S*) by single-crystal X-ray structure analysis (see Fig. 2).

A detailed analysis of the condensation is now presented.

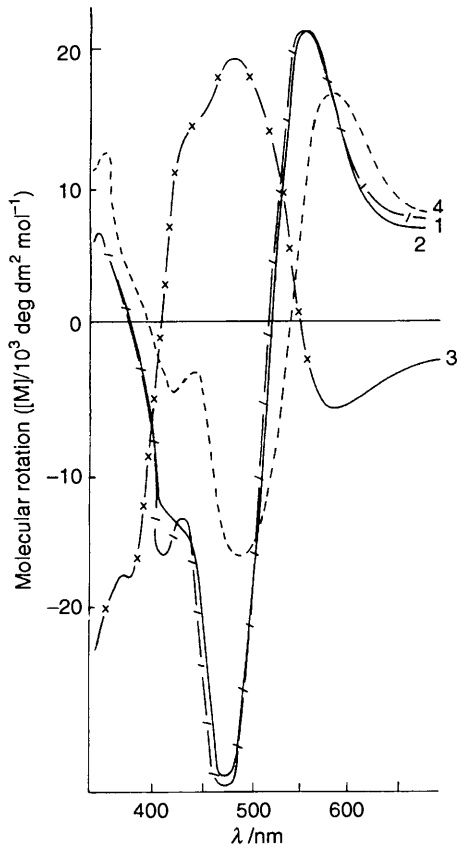


Fig. 1 ORD curves of the diastereoisomerically pure complexes Ni-(*S*)-BPB-(*S* or *R*)-Aa (*c* 5.3 × 10^{-4}–7 × 10^{-4} mol dm^{-3}) at 25 °C. Curve 1, **3q** in MeOH; Curve 2, **3q** and 10 mol equiv. of MeONa in MeOH; Curve 3, Ni-(*S*)-BPB-(*R*)-Ser in MeOH; Curve 4, Ni-(*S*)-BPB-(*R*)-Ser in 0.1 mol dm^{-3} MeONa solution in MeOH.

Condensation of Fluorine-substituted Benzaldehydes and Trifluoroacetone with Complex **1** (*Method A*).—Condensation of complex **1** with fluoro-substituted benzaldehydes **2a–l** (see Scheme 2) resulted in a mixture of isomers **5** and **4** [the configuration of the side chain is *syn*-(2*R*) and *syn*-(2*S*), respectively]. As expected, [16a,b] the reaction produced a large excess of **5** over **4** (see Table 1). Other possible isomers, *anti*-(2*S*) and *anti*-(2*R*) (**3** and **6**, respectively), were either not detected or were formed in minute amounts. The condensation and the equilibration of the resultant diastereoisomers were essentially complete within 10 min from the start of the reaction. There was almost no change or an insignificant change in the ratio of the diastereoisomers after a further 60 min, as the data summarized in Table 1 indicate. The only exception was the reaction of perfluorobenzaldehyde **2k** with complex **1**. After 10 min from the beginning of the reaction of compounds **1** and **2k** a mixture of products **3k** and **4k** in the ratio 1:1 was obtained. Subsequently, the mixture of isomers was converted into compound **5l**. The ratio of **5l**:**4l** was 8:1 and the amino acid moiety was found to be tetrafluoro(4-methoxy)phenylserine. Clearly, the *para*-fluorine atom in the pentafluorophenyl ring was substituted by the MeO group. Most likely, the substitution occurred mainly at the product of the condensation of aldehyde **2k** with complex **1** because aldehyde **2k** itself was not stable under the experimental conditions as the result of a halogenoform decomposition,[18] and the aldehyde decomposed faster than it was converted into tetrafluoro(*p*-methoxy)benzaldehyde (the yield of the latter was less than 5%).

Condensation of trifluoroacetone with complex **1** gave a large excess of one diastereoisomer with a (2*S*,3*S*)-configuration of the side chain (see Fig. 2), 10% of initial complex **1** and some unidentified products of side reactions, totalling 10%. No other diastereoisomeric complexes were detected in the mixture.

Condensation of Aliphatic Perfluoroalkyl Aldehydes (*Method A'*).—Fluoroalkyl aldehydes **2m** and **2n** would not react with complex **1** under the conditions of method A at ambient temperature. Apparently, this is connected with the formation of the corresponding unreactive hemiacetals from the substrates in MeOH solution.[19] However, brief heating of the reaction mixture (method A') gave diastereoisomeric complexes of the corresponding β-hydroxy-α-amino acids in high yields and a ratio of **4**:**5** [or *syn*-(2*S*)-*syn*-(2*R*) of the side chain] (see Scheme 2) equal to 96:4 for compounds **2m** and **2n** (Table 1). For the complete conversion of complex **1** no more than 10 min and a 10% excess of the perfluoroalkyl aldehydes **2m** and **2n** was required. Earlier it was shown[17] that polyfluoro compounds **2o** and **2q** reacted with complex **1** in the same manner. Neither prolonged heating of the reaction mixture nor storing it at ambient temperature had any effect on the ratio of the diastereoisomers, although the formation of some by-products was observed.

Condensation of Fluorine-substituted Benzaldehydes with Complex **1** *in MeOH–NEt_3* (2:1 *by Volume*) (*Method B*), *and in $CHCl_3$–DABCO* (*Method C*).—The reaction of complex **1** with aldehydes **2b–g**, **k** was carried out under the experimental conditions of method B. The conversion of complex **1** was 90% after 48 h and all four theoretically possible diastereoisomeric complexes **3–6** were found in the reaction mixture. 2*S* Products **3** and **4** accounted for 80–95% of the reaction product, and only 5–20% of it were complexes **5** and **6**. Unfortunately, only compounds **3d**, **f** and **4d**, **f** could be separated chromatographically. The ratio of the diastereoisomeric complexes of other amino acids could be assessed by measuring (chiral HPLC or ^{19}F NMR) the relative proportions of *syn*-(2*S*)-, *syn*-(2*R*)-, *anti*-(2*R*)-, and *anti*-(2*S*)-amino acids, recovered from the reaction mixture after decomposition of the complexes. The experimental results are summarized in Table 2. The ratio **4**:**3** (*syn*:*anti*) was almost 1:1 for most of the products but the introduction of large *ortho*-substituents into the aldehyde molecule increased the proportion of the *syn*-isomers in the final product (Table 2, runs 3 and 5). In order to avoid the fluorine-substitution reaction, condensation of compound **2k** with complex **1** was conducted in $CHCl_3$, with DABCO as a catalyst (method C). As expected, a mixture of products **3k** and **4k** was formed.

Condensation of Aliphatic Perfluoroalkyl Aldehydes with Complex **1** *in $CHCl_3$–DABCO* (*Method C*).—It should be mentioned that the condensation of complex **1** with the unsubstituted benzaldehyde, **2a**, under method C conditions did not take place. On the other hand all attempts to conduct the reaction of fluorine-substituted aliphatic aldehydes with complex **1** under method B conditions were also unsuccessful, probably because the aldehydes exist in methanol solution as unreactive hemiacetals and so the concentration of the free aldehydes was too low to effect the condensation at such a low pH. Et_3N was easily oxidized in aprotic solvents by the aldehydes. However, the condensation of the fluoro-substituted aliphatic aldehydes **2o** and **2q** with complex **1** could be carried out successfully, using method C (DABCO in $CHCl_3$). Table 2 summarizes the experimental results. As can be seen from the data, isomers **4** and **3** were formed in the ratio 1:1.

Condensation of Fluorine-substituted Benzaldehydes with Complex **1** *in MeOH–NEt_3* (1:1), *Second-order Asymmetric*

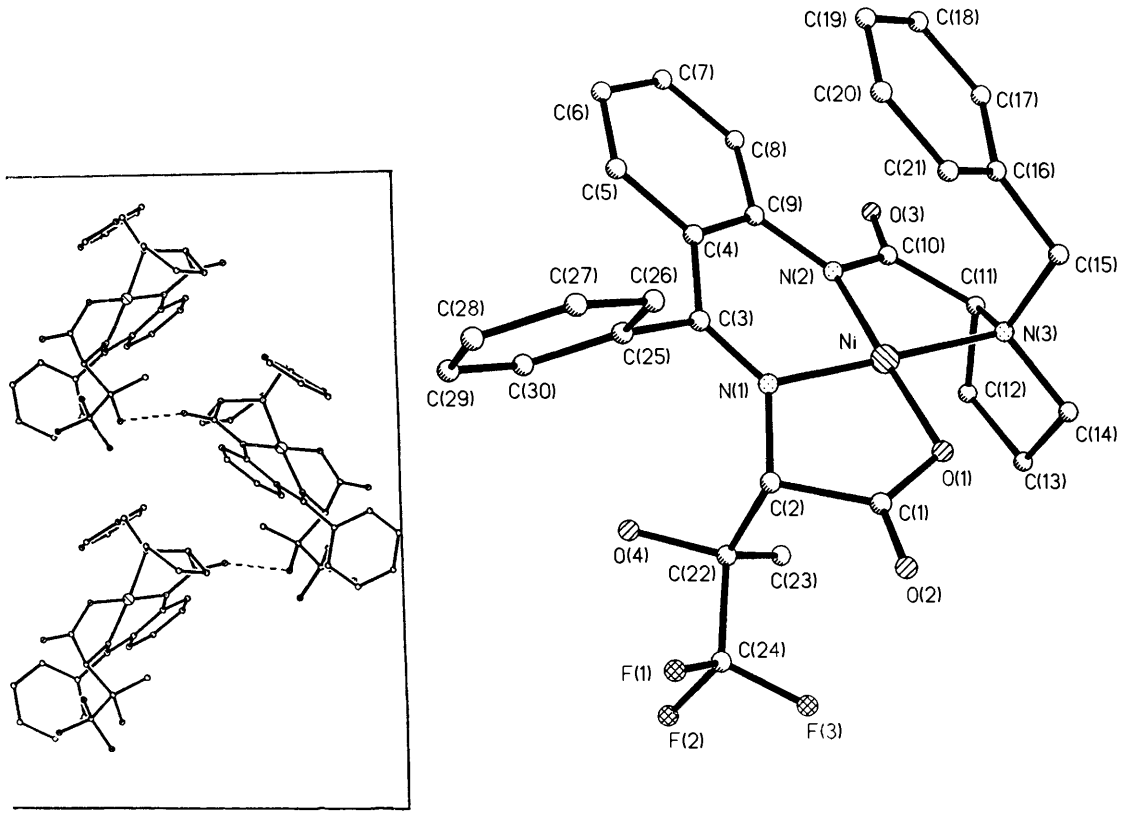


Fig. 2 Structure of Ni^{II} complex of (2*S*,3*S*)-2-(trifluoromethyl)threonine Schiff's base with (*S*)-BPB as revealed by X-ray analysis. The inset illustrates packing of the molecule in the crystal.

Table 1 Condensation of RCHO **2a–n** with complex **1** in MeOH, catalysed by MeONa at ambient temperature (Method A) and at 50 °C (Method A')

		Relative proportions of isomers (%)[b]			
		10 min		60 min	
Run[a]	R	[*syn*-(2*R*)] **5**	[*syn*-(2*S*)] **4**	[*syn*-(2*R*)] **5**	[*syn*-(2*S*)] **4**
1	Ph (**a**)	95	5	95	5
2	2-FC_6H_4 (**b**)	94	6	94	6
3	4-FC_6H_4 (**c**)	95	5	96	4
4	2-$(CHF_2O)C_6H_4$ (**d**)	88	12	90	10
5	4-$(CHF_2O)C_6H_4$ (**e**)	87	13	93	7
6	2-$CF_3C_6H_4$ (**f**)	89	11	90	10
7	4-$(CF_3O)C_6H_4$ (**g**)	88	12	92	8
8	3-F,4-$MeOC_6H_3$ (**h**)	100	*c*	100	*c*
9	3,4,5-$(MeO)_3C_6H_2$ (**i**)	100	*c*	100	*c*
10	4-$NO_2C_6H_4$ (**j**)	83	17	90	10
11	CF_3 (**m**)	4	96	*d*	*d*
12	C_4F_9 (**n**)[e]	4	96	*d*	*d*

[a] Runs 1–10, method A; runs 11–13, method A'. [b] Isolated complexes, chemical yields were 70–82%. [c] The isomer was not found in solution. [d] Although the ratio of isomers did not change, some side reactions were revealed by TLC. [e] Preliminary results[17] indicate that other perfluoroalkyl aldehydes (**2o–q**) gave the same ratio of isomers.

Transformation of Products **3–5a–c, e** *into* **6a–c, e** *and Synthesis of* anti-(2R)-*Phenylserines. (Method B').*—An increase in the concentration of Et_3N in the reaction solution did not influence the relative proportions of products **3–6a–c, e**, formed in the condensation at ambient temperature. The ratio of major isomers **4**:**3** was as indicated in Table 1. Isomers **5** and **6** were, as expected, obtained in minute amounts. However, an increase in the concentration of NEt_3 in MeOH solution effected the relative solubility of the diastereoisomeric complexes. As a result, the second-order asymmetric transformation may be successfully carried out under the experimental conditions of method B', and the sparingly soluble **6a–c, e** [configuration of the side chain is *anti*-(2*R*)] diastereoisomeric complexes, present in the solution as minute admixtures, slowly precipitated from the solution at ambient temperature, shifting the equilibrium between the isomers. Crystalline products **6a–c, e** could sometimes be obtained in 50–65% yield within 2 weeks. *anti*-(2*R*)-Phenylserines were easily recovered from the complexes.

Equilibration of the Diastereoisomeric Complexes under Conditions of Methods A, B, C and A'.—Diastereoisomeric complexes **3a–j, l, 4a–j, l, 5a–j, l** or **6a–c, e**, derived from the

Table 2 Condensation of RCHO (**2a–g, o, q**) with complex **1** in MeOH, catalysed by Et_3N at ambient temperature (Method B) and in $CHCl_3$ catalysed by DABCO (Method C)

Run[a]	R	Relative proportions of isomers[b,c] [*syn*-(2*S*)] **4**	[*anti*-(2*S*)] **3**
1	2-FC_6H_4 (**b**)	61	38
2	4-FC_6H_4 (**c**)	63	37
3	2-$(CHF_2O)C_6H_4$ (**d**)	91	9
4	4-$(CHF_2O)C_6H_4$ (**e**)	60	40
5	2-$CF_3C_6H_4$ (**f**)	91	9
6	4-$(CF_3O)C_6H_4$ (**g**)	64	36
7	C_6F_5 (**k**)	50[d]	50[d]
8	C_6F_5 (**k**)	50[d]	50[d]
9	$H[CF_2]_6$ (**o**)	50	50
10	$H[CF_2]_4$ (**q**)[e]	50	50

[a] Runs 1–7, method B, several days; runs 8–10, method C. [b] Isolated complexes, chemical yields were 70–82%. [c] The other diastereoisomeric complexes (**5, 6**) were found in the reaction mixture in amounts totalling 5–20%. [d] A yield of several percent of the product of a side reaction was found in solution. [e] Preliminary results indicate that other perfluoroalkyl aldehydes (**2m, n, p**) gave the same ratio of isomers.

corresponding benzaldehydes, having been treated with MeONa in MeOH at the ambient temperature, gave complex **1** and the same ratio of isomers with a predominance of isomers **5** (*syn*-2*R* amino acid side chains), as expected for the experimental conditions of method A.[16] Products **3a–j, l, 4a–j, l, 5a–j, l** or **6a–c, e** under the experimental conditions of method B gave complex **1** and the same mixture of isomers, with great predominance of the corresponding complexes of *syn*-2*S* amino acids, **4**, and *anti*-2*S* amino acids, **3**, over the other isomers, reproducing the corresponding ratios of the isomers in the condensations.

All attempts to effect equilibration of compound **4o**, or **4q** and **3o** or **3q** in MeOH in the presence of MeONa or Et_3N during several hours at ambient temperature failed. Similarly unsuccessful were our efforts to induce epimerization of the complexes in $CHCl_3$–DABCO (Method C). Only heating of a solution of compound **3o** or **3q** in MeOH in the presence of MeONa at 50 °C brought about the conversion of the diastereoisomers into a mixture, containing predominantly isomer **4o** or **4q** (as expected for the method A′ conditions) some isomer **5o** or **5q**, and some complex **1**.

Base-catalysed Deuterium Exchange of the α-Proton of the Amino Acid Moiety of Complex **4o** *or* **3o** *in* CD_3OD.—The exchange, monitored with ^1H NMR spectroscopy, was easily effected by Et_3N at ambient temperature. The reaction proceeded with complete retention of configuration of the amino acid moieties, as TLC of the complexes and HPLC of the amino acids recovered from the reaction mixture indicated.

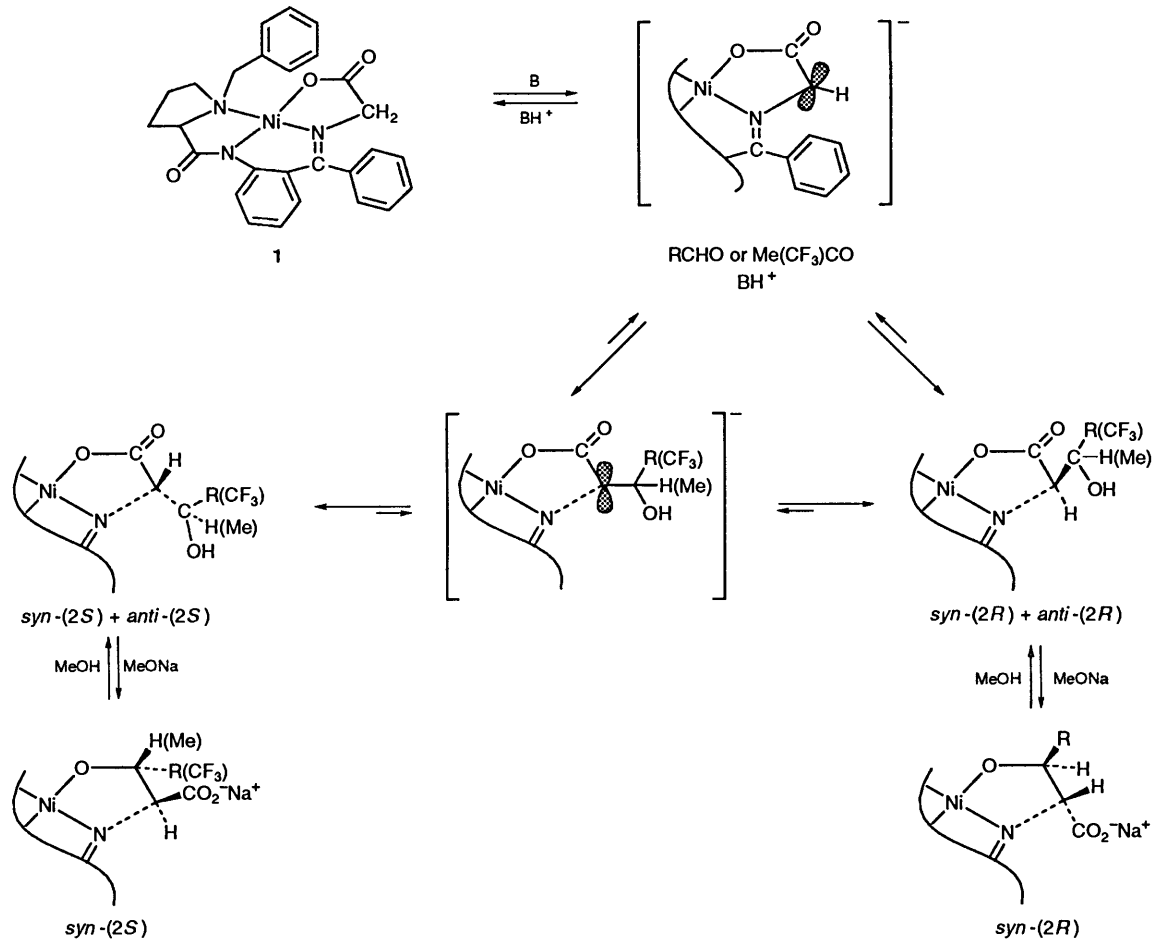
Discussion

Condensation of Fluoro-substituted Benzaldehydes with Complex **1** *Solutions of Low Basicity (Methods B and B′).*—The mechanism of aldol condensation of fluoro-substituted aldehydes with complex **1** seems to be similar to that generally accepted for the condensation of other CH-acids with aldehydes.[20] It is assumed to consist of two main steps, the first being a base-catalysed abstraction of the α-proton from the Gly moiety, followed by the addition of the carbanion to the carbonyl group of the aldehyde (Scheme 4). As was shown earlier,[16] the condensation was a reversible process and the position of the equilibrium was influenced by many factors, including the nature of the corresponding aldehydes and reaction conditions. As might be expected, fluoro-substituted benzaldehydes **2a–h** reacted similarly to other aldehydes. Under the experimental conditions of methods B and B′ the condensation products had the usual structure of Ni^{II}–amino acid complexes, with co-ordinated carboxy and unco-ordinated hydroxy groups (see Fig. 2). Complete equilibration of the diastereoisomers took place, as the corresponding equilibration experiments and the second-order asymmetric transformation of compounds **3–5a–c, e** indicated (see above). There are two types of equilibration process possible in the system. The labilization of the α-proton of the amino acid moiety may lead to the conversion of *syn*-2*S* isomers into *anti*-2*R* ones (or *vice versa*). The equilibration might involve C–C bond scission, otherwise there would be no transformation (Scheme 4) of *anti*-2*S* isomers into *syn*-2*S* isomers (or *vice versa*) of the amino acid moieties. As usual for the complexes of Ni^{II}–(*S*)-BPB-Aa,*[2,6,16] thermodynamic diastereoselectivity favours a 2*S* configuration for the α-carbon atom of the amino acid moiety (see Table 2). Non-bonding interaction of the amino acid side chain with the phenyl substituent at the C=N bond, significant in the Ni^{II}–(*S*)-BPB-(2*R*)-Aa and insignificant in the Ni^{II}–(*S*)-BPB-(2*S*)-Aa diastereoisomers, was supposed to be responsible for the excess of the latter at equilibrium.[2,16b] It is more difficult to rationalize a greater proportion of compounds **4d** and **4f** (*syn*-2*S* side chain) isomers relative to **3d** and **3f** (*anti*-2*S*) at equilibrium. One explanation could be a weak attractive interaction of the central metal ion with the large fluorine-containing *ortho*-substituents of compounds **4d** and **4f**, stabilizing the *syn*-2*S* configuration of the side chain. An interaction of that kind was earlier believed to account for the selective formation of anti-β-substituted (2*S*)-2-aminobutanoic acid in the reaction of alcohols and thiols with a Ni^{II} complex of the Schiff's base derived from BPB and α-aminobut-2-enoic acid.[2]

Condensation of Aliphatic Perfluoroalkyl Aldehydes with Complex **1** *in a Solution of Low Basicity (Method C).*—Perfluoroaldehydes are very reactive compounds, forming strong C–C bonds with complex **1**. The diastereoselectivity of the reaction of aldehydes **2o** and **2q** with complex **1**, catalysed by DABCO in $CHCl_3$ solution, probably reflects a mixed case of both thermodynamic and kinetic effects influencing the stereochemical outcome of the reaction. On the one hand there was no equilibration of products **4o, q** and **3o, q** in the solution, as the corresponding experiments indicated (see above). On the other hand, deuterium exchange of the α-proton of the amino acid moiety in products **4o, q** and **3o, q** occurred readily when catalysed by Et_3N in CD_3OD. In other words, the initially formed kinetically controlled ratio of the isomers might have been changed at the later stages of the reaction by epimerization of the amino acid moiety at the α-carbon atom, without fission of the C–C bond and, thus, without changing the configuration of the β-carbon atom. Consequently, the excess of the diasteroisomers with a 2*S* configuration of the amino acid side chain might be a reflection of the thermodynamic stabilization of the diastereoisomers, Ni^{II}–(*S*)-BPB-(*S*)-Aa, as usual for the complexes of that kind. The configurations of the β-carbon atom reflects kinetic recognition (or, taking into consideration the 1:1 ratio of products **4o, q**:**3o, q**, the absence of such recognition) of the two enantiotopic faces of the aldehydes during the condensation.

Condensation of Fluoro-substituted Benzaldehydes with Complex **1** *in a Solution of High Basicity (Method A).*—As was shown earlier for the case of other aldehyde condensations

* Aa = amino acid.



Scheme 4

with complex **1**, in a solution of high pH (method A) the sense of asymmetric induction was reversed,[2,16] as a consequence of ionization of the hydroxy group and the concomitant rearrangement with substitution, by this group, of the ionized carboxy group in the main co-ordination plane of the complex (Scheme 4). The complexes acquired a negative charge and became soluble in water. *syn*-(2*R*)-β-Hydroxy-α-amino acids were the main products of this thermodynamically controlled, reversible process (see the equilibration experiments above), in agreement with molecular mechanics calculations. The non-bonding interaction of the free carboxy group with the phenyl substituent at the carbon atom of the C=N bond might be implicated as the main reason for the reversal of the sense of asymmetric induction.[16]

The postulated rearrangement stabilizes the addition product and allows the involvement of sterically demanding aldehydes or ketones in the condensation. For example, acetone would not react with complex **1** under method B conditions but undergoes condensation under the conditions of method A.[16a]

Condensation of Aliphatic Perfluoroaldehydes **2m**, **n** *and Trifluoroacetone with Complex* **1** (*Methods A' and A*).—The formation of a large excess of the diastereoisomers **4m**, **n** and **4o**, **q**[17] (*syn*-2*S* amino acid moiety), and the complex of (2*S*,3*S*)-3-(trifluoromehyl)threonine in the case of trifluoroacetone condensation, was totally unexpected. In line with other aldehyde condensations, molecular mechanics calculations (without taking into consideration any electrostatic interactions) predicted a *syn*-(2*R*) [or (2*R*,3*R*) in the case of trifluoroacetone] configuration for the amino acid moieties, as the most energetically favourable one in solution for the rearranged products (see Scheme 4) of the condensations of aldehydes **2m**, **n**, **o**, **q**, and trifluoroacetone with complex **1**.

The essential feature of the complexes, as Ni^{II} complexes of Schiff's bases, was intact in a solution of MeONa in MeOH, as the presence of the corresponding relatively strong UV–visible transitions at λ 440 nm indicated.[16]

The first plausible explanation for this phenomenon would be to assume that there was no equilibration of the isomers in the reaction mixture and that it was the kinetic stereoselectivity that was reflected in the final ratio of isomers. The equilibration and deuterium-exchange experiments mitigate against the idea, however. Compounds **3o**, **q** might be converted into stereoisomers **4o**, **q** under the conditions of method A' and their amino acid α-protons were labile even in the presence of Et_3N. The result of the thermodynamic control of the reaction brought about the reversal of the stereoselectivity in cases of aliphatic perfluoroaldehyde condensations at high pH.

Another possibility would be the absence of the rearrangement, leading to the hydroxy-co-ordinated structure, in the case of the products of the perfluoroalkyl aldehyde condensation. Either the low acidity of the hydroxy group or (and) the instability of the rearranged product might have been the underlying reason for such behaviour. To test this hypothesis, aq. 1 mol dm^{-3} NaOH extraction experiments were performed with $CHCl_3$ solutions of compounds **3q**, **4q**, and the condensation product of trifluoroacetone. As a result, 70% of the (trifluoromethyl)threonine complex, 50% of **4q**, and none of **3q** were extracted into the aqueous solution. Clearly, the two former complexes were ionized by the basic aqueous solution, whereas the latter was not. A final test of the rearrangement of compound **4q** in solution and the lack of such a rearrangement

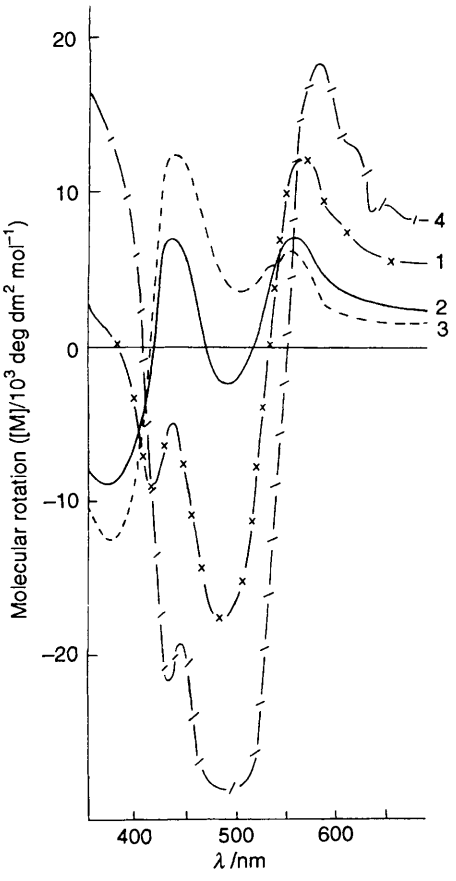


Fig. 3 ORD curves of compound **4q** (*c* 5.4 × 10^{-4} mol dm^{-3}) in MeOH at 25 °C. Curve 1 was taken in MeOH solution; curve 2 was run in a MeOH solution to which 1 mol equiv. of MeONa was added; curve 3 represents several overlapping curves of MeOH solutions with 2, 3 and 10 mol equiv. of MeONa added; curve 4 was taken after acetic acid had been added to the basic solution (curve 3) to make it weakly acidic.

for the isomer **3q** came from the observation of the variation of ORD curves of the isomers in MeOH solution in the presence of different amounts of MeONa (see Fig. 3). As was discussed earlier,[16a] the substitution of the carboxy group by the hydroxy group in the co-ordination sphere of the metal influenced the circular dichroism (CD) spectra (or ORD curves) of the complexes greatly. Alteration of the ORD curve of the corresponding complex of (*R*)-serine in the presence of MeONa is shown in Fig. 1. As can be seen from Fig. 3 and Fig. 1, it was only isomer **4q**, whose ORD curve was greatly and reversibly changed by the addition of 1–2 mol equiv. of base (similar changes were observed in the case of trifluoroacetone addition product). In fact, even neutral solutions of the complex in MeOH contained enough ionized form to be influenced by the addition of acetic acid (see Fig. 3). It took isomer **3q** several days and a higher pH to undergo an irreversible transition of its ORD curve, which was an indication of slow decomposition of compound **3q** to complexes **1** and **4q**, as TLC (SiO_2) confirmed.

Obviously, the structure with a co-ordinated hydroxy group favours a *syn*-(2*S*) configuration for the perfluoroalkylamino acid and could not be organized if the configuration of the amino acid moiety was *anti*-(2*S*). In other words, the carboxy group and perfluoroalkyl group had to be arranged on different sides of the amino acid chelate ring (Fig. 4). Of paramount importance was the condition that the perfluoro group be situated on the side of the co-ordination plane opposite to the *N*-benzyl substituent of the proline moiety of the complexes, as the results of the trifluoroacetone condensation indicated.

The electrostatic attraction between the partially positively charged Ni^{II} and partially negatively charged trifluoro (or perfluoro) group of the amino acid moiety may be the underlying cause of the unusual effects. The *syn*-2*S* complexes had the closest distance of the fluorine atoms and the Ni^{II} atom in the hydroxy group co-ordinated structures as revealed by molecular mechanics calculations. The computer-derived structure of the complex of *syn*-(2*S*)-**m** is depicted in Fig. 4. The calculated nearest distance between Ni^{II} and the fluorine atoms was equal to 2.83 Å in the complex. There are grounds

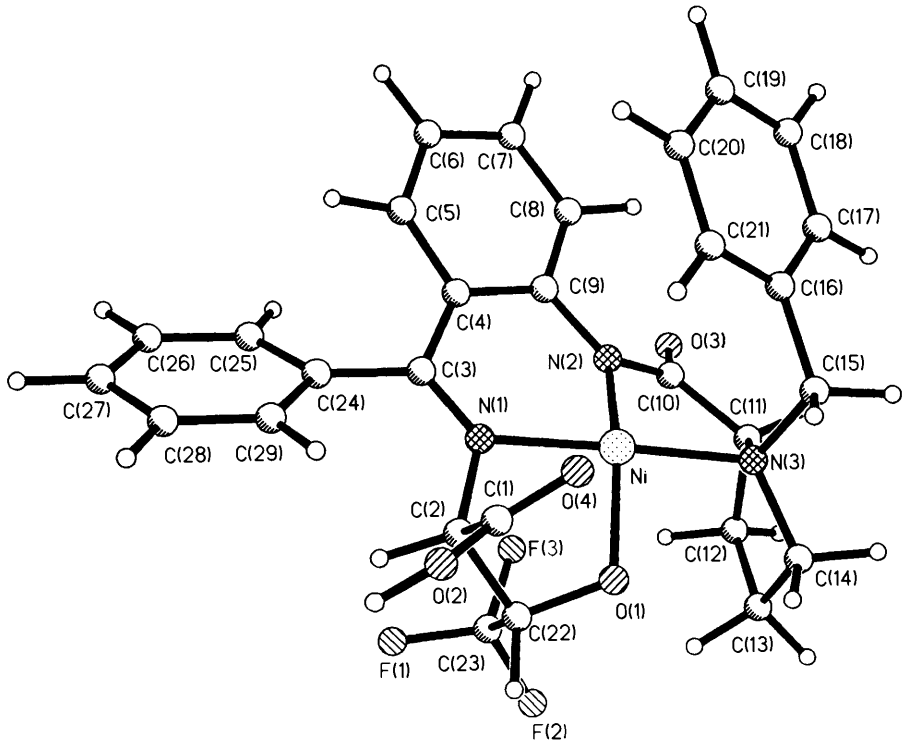


Fig. 4 The computer-generated (MMX calculated) structure of the Ni^{II} complex of *syn*-(2*S*)-trifluorothreonine with the co-ordinated hydroxy group.

Table 3 Some stretching parameters used in molecular mechanics calculations (MMX method)

Atom type (Ni)[a]	Atom type (X)[a]	R_o(A)[b]	K_s (mdyn Å^{-1})
44	6	1.86 (1.8)	2.0
44	8	1.95 (1.98)	2.0
44	9	1.84 (1.91)	2.0
44	37	1.86 (1.87)	2.0

[a] The designations of the atoms are those used in the MMX program. [b] The figures in the brackets are the initial parameters installed in the MMX program.

to believe that the metal ion bears a positive charge. The complexes of (trifluoromethyl)threonine in the crystal are interconnected by hydrogen bonds between the hydroxy group of one molecule and the oxygen atom of the amide group of the second one (see Fig. 2). It indicates clearly that the amide group serves as a donor and bears a partial negative charge. The most likely candidate having a positive charge to neutralize this negative charge would be the metal ion. Calculations repeated with electrostatic terms included and Ni^{II} ion assigned a charge of 1 + disclosed that, in agreement with the experimental results, it was really the *syn*-2*S* configuration that was energetically most favourable, as compared with the complexes of *syn*-(2*R*)-**6m**, *anti*-(2*S*)-**4m**, and *anti*-(2*R*)-**5m**. The electrostatic repulsion between the perfluoroalkyl group and the carboxy group might also destabilize the *anti* disposition of the groups in the hydroxy co-ordinated complexes.

Surprising differences in the reactivity (both regio- and stereo-chemical) of CH_3- and CF_3-substituted compounds were also recently observed by Prof. Seebach's group.[21]

Whatever the source of this unusual stereoselectivity, the synthetic results were impressive. The condensation of trifluoroacetone with complex **1** might be used for the synthesis of enantio- and diastereo-pure (2*S*,3*S*)-(trifluoromethyl)-threonine or, putting it differently, the condensation was capable of distinguishing stereochemically between methyl and trifluoromethyl groups.

Conclusions.—The method elaborated in this work is suitable for the production of enantiomerically and diastereoisomerically pure fluoro-substituted β-hydroxy-α-amino acids and is based on a simple series of reactions and the use of relatively inexpensive reagents, starting from glycine and the commercially available chiral auxiliary BPB. Relatively high chemical and optical yields, the simplicity of the synthetic procedure, and the possibility of obtaining both enantiomers or diastereoisomers of the amino acids, by employing the same chiral auxiliary, might make the method useful.

Experimental

General.—Reagents were purchased from Reakhim (Russia), with the exception of complex **1** synthesized according to ref. 16(*b*), precoated silica gel 60 PF_{254} plates (Merck), Sephadex LH-20 (Pharmacia), and silica gel for column chromatography L40/100 (Chemapol). Solvents were purified in the usual way.[22]

M.p.s were taken in open capillaries and were uncorrected. ^1H NMR and ^{19}F NMR spectra were recorded on Varian WXP-300 and Bruker WP-200 instruments, using $SiMe_4$ and $CFCl_3$ as internal reference in $CDCl_3$ solutions and hexamethyldisiloxane (HMDS) and trifluoroacetic acid (TFA) sealed in a glass capillary for the D_2O solutions. *J* Values are given in Hz. Assignments of the protons in the complexes under study were made by decoupling each, separately observable, proton multiplet and observing the collapse of the splitting thus produced. ORD curves ([M] values in 10^3 deg dm^2 mol^{-1}) were recorded on a JASCO ORD/UV-5 instrument; specific rotations ($[\alpha]_D$ values in 10^{-1} deg cm^2 g^{-1}) were measured on a Perkin-Elmer 241 polarimeter. UV–visible spectra were run on a Specord M-40 instrument. HPLC analyses were done on a LKB instrument packed with Si 100 Polyol-Oro-Cu, with bonded L-proline (Serva) on 250 × 4.6 mm columns with 5 μm thickness of sorbent.

Molecular Mechanics Calculations.—The calculations were performed on a IBM-compatible 386-processor computer, using the MMX force field, 'PC-model' program, 1988 year version, available from Serena Software. To simplify the calculation of the complexes with the co-ordinated hydroxy group, their carboxy groups were assumed to be protonated. Before the calculations were commenced, a new set of parameters of stretching Ni–X (see Table 3) and bending X–Ni–X (X = N, O) parameters (0.1 mdyn Å/rad^2) had to be introduced into the program to accommodate the experimental structure revealed by the X-ray analysis data (see Fig. 2) and the calculated one of the same complex.

X-Ray Analysis.—Red crystals of the major diastereoisomer found in the reaction of compound **1** with trifluoroacetone were obtained from MeCN. Crystal data: $C_{30}H_{28}F_3N_3NiO_4$, M = 610.3, orthorhombic, a = 10.554(4), b = 14.242(5), c = 18.053(8) Å, V = 2713(2) Å^3, Z = 4, D_c = 1.494 g cm^{-3}, space group $P2_12_12_1$, μ = 0.778 mm^{-1}, F(000) = 1264. The unit-cell parameters and reflection intensities from a plate-like crystals of dimensions ~0.5 × 0.3 × 0.1 mm were measured with a four-circle automated Siemens P3/PC diffractometer (T 188 K, Mo-Kα radiation, λ 0.710 73 Å, graphite monochromator, $\theta/2\theta$ scan, $2\theta < 42°$, scan speed 2–15 deg min^{-1}, scan width 1.7; no crystal decay was observed. 2600 Independent observed reflections had $F^2 > 3\sigma$). The structure was solved by direct methods. No absorption correction was applied. All non-hydrogen atoms were refined anisotropically; hydrogen atoms were included as fixed contributions in calculated positions (C–H bond distances of 0.96 Å, O–H of 0.85 Å; only thermal parameters were refined). The weighting scheme $w = [\sigma^2(F) + 0.0001\ F_o^2]^{-1}$ was used. The full-matrix least-squares refinement led to R = 0.0329 (R_w = 0.0324) for the absolute configuration to the known (*S*)-proline, and to R = 0.0475 (R_w = 0.0476) for the inverted structure, thus confirming the former structure with a 99.5% probability according to Hamilton's test. The calculations were carried out with an IBM PC/At-286 computer using the SHELXTL PLUS (PC Version) programs. Atomic co-ordinates, bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre.* In the complex (Fig. 2) the Ni atom is co-ordinated by the square of three nitrogen atoms and the O(1) atom at distances 1.859(3)–1.933(3) Å, the deviations from the mean plane are within 0.03 Å. N(1) and N(2) atoms have planar co-ordination (with an angle sum of 357.9 and 359.1°), whereas N(3) has tetrahedral co-ordination with angles from 103 to 117°. The angles between the base plane NiN(1)N(2)N(3)O(1) and the aromatic rings are as follows: C(4)–C(9) 151.9°, C(16)–C(21) 143.0°, C(25)–C(30) 120.5°. The carboxylic group is essentially asymmetric [C(1)–O(1) 1.300(5) and C(1)–O(2) 1.214(5) Å], being co-ordinated to the Ni atom through O(1). The C(22) atom has the *S* configuration. Intermolecular H-bonds between hydroxy group O(4) and carbonyl oxygen O(3) of the ($x - 1/2$, $3/2 - y$, $1 - z$) molecule (O···O 2.665 Å) link molecules of the complex into chains along the x-axis.

* *Supplementary data:* see 'Instructions for Authors', in the January issue.

Aqueous NaOH *Extraction of Isomers* **4q**, **3q** *and the Product of Trifluoroacetone Condensation with Complex* **1**.—A chloroform solution (5 cm^3) of the complex (3 mmol) was vigorously shaken with 1 mol dm^{-3} NaOH (5 cm^3) for 1 min. The layers were separated and the relative decrease in the concentration of the initial complex in $CHCl_3$ solution was registered at λ 440 nm.

Base-catalysed Deuterium Exchange of the α-Proton of the Amino Acid Moieties of Compound **4o** *or* **3o** *in* CD_3OD.—The complex (0.01 g, 0.012 mmol) was dissolved in CD_3OD (1.3 cm^3) and Et_3N (0.2 cm^3) was added. The solution was filtered. The disappearance of the α-protons of the amino acid moieties of the complexes was monitored at δ 4.31 for **3o** and δ 4.26 for **4o**. It took from 30 min to 1 h for the process to be completed.

Isolation of Amino Acids and Recovery of BPB from the Complexes.—The isolation and recovery were carried out according to the standard procedure described in refs. 2 and 16(*b*).

Determination of the syn- *or* anti-*Configuration of Fluoro-substituted* β-*Hydroxy-α-amino Acids.*—With the exception of the clear cases of the X-ray-determined absolute configuration, the determination of the β-carbon atom configuration was made on a case-by-case basis. For example, it was assumed that the reaction of complex **1** with the fluorine-substituted benzaldehydes under the experimental conditions of method A, as in the case of other substituted benzaldehydes, gave predominantly the diastereoisomer containing *syn*-(2*R*)-β-hydroxy-α-amino acid (*threo*-isomers), isomers **5**.[16a,b] The comparison of the R_f-value of the amino acids recovered from compounds **5b**–**k** with the corresponding R_f-value of *syn*- and *anti*-phenylserines (TLC, cellulose) supports this notion. The absolute configuration of the β-carbon atom of phenylserines, obtained by method B, was determined by comparing R_f data (cellulose), ^1H NMR spectra, and specific rotations of the amino acids, recovered from the diastereoisomerically pure complexes, with samples of the amino acids derived under method A conditions. The *syn*-, *anti*-configurations of the perfluoroalkylserines were assigned in the same manner, employing as a standard the amino acids, the configuration of which was determined by the X-ray analysis.

Method A. Condensation of Aldehydes **2a**–**j** *and Trifluoroacetone with Complex* **1** *in MeOH Catalysed by MeONa at* 25 °C. *Synthesis of* syn-(2R)-3-*Fluorophenyl)serines.*—The procedure is illustrated by the synthesis of *syn*-(2*R*)-β-(2-fluorophenyl)serine, *syn* -(2*R*)-**5b**. To a solution of complex **1** (1.5 g, 3.0 mmol) in 2.25 mol dm^{-3} MeONa in MeOH (3 cm^3) was added 2-fluorobenzaldehyde **2b** (0.5 g, 4.2 mmol) and the mixture was stirred at ambient temperature for 10 min (or 1 h) under Ar, then was added slowly to a solution of 20% aq. AcOH (80 cm^3). The precipitated thick red suspension of the diastereoisomeric complexes was filtered off, washed with water, and dried over P_2O_5 *in vacuo*. The residue was subjected to chromatography on an SiO_2 column [25 × 4 cm; $CHCl_3$–acetone (7:1)]. Two main bands, separated in order of their emergence from the column, yielded compound **5b** (1.3 g, 70%) and its isomer **4b** (0.08 g, 4.3%). *Complex* **5b** had m.p. 140–145 °C (Found: C, 65.7; H, 5.0. $C_{34}H_{30}FN_3NiO_4$ requires C, 65.62; H, 4.86%); $[\alpha]_D^{25}$ (*c* 0.6, $CHCl_3$) −2375; $\delta_H(CDCl_3)$ 8.44–6.79 (18 H, m, ArH), 4.94 (1 H, d, *J* 9, OH), 4.67 (1 H, dd, *J* 9 and 6, β-H), 4.38 (1 H, d, *J* 6, amino acid α-H), 3.74 and 3.53 (2 H, AB, *J* 14, benzyl CH_2) and 3.70–1.26 (7 H, m, Pro); $\delta_F(CDCl_3)$ −113.83 (1 F, m, CF). *Isomer* **4b** had m.p. 207–212 °C (Found: C, 65.4; H, 4.8%); $[\alpha]_D^{25}$ (*c* 0.3, $CHCl_3$) +2314; $\delta_H(CDCl_3)$ 8.29–6.68 (18 H, m, ArH), 5.12 (1 H, d, *J* 9, OH), 4.56 (1 H, dd, *J* 9 and 5, β-H), 4.41 (1 H, d, *J* 5, α-H), 4.15 and 3.41 (2 H, AB, *J* 13, CH_2) and 3.70–1.62 (7 H, m, Pro); $\delta_F(CDCl_3)$ −114.47 (m, CF).

Compound **5b** (1.9 g, 3.0 mmol) was decomposed in the usual manner, and the amino acid was recovered, and recrystallized from EtOH to yield (2R,3S)-3-(2′-*fluorophenyl)serine* [syn-(2R)-**b**] as crystals (0.56 g, 93%); m.p. 190–193 °C (decomp.) [lit.,[9] for *syn*-(2*S*)-**b** 184–186 °C] (Found: C, 54.1; H, 5.1. $C_9H_{10}FNO_3$ requires C, 54.27; H, 5.06%); $[\alpha]_D^{25}$ (*c* 0.32, water) +20.60 {lit.,[9] for *syn*-(2*S*)-**b** $[\alpha]_D^{20}$ (*c* 0.8, water) −18.5}; $\delta_H(D_2O)$ 7.37 and 7.14 (4 H, m, ArH), 3.89 (1 H, d, *J* 5, α-H) and 5.23 (1 H, d, *J* 15, β-H).

Syn-(2*R*)-**a** [(2*R*,3*S*)-3-Phenylserine] was obtained from compound **5a** which was procured by condensation of complex **1** with benzaldehyde **2a**. Two fractions were separated, the major containing **5a** and the minor containing isomer **4a**. The *diastereoisomer* **5a** (1.29 g, 71%) had m.p. 120–129 °C (Found: C, 67.6; H, 5.0. $C_{34}H_{31}N_3NiO_4$ requires C, 67.57; H, 5.17%); $[\alpha]_D^{25}$ (*c* 0.2, $CHCl_3$) −1925; $\delta_H(CDCl_3)$ 8.63–6.81 (19 H, m, ArH), 5.35 (1 H, d, *J* 9, OH), 4.81 (1 H, dd, *J* 9 and 6, β-H), 4.34 (1 H, d, *J* 6, α-H), 3.97 and 3.50 (2 H, AB, *J* 14, benzyl CH_2) and 3.81–1.53 (7 H, m, Pro). *Complex* **4a** (0.07 g, 3.7%) had m.p. 111–118 °C (Found: C, 67.7; H, 5.1%); $[\alpha]_D^{25}$ (*c* 0.3, $CHCl_3$) +2177; $\delta_H(CDCl_3)$ 7.67–6.60 (19 H, m, ArH), 5.48 (1 H, d, *J* 9, OH), 4.65 (1 H, dd, *J* 9 and 5.5, β-H), 4.36 (1 H, d, *J* 5.5, α-H), 3.63 and 3.38 (2 H, AB, *J* 13, benzyl CH_2) and 3.71–1.72 (7 H, m, Pro).

Compound **5a** (1.2 g, 2 mmol) afforded syn-(2*R*)-**a** (0.28 g, 80%), m.p. 200–203 °C (decomp.) [lit.,[8] for *syn*-(2*S*)-**a** 183–186 °C] (Found: C, 59.9; H, 6.3. $C_9H_{11}NO_3$ requires C, 59.66; H, 6.12%); $[\alpha]_D^{25}$ (*c* 0.40, water) +29.5 {lit.,[8] for *syn*-(2*S*)-**b** $[\alpha]_D^{20}$ (*c* 1, water) −34.3}; $\delta_H(D_2O)$ 7.22 (5 H, m, ArH), 5.18 (1 H, d, *J* 4.8, β-H) and 3.88 (1 H, *J* 4.8, α-H).

Syn-(2*R*)-**c** [(2*R*,3*S*)-3-(4′-*Fluorophenyl)serine* was obtained from compound **5c**, which was procured by condensation of compound **1** with aldehyde **2c**. Two fractions were separated, the major containing **5c** and the minor containing **4c**. *Complex* **5c** (1.3 g, 68.5%) had m.p. 145–149 °C (Found: C, 65.5; H, 4.8. $C_{34}H_{30}FN_3NiO_4$ requires C, 65.62; H, 4.86%); $[\alpha]_D^{25}$ (*c* 0.2, $CHCl_3$) −2026; $\delta_H(CDCl_3)$ 8.43–6.79 (18 H, m, ArH), 4.92 (1 H, d, *J* 9, OH), 4.68 (1 H, dd, *J* 9 and 6, β-H), 4.37 (1 H, d, *J* 6, α-H), 3.74 and 3.52 (2 H, AB, *J* 14, benzyl CH_2) and 3.70–1.25 (7 H, m, Pro). *Complex* **4c** (0.07 g, 3.6%) had m.p. 126–135 °C (Found: C, 65.7; H, 4.6%); $[\alpha]_D^{25}$ (*c* 0.1, $CHCl_3$) +2250; $\delta_H(CDCl_3)$ 8.29–6.64 (18 H, m, ArH), 5.11 (1 H, d, *J* 9, OH), 4.55 (1 H, dd, *J* 9 and 5, β-H), 4.40 (1 H, d, *J* 5, α-H), 4.17 and 3.42 (2 H, AB, *J* 13, benzyl CH_2) and 3.71–1.64 (7 H, m, Pro).

Compound **5c** (1.2 g, 2 mmol) afforded syn-(2R)-**c** (0.33 g, 85%), m.p. 207–208 °C (decomp.) (Found: C, 54.2; H, 5.1. $C_9H_{10}FNO_3$ requires C, 54.27; H, 5.06%); $[\alpha]_D^{25}$ (*C* 0.21, water) +20.50; $\delta_H(D_2O)$ 7.42 and 7.18 (4 H, AA′BB′, ArH), 5.21 (1 H, d, *J* 5, β-H) and 3.92 (1 H, d, *J* 5, α-H).

Syn-(2*R*)-**d** {(2*R*,3*S*)-3-[2′-(*Difluoromethoxy)phenyl)serine*} was obtained from compound **5d**, which was procured by condensation of complex **1** with aldehyde **2d**. Two fractions were separated, the major containing **5d** and the minor containing **4d**. *Complex* **5d** (1.5 g, 76%) had m.p. 124–128 °C (Found: C, 62.6; H, 4.7. $C_{35}H_{31}F_2N_3NiO_5$ requires C, 62.71; H, 4.66%); $[\alpha]_D^{25}$ (*c* 0.2, $CHCl_3$) −1370; $\delta_H(CDCl_3)$ 8.46–6.99 (18 H, m, ArH), 6.37 (1 H, dd, *J* 75.3 and 72, $OCHF_2$), 5.26 (1 H, dd, *J* 10 and 5, β-H), 4.91 (1 H, d, *J* 10, OH), 4.34 (1 H, d, *J* 5, α-H), 3.83 and 3.49 (2 H, AB, *J* 14, CH_2), 3.61–1.41 (7 H, m, Pro); $\delta_F(CDCl_3)$ −80.63 and −82.91 (2 F, AB, *J* 171.4, $OCHF_2$). *Complex* **4d** (0.2 g, 10.5%) had m.p. 198–203 °C (Found: C, 63.0; H, 4.5%); $[\alpha]_D^{25}$ (*c* 0.3, $CHCl_3$) +2494; $\delta_H(CDCl_3)$ 8.36–6.64 (19 H, m, ArH), 4.86 (1 H, d, *J* 9.5, OH), 6.25 (1 H, dd, *J* 74.8 and 72.2, CHF_2), 5.17 (1 H, dd, *J* 9.5 and 5, β-H), 4.33 (1 H, d, *J*

5, α-H), 4.14 and 3.44 (2 H, AB, *J* 13, benzyl CH_2) and 3.31–1.61 (7 H, m, Pro); $\delta_F(CDCl_3)$ −80.25 and −82.55 (2 F, AB, *J* 171, $OCHF_2$).

Compound **5d** (1.4 g, 2 mmol) afforded syn-(2R)-**d** (0.45 g, 90%), m.p. 216–217 °C (decomp.) (Found: C, 48.7; H, 4.55. $C_{10}H_{11}F_2NO_4$ requires C, 48.59; H, 4.49%); $[\alpha]_D^{25}$ (*c* 0.13, water) +28.00; $\delta_H(D_2O)$ 7.54–7.17 (4 H, m, ArH), 6.82 (1 H, t, *J* 73.5, $OCHF_2$), 5.56 (1 H, d, *J* 4.3, β-H) and 4.05 (1 H, d, *J* 4.3, α-H).

syn-(2*R*)-**e** {(2*R*,3*S*)-3-[4′-(*Difluoromethoxy*)*phenyl*]*serine*} was obtained from compound **5e**, which was procured by condensation of complex **1** with aldehyde **2e**. Two fractions were separated, the major containing **5e** and the minor containing **4e**. *Complex* **5e** (1.4 g, 70.5%) had m.p. 135–142 °C (Found: C, 62.7; H, 4.6. $C_{35}H_{31}F_2N_3NiO_5$ requires C, 62.71; H, 4.66%); $[\alpha]_D^{25}$ (*c* 0.3, $CHCl_3$) −1724.1; $\delta_H(CDCl_3)$ 7.55–6.74 (18 H, m, ArH), 6.35 (1 H, t, *J* 73.3, CHF_2), 4.92 (1 H, d, *J* 8, OH), 4.63 (1 H, dd, *J* 8 and 5.3, β-H), 4.32 (1 H, d, *J* 5.3, α-H), 3.78 and 3.49 (2 H, AB, *J* 13.8, benzyl CH_2) and 3.61–1.45 (7 H, m, Pro). *Complex* **4e** (0.18 g, 8.7%) had m.p. 118–122 °C (Found: C, 62.85; H, 4.5%); $[\alpha]_D^{25}$ (*c* 0.2, $CHCl_3$) +1900; $\delta_H(CDCl_3)$ 8.34–6.63 (19 H, m, ArH), 7.09 (1 H, t, *J* 73.4, $OCHF_2$), 5.57 (1 H, d, *J* 8, OH), 4.74 (1 H, dd, *J* 8 and 5, β-H), 4.20 (1 H, d, *J* 5, α-H), 4.05 and 3.43 (2 H, AB, *J* 12, benzyl CH_2) and 3.69–1.74 (7 H, m, Pro).

Compound **5e** (1.4 g, 2 mmol) afforded syn-(2R)-**e** (0.48 g, *95%*), m.p. 190–195 °C (decomp.) (Found: C, 48.5; H, 4.5. $C_{10}H_{11}F_2NO_4$ requires C, 48.59; H, 4.49%); $[\alpha]_D^{25}$ (*c* 0.26, water) +15.90; $\delta_H(D_2O)$ 7.43 and 7.17 (4 H, m, ArH), 6.74 [*1 H, t, J* 74, $OCHF_2$), 5.26 (1 H, d, *J* 5, β-H) and 3.94 (1 H, d, *J* 5, α-H).

syn-(2*R*)-**f** {(2*R*,3*S*)-3-[2′-(*Trifluoromethyl*)*phenyl*]*serine*} was obtained from compound **5f**, which was procured by condensation of complex **1** with aldehyde **2f**. Two fractions were separated, the major containing **5f** and the minor containing **4f**. *Complex* **5f** (1.45 g, 71.5%) had m.p. 122–125 °C (Found: C, 62.6; H, 4.5. $C_{35}H_{30}F_3N_3NiO_4$ requires C, 62.53; H, 4.50%); $[\alpha]_D^{25}$ (*c* 0.4, $CHCl_3$) −1050; $\delta_H(CDCl_3)$ 6.60–6.57 (18 H, m, ArH), 6.00 (1 H, d, *J* 7.5, OH), 5.54 (1 H, dd, *J* 7.5 and 4.5, β-H), 4.80 and 3.86 (2 H, AB, *J* 13.5, benzyl CH_2), 4.42 (1 H, d, *J* 4.5, α-H) and 3.80–1.57 (7 H, m, Pro); $\delta_F(CDCl_3)$ − 56.11 (s, CF_3). *Complex* **4f** (0.2 g, 10.5%) had m.p. 199–205 °C (Found: C, 62.5; H, 4.5%); $[\alpha]_D^{25}$ (*c* 0.2, $CHCl_3$) +2593; $\delta_H(CDCl_3)$ 8.31–6.46 (18 H, m, ArH), 5.54 (1 H, dd, *J* 8 and 4, β-H), 5.34 (1 H, d, *J* 8, OH), 4.26 (1 H, d, *J* 4, α-H), 4.20 and 3.37 (2 H, AB, *J* 13, benzyl CH_2) and 3.63–1.81 (7 H, m, Pro); $\delta_F(CDCl_3)$ −59.20 (s, CF_3).

Compound **5f** (1.4 g, 2 mmol) afforded syn-(2R)-**f** (0.44 g, 90%), m.p. 223–224 °C (decomp.) (Found: C, 48.3; H, 4.1. $C_{10}H_{10}F_3NO_3$ requires C, 48.20; H, 4.05%); $[\alpha]_D^{25}$ (*c* 0.14, water) +5.63; $\delta_H(D_2O)$ 7.18 (4 H, m, ArH), 5.52 (1 H, d, *J* 4.5, β-H) and 4.02 (1 H, d, *J* 4.5, α-H).

syn-(2R)-**g** {(2*R*,3*S*)-3-[4′-(*Trifluoromethoxy*)*phenyl*]*serine*} was obtained from compound **5g**, which was procured by condensation of complex **1** with aldehyde **2g**. Two fractions were separated, the major containing **5g** and the minor containing **4g**. *Complex* **5g** (1.56 g, 74%) had m.p. 145–152 °C (Found: C, 61.2; H, 4.4. $C_{35}H_{30}F_3N_3NiO_5$ requires C, 61.07; H, 4.39%); $[\alpha]_D^{25}$ (*c* 0.3, $CHCl_3$) −1820; $\delta_H(CDCl_3)$ 7.50–6.73 (18 H, m, ArH), 4.91 (1 H, d, *J* 8.5, OH), 4.65 (1 H, dd, *J* 8.5 and 5.5, β-H), 4.33 (1 H, d, *J* 5.5, α-H), 3.77 and 3.50 (2 H, AB, *J* 13.5, benzyl CH_2) and 3.64–1.51 (7 H, m, Pro); $\delta_F(CDCl_3)$ −58.09 (s, CF_3). *Complex* **4g** (0.2 g, 10%) had m.p. 178–184 °C (Found: C, 61.1; H, 4.4%); $[\alpha]_D^{25}$ (*c* 0.6, $CHCl_3$) +1690; $\delta_H[(CD_3)_2CO]$ 8.40–6.66 (18 H, m, ArH), 5.69 (1 H, d, *J* 8.5, OH), 4.80 (1 H, dd, *J* 8.5 and 5.5, β-H), 4.17 (1 H, d, *J* 5.5, α-H), 4.07 and 3.46 (2 H, AB, *J* 12, benzyl CH_2), 3.60–1.80 (7 H, m, Pro); $\delta_F[(CD_3)_2CO]$ −58.33 (s, CF_3).

Compound **5g** (1.5 g, 2.2 mmol) afforded syn-(2R)-**g** {(2R,3S)-3-[4′-(*trifluoromethoxy*)*phenyl*]*serine*} (0.53 g, 91%), m.p. 202–205 °C (decomp.) (Found: C, 45.4; H, 3.9. $C_{10}H_{10}F_3NO_4$ requires C, 45.29; H, 3.80%); $[\alpha]_D^{25}$ (*c* 0.16, water) +16.46; $\delta_H(D_2O)$ 7.39 and 7.21 (4 H, m, ArH), 5.20 (1 H, d, *J* 4.7, β-H), and 3.94 (1 H, d, *J* 4.7, α-H).

syn-(2*R*)-**h** [(2*R*,3*S*)-3-(3′-*Fluoro*-4′-*methoxyphenyl*)*serine*] was obtained from compound **5h**, which was procured by condensation of complex **1** with aldehyde **2h**. Two fractions were separated, the major containing **5h** and the minor containing **4h**. *Complex* **5h** (1.24 g, 63%) had m.p. 224–230 °C (Found: C, 64.5; H, 5.1. $C_{35}H_{32}FN_3NiO_5$ requires C, 64.44; H, 4.95%); $[\alpha]_D^{25}$ (*c* 0.1, $CHCl_3$) −733; $\delta_H(CDCl_3)$ 8.49–6.80 (17 H, m, ArH), 4.80 (1 H, d, *J* 10, OH), 4.63 (1 H, dd, *J* 10 and 5.5, β-H), 4.37 (1 H, d, *J* 5.5, α-H), 4.00 and 3.60 (2 H, AB, *J* 14, benzyl CH_2), 3.77 (3 H, s, OMe), and 3.66–1.49 (7 H, m, Pro).

Compound **5h** (1.2 g, 1.8 mmol) afforded syn-(2R)-**h** [(2R,3S)-β-(3-*fluoro*-4-*methoxyphenyl*)*serine*] (0.35 g, 84%), m.p. 190–195 °C (decomp.) (Found: C, 52.3; H, 5.3. $C_{10}H_{12}FNO_4$ requires C, 52.40; H, 5.28%); $[\alpha]_D^{25}$ (*c* 0.15, water) +17.57; $\delta_H(D_2O)$ 7.14 (3 H, m, ArH), 5.16 (1 H, d, *J* 4.5, β-H), 3.89 (1 H, d, *J* 4.5, α-H) and 3.84 (3 H, s, OMe).

syn-(2*R*)-**i** [(2*R*,3*S*)-3-(3′,4′,5′-*Trimethoxyphenyl*)*serine*] might be obtained from complex **5i**, which was procured by condensation of complex **1** with aldehyde **2i**. Two fractions were separated, the major containing **5i** and the minor containing **4i**. Only one fraction was separated, containing complex **5i**. *Complex* **5i** (1.33 g, 64%) had m.p. 151–155 °C (Found: C, 64.2; H, 5.5. $C_{37}H_{37}N_3NiO_7$ requires C, 63.99; H, 5.37%); $[\alpha]_D^{25}$ (*c* 0.1, $CHCl_3$) −1177; $\delta_H(CDCl_3)$ 7.55–6.73 (16 H, m, ArH), 4.77 (1 H, d, *J* 9.1, OH), 4.64 (1 H, dd, *J* 9.1 and 5.1, β-H), 4.28 (1 H, d, *J* 5.1, α-H), 4.09 and 3.61 (2 H, AB, *J* 13.7, benzyl CH_2), 3.69–1.45 (7 H, m, Pro), 3.72 (3 H, s, OMe) and 3.63 (6 H, s, 2 × OMe). Preliminary results indicated that *syn*-(2*R*)-**i** might be recovered from complex **5i** in the usual way.

syn-(2*R*)-**j** [(2*R*,3*S*)-3-(4′-*Nitrophenyl*)*serine*] might be obtained from compound **5j**, which was procured by condensation of complex **1** with aldehyde **2j**. Two fractions were separated, the major containing **5j** and the minor containing **4j**. *Complex* **5j** (1.42 g, 73%) had m.p. 122–128 °C (Found: C, 63.0; H, 4.8. $C_{34}H_{30}N_4NiO_6$ requires C, 62.89; H, 4.66%; $[\alpha]_D^{25}$ (*c* 0.1, $CHCl_3$) −1410; $\delta_H(CDCl_3)$ 8.50–6.75 (18 H, m, ArH), 5.04 (1 H, d, *J* 9.3, OH), 4.75 (1 H, dd, *J* 9.3 and 5.6, β-H), 4.35 (1 H, d, *J* 5.6, α-H), 3.75 and 3.44 (2 H, AB, *J* 13.8, benzyl CH_2) and 3.56–1.50 (7 H, m, Pro). Complex **4j** (0.29 g, 15%) had m.p. 111–115 °C (Found: C, 62.9; H, 4.7%); $[\alpha]_D^{25}$ (*c* 0.05, $CHCl_3$) +1413; $\delta_H(CDCl_3)$ 8.30–6.65 (18 H, m, ArH), 4.98 (1 H, d, *J* 9, OH), 4.65 (1 H, dd, *J* 9 and 5.5, β-H), 4.40 (1 H, d, *J* 5.5, α-H), 4.13 and 3.38 (2 H, AB, *J* 13.5, benzyl CH_2) and 3.58–1.35 (7 H, m, Pro). Preliminary results indicate that *syn*-(2*R*)-**j** might be recovered from compound **5j** in the usual way.

syn-(2*R*)-**l** [(2*R*,3*S*)-3-(*Tetrafluoro*-4′-*phenyl*)*serine*] was obtained from compound **5l**, which was procured by condensation of complex **1** with aldehyde **2k**. To ensure complete substitution of the *p*-fluoro substituent and transformation of the mixture of the initially formed complexes into isomers **5l** and **4l**, additional portions of MeONa had to be added to the mixture and its temperature had to be elevated to 50 °C. The reaction was stopped when there was no longer any change in the ratio of the compounds in the reaction mixture as monitored by TLC. Two fractions were separated, the major containing **5l** and the minor containing **4l**. *Complex* **5l** (1.1 g, 52%) had m.p. 127–132 °C (Found: C, 60.1; H, 4.1. $C_{35}H_{29}F_4N_3NiO_5$ requires C, 59.52; H, 4.14%); $[\alpha]_D^{25}$ (*c* 0.02, $CHCl_3$) −1141; $\delta_H(CDCl_3)$ 6.70–8.60 (14 H, m, ArH), 5.46 (1 H, dd, *J* 7.4 and 10.2, β-H), 4.36 (1 H, d, *J* 7.4, α-H), 4.02 (1 H, d, *J* 10.2, OH) 4.00 (3 H, t, *J* 1.6, Me), 3.83 and 4.43 (2 H, AB, *J* 13.6, benzyl CH_2) and 1.50–3.75 (7 H, m, Pro);

$\delta_F(CDCl_3)$ −143.5 (2 F, m, 2 × CF) and −158.5 (2 F, m, 2 × CF). *Complex* **4l** (0.15 g, 7%) had m.p. 127–132 °C (Found: C, 59.8; H, 4.4%); $[\alpha]_D^{25}$ (*c* 0.01, $CHCl_3$) +2200; $\delta_H(CDCl_3)$ 6.60–8.30 (14 H, m, ArH), 5.61 (1 H, dd, *J* 7.6 and 10.2, β-H), 4.38 (1 H, d, *J* 7.6, α-H), 4.10 (3 H, t, *J* 1.4, Me), 4.05 (1 H, d, *J* 10.2, OH), 3.51 and 4.29 (2 H, AB, *J* 12.6, benzyl CH_2) and 1.60–3.54 (7 H, m, Pro); $\delta_F(CDCl_3)$ −144.1 (2 F, m, 2 × CF) and −158.4 (2 F, m, 2 × CF).

Compound **5l** (1 g, 1.4 mmol) afforded *compound* syn-(2R)-**l** (0.32 g, 79%), m.p. 195–197 °C (decomp.) (Found: F, 26.75; N, 4.9. $C_{10}H_9F_4NO_4$ requires F, 26.83; N, 4.95%); $[\alpha]_D^{25}$ (*c* 1.0, 6 mol dm^{-3} HCl) −14.68; $\delta_H(D_2O)$ 5.25 (1 H, d, *J* 8.7, β-H), 4.00 (3 H, t, *J* 1, Me), and 4.05 (1 H, d, *J* 8.7, α-H); $\delta_F(D_2O)$ −145.0 (2 F, m, 2 × CF) and −158.1 (2 F, m, 2 × CF).

Compound **4l** (0.7 g, 0.9 mmol) afforded *compound* syn-(2S)-**l** (0.23 g, 89%), m.p. 195–199 °C (decomp.) (Found: F, 26.6; N, 5.0%); $[\alpha]_D^{25}$ (*c* 1.0, 6 mol dm^{-3} HCl) +14.58; $\delta_H(D_2O)$ 5.20 (1 H, d, *J* 8.7, β-H), 4.06 (1 H, d, *J* 8.7, α-H) and 4.00 (3 H, t, *J* 1.1 Me); $\delta_F(D_2O)$ −145.0 (2 F, m, 2 × CF) and −158.2 (2 F, m, 2 × CF).

(2*S*,3*S*)-3-(*Trifluoromethyl*)*threonine* was obtained from the corresponding diastereoisomerically pure complex which was procured by condensation of complex **1** (0.87 g, 1.74 mmol) with trifluoroacetone (1.16 g, 10.4 mmol). The reaction took 5–10 min for its completion (TLC). The only fraction of the *complexes*, which contained the amino acid, was purified by chromatography (0.71 g, 69%), m.p. 163–170 °C (Found: C, 59.25; H, 4.6; F, 9.4. $C_{30}H_{28}F_3N_3NiO_4$ (requires C, 59.05; H, 4.62; F, 9.34%); $\delta_H(CDCl_3)$ 8.40–6.60 (14 H, m, ArH), 4.84 (1 H, br s, OH), 4.26 and 3.37 (2 H, AB, *J* 12.6, benzyl CH_2), 4.21 (1 H, br s, α-H), 3.48–1.85 (7 H, m, Pro-H) and 1.47 (3 H, s, Me); $\delta_F(CDCl_3)$ −77.8 (s, CF_3).

The complex was decomposed in the usual manner to give (2S,3S)-β-(*trifluoromethyl*)*threonine* (0.12 g, 77%), m.p. 125–130 °C (decomp.) (Found: C, 32.2; H, 4.3; F, 30.45. $C_5H_8F_3NO_3$ requires C, 32.09; H, 4.31; F, 30.46%); $[\alpha]_D^{25}$ (*c* 1, 6 mol dm^{-3} HCl) +7.13; $\delta_H(D_2O)$ 4.31 (1 H, br s, α-H) and 1.51 (3 H, s, Me).

Method A'. Condensation of Aldehydes **2m–p** *with Complex* **1** *in MeOH Catalysed by MeONa at* 50 °C. *Synthesis of* syn-(2S)-3-(*Perfluoroalkyl*)*serines*.—The procedure is illustrated by the synthesis of *syn*-(2*S*)-**n** [(2*S*,3*S*)-3-(nonafluorobutyl)serine]. To a solution of complex **1** (1.5 g, 3 mmol) in 2.25 mol dm^{-3} MeONa in MeOH (3 cm^3) was added aldehyde **2n** (0.74 g, 6 mmol), and the mixture was heated at 50–60 °C for 10 min, then the reaction mixture was added to a stirred solution of 20% aq. AcOH (80 cm^3). The precipitated thick red suspension of the diastereoisomeric complexes was filtered off, washed with water, and dried over P_2O_5 *in vacuo*. The residue was subjected to chromatography on an SiO_2 column [25 × 4 cm; $CHCl_3$–acetone (7:1)]. Two main bands, separated in the order of their emergence from the column, contained compounds **5n** (minor) and **4n** (major).

Compound **4n** (1.75 g, 78.1%) had m.p. 110–116 °C (Found: C, 51.2; H, 3.8; F, 22.7. $C_{32}H_{26}F_9N_3NiO_4$ requires C, 51.50; H, 3.51; F, 22.91%); $[\alpha]_D^{25}$ (*c* 0.01, $CHCl_3$) +2330; $\delta_H(CDCl_3)$ 8.18–6.50 (14 H, m, ArH), 5.65 (1 H, d, *J* 10, OH), 4.27 and 3.45 (2 H, AB, *J* 12.0, benzyl CH_2), 4.25 (1 H, d, *J* 5.4, α-H), 3.82 (1 H, ddd, *J* 10.26 and 5.4, β-H) and 3.35–1.94 (7 H, m, Pro); $\delta_F(CDCl_3)$ 79.53 (3 F, m, CF_3), 112.03 and 124.03 (2 F, AB, *J* 27, CF_2), 120.53 and 123.03 (2 F, AB, *J* 300, CF_2) and 123.33 and 126.53 (2 F, AB, *J* 287, CF_2).

Compound **5n** (0.07 g, 3.3%) had m.p. 210–212 °C (Found: C, 51.2; H, 3.65; F, 22.8%); $[\alpha]_D^{25}$ (*c* 0.05, $CHCl_3$) −1584; $\delta_H(CDCl_3)$ 8.50–6.81 (14 H, m, ArH), 5.95 (1 H, m, OH), 4.94 and 4.05 (2 H, AB, *J* 13, benzyl CH_2), 4.40 (1 H, d, *J* 4, α-H), 4.31–1.78 (7 H, m, Pro) and 3.65 (1 H, dd, *J* 4 and 9, β-H).

Compound **4n** (1.5 g, 2 mmol) was decomposed in the usual manner and the amino acid was recovered and recrystallized from EtOH to yield compound syn-(2S)-**n** (0.54 g, 85%), m.p. 145–148 °C (decomp.) (Found: C, 26.2; H, 1.8; F, 52.9. $C_7H_6F_9NO_3$ requires C, 26.02; H, 1.87; F, 52.92%); $[\alpha]_D^{25}$ (*c* 1.3, water) −7.9; $[\alpha]_D^{25}$ (*c* 2, 6 mol dm^{-3} HCl) +5.21.

syn-(2*S*)-**m** [(2*S*,3*S*)-4,4,4-*Trifluorothreonine*] was obtained from compound **4m**, which was procured by condensation of complex **1** with aldehyde **2m** as described above. *Compound* **4m** (1.26 g, 71.5%) had m.p. 202–205 °C (Found: C, 58.2; H, 4.5; F, 9.6. $C_{29}H_{26}F_3N_3NiO_4$ requires C, 58.42; H, 4.40; F, 9.56%); $[\alpha]_D^{25}$ (*c* 0.02, $CHCl_3$) +3252; $\delta_H(CDCl_3)$ 8.25–6.58 (14 H, m, ArH), 5.55 (1 H, d, *J* 10, OH), 4.27 (1 H, d, *J* 5.5, α-H), 4.30 and 3.53 (2 H, AB, *J* 13.0, benzyl CH_2), 3.58 (1 H, m, β-H) and 3.45–1.65 (7 H, m, Pro); $\delta_H(CDCl_3)$ 71.31 (3 F, d, *J* 7.5, CF_3).

Compound **5m** (0.05 g, 3.3%) had m.p. 215–220 °C (Found: C, 58.2; H, 4.6; F, 9.3%); $[\alpha]_D^{25}$ (*c* 0.02, $CHCl_3$) −1292; $\delta_H(CDCl_3)$ 8.45–6.74 (14 H, m, ArH), 5.91 (1 H, m, OH), 4.91 and 3.95 (2 H, AB, *J* 13, benzyl CH_2), 4.41 (1 H, m, α-H), 4.01–1.74 (7 H, m, Pro) and 3.64 (1 H, m, β-H).

Compound **4m** (1.2 g, 2 mmol) afforded *syn*-(2*S*)-**m** (0.3 g, 85%), m.p. 210–212 °C (decomp.) [lit.,[8] for *syn*-(2*S*)-**m** 209–213 °C] (Found: C, 27.8; H, 3.6; F, 32.8. Calc. for $C_4H_6F_3NO_3$. C, 27.76; H, 3.49; F, 32.93%); $[\alpha]_D^{25}$ (*c* 1.5, water) −12.7; $[\alpha]_D^{25}$ (*c* 2.0, 6 mol dm^{-3} HCl) +1.77; {lit.,[8] $[\alpha]_D^{18-25}$ (*c* 1, water) −12.4}.

Compound *syn*-(2*S*)-**o** might be obtained from compound **4o**, which was procured by condensation of complex **1** with aldehyde **2o** as described above. Complex **4o** (2.4 g, 94%) had m.p. 125–130 °C (Found: C, 49.1; H, 3.1; F, 27.6. $C_{34}H_{27}F_{12}N_3NiO_4$ requires C, 49.30; H, 3.29; F, 27.52%); $[\alpha]_D^{25}$ (*c* 0.04, $CHCl_3$) +2180; $\delta_H(CDCl_3)$ 8.11–6.55 (14 H, m, ArH), 6.07 (1 H, tt, *J* 50 and 6), 5.63 (1 H, d, *J* 10, OH), 4.37 and 3.58 (2 H, AB, *J* 12.7, benzyl CH_2), 4.26 (1 H, d, *J* 4.6, α-H), 3.86 (1 H, ddd, *J* 10.25 and 4.6, β-H) and 3.45–1.95 (7 H, m, Pro). Complex **5o** (0.14 g, 5.5%) had m.p. 185–190 °C (Found: C, 49.1; H, 3.2; F, 27.9%); $[\alpha]_D^{25}$ (*c* 0.03, $CHCl_3$) −1946. Preliminary experiments indicated that *syn*-(2*S*)-**o** might be recovered from compound **4o** in the usual way.

Compound *syn*-(2*S*)-**p** might be obtained from compound **4p**, which was procured by condensation of complex **1** with aldehyde **2p**. *Complex* **4o** (1.76 g, 68.9%) had m.p. 101–103 °C (Found: C, 48.3; H, 2.9; F, 28.9. $C_{34}H_{26}F_{13}N_3NiO_4$ requires C, 48.26; H, 3.10; F, 29.18%); $[\alpha]_D^{25}$ (*c* 0.03, $CHCl_3$) +1712. Preliminary experiments indicated that *syn*-(2*S*)-**p** might be recovered from compound **4p** in the usual way.

Method B. Condensation of Aldehydes **2b–g, k** *with Complex* **1** *in* MeOH *Catalysed by* Et_3N. *Synthesis of* syn-(2S)-3-(*Fluorophenyl*)*serines* [syn(2S)-**d** *and* syn-(2S)-**f**].—*Procedure B is illustrated by the synthesis of syn*-(2*S*)-**f** {(2*S*,3*R*)-3-[2'-(trifluoromethyl)phenyl]serine}. To a solution of complex **1** (1.5 g, 3 mmol) in MeOH (3.3 cm^3) were added the benzaldehyde **2f** (1.2 g, 7 mmol) and Et_3N (1.5 cm^3) and the mixture was kept at ambient temperature for 3 days. The reaction mixture was then added slowly to 20% aq. AcOH (80 cm^3). The product was extracted by $CHCl_3$ and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to chromatography on SiO_2 [column 25 × 4 cm; $CHCl_3$–Me_2CO (7:1)]. Two major fractions in the ratio 10:1 were collected in order of emergence from the chromatographic column. The first fraction consisted of the diastereoisomerically pure complex of *syn*-(2*S*)-**f** (**4f**), the second was found to be compound **3f**. Complex **4f** (1.05 g, 52%) had the same set of parameters as described above (Method A).

Compound **4f** (1 g, 1.5 mmol) was decomposed in the usual manner and the amino acid was recovered and recrystallized from EtOH to yield *syn*-(2*S*)-**f** 0.3 g, 80%), m.p. 215–217 °C,

(decomp.); $[\alpha]_D^{25}$ (*c* 0.1, water) −6.45. Compound *syn*-(2*S*)-**f** had the same elemental analysis and ^{1}H NMR spectrum as did *syn*-(2*R*)-**f** described above.

Compound *syn*-(2*S*)-**d** {(2*S*,3*S*)-3-[2′-(difluoromethoxy)-phenyl]serine} was obtained from compound **4d**, which was procured by condensation of complex **1** with aldehyde **2d** as described above. Compound **4d** (1.01 g, 50%) had m.p. 198–203 °C; $[\alpha]_D^{25}$ (*c* 0.05, $CHCl_3$) +2494. The complex had the same set of parameters as described above (Method A).

Compound **4d** (0.94 g, 1.4 mmol) was decomposed in the usual manner and the amino acid was recovered and recrystallized from EtOH to yield *syn*-(2*S*)-**d** (0.28 g, 77%), m.p. 214–216 °C (decomp.); $[\alpha]_D^{25}$ (*c* 0.1, water) −28.21.

Method C. Condensation of Aldehydes **2k**, **o**, **q**, *with Complex* **1** *in* $CHCl_3$ *Catalysed by DABCO: Synthesis of* (2S,3R)-3-(*Pentafluorophenyl*)*serine* [syn-(2S)-**k**], (2S,3S)-3-(*Pentafluorophenyl*)*serine*[anti(2S)-**k**],(2S,3S)-3-(1,1,2,2,3,3,4,4-*Octafluorobutyl*)*serine* [syn-(2S)-**q**] *and* (2S,3R)-3-(1,1,2,2,3,3,4,4-*Octafluorobutyl*)*serine* [anti-(2S)-**q**].—The procedure is illustrated by the synthesis of *syn*-(2*S*)-**k** and *anti*-(2*S*)-**k**. To a solution of complex **1** (3 g, 6 mmol) in $CHCl_3$ (7 cm^3) were added pentafluorobenzaldehyde **2k** (1.3 g, 6.6 mmol) and DABCO (0.7 g, 6.3 mmol) and the mixture was kept at ambient temperature for 2 h; it was then was added slowly to 20% aq. AcOH (100 cm^3). The product was extracted with $CHCl_3$ and dried over $MgSO_4$. The solvent was evaporated off under reduced pressure. The residue was subjected to chromatography on SiO_2 (column 30 × 5 cm; $CHCl_3$). Three major fractions were collected in order of emergence from the chromatographic column: compounds **7** (complex of pentafluoroaminocinnamic acid derived from **4k** and **3k** *via* dehydration of the amino acid moiety), **4k** and **3k**. Complex **7** (0.12 g, 3%) had m.p. 193–197 °C (Found: C, 60.3; H, 3.5. $C_{34}H_{24}F_5N_3NiO_3$ requires C, 60.38; H, 3.58%); $[\alpha]_D^{25}$ (*c* 0.05, $CHCl_3$) +1654; $\delta_H(CDCl_3)$ 6.60–8.20 (14 H, m, ArH), 5.28 (1 H, t, *J* 1.2. =CH), 3.31 and 4.25 (2 H, AB, *J* 12.6, benzyl CH_2) and 2.00–4.00 (7 H, m, Pro); $\delta_F(CDCl_3)$ −137.0 (2 F, m, 2 × CF), −153.6 (1 F, m, CF) and −161.8 (2 F, m, 2 × CF). Complex **4k** (1.2 g, 29%) had m.p. 134–140 °C (Found: C, 58.3; H, 3.5. $C_{34}H_{26}F_5N_3NiO_4$ requires C, 58.82; H, 3.78%); $[\alpha]_D^{25}$ (*c* 0.04, $CHCl_3$) +2295; $\delta_H(CDCl_3)$ 6.60–8.20 (14 H, m, ArH), 5.92 (1 H, br t, *J* 7.8, β-H), 4.81 (1 H, br d, *J* 7.8, OH) 4.36 (1 H, d, *J* 7.8, α-H), 3.44 and 4.27 (2 H, AB, *J* 12.6, benzyl CH_2), 1.70–3.41 (7 H, m, Pro); $\delta_F(CDCl_3)$ −141.7 (2 F, m, 2 × CF) and −154.6 (1 F, m, CF).

Compound **3k** (1.46 g, 35%) had m.p. 198–203 °C (Found: 58.7; H, 3.7%); $[\alpha]_D^{25}$ (*c* 0.5, $CHCl_3$) +2400; $\delta_H(CDCl_3)$ 6.58–8.20 (14 H, m, ArH), 5.30 (1 H, d, *J* 4.4, β-H), 4.07 (1 H, d, *J* 4.4, α-H), 3.45 and 4.34 (2 H, AB, *J* 12.6, benzyl CH_2); $\delta_F(CDCl_3)$ −141.6 (2 F, m, 2 × CF), −155.9 (1 F, m, CF), −163.8 (2 F, m, 2 × CF).

Compound **4k** was decomposed and the amino acid recovered in the usual manner. The amino acid was recrystallized from EtOH to yield syn-(2S)-**k** (0.38 g, 81%); it had m.p. 200–203 °C (decomp.) (Found: F, 35.0; N, 5.15. $C_9H_6F_5NO_3$ requires F, 35.25; N, 5.15%); $[\alpha]_D^{25}$ (*c* 1.0, 6 mol dm^{-3} HCl) + 13.03; $\delta_H(D_2O)$ 5.13 (1 H, d, *J* 9.4, β-H) and 3.93 (1 H, d, *J* 9.4, α-H); $\delta_F(D_2O)$ −148.53 (2 F, m, 2 CF), −159.33 (1 F, m, CF) and −167.63 (2 F, m, 2 × CF).

Compound **3k** (1.4 g, 2 mmol) yielded anti-(2S)-**k** (0.43 g, 80%), m.p. 213–215 °C (decomp.) (Found: F, 35.1; N, 5.35%); $[\alpha]_D^{25}$ (*c* 0.5, 6 mol dm^{-3} HCl) +37.4; δ_H(6 mol dm^{-3} DCl) 3.54 (1 H, d, *J* 4.8, β-H) and 2.30 (1 H, d, *J* 4.8, α-H).

syn-(2*S*)-**q** [(2*S*,3*S*)-3-(1,1,2,2,3,3,4,4-*O*-Octafluorobutyl)-serine] was obtained from compound **4q**, which was procured by condensation of complex **1** with aldehyde **2q** as described above. *Compound* **4q** (3.69 g, 35%) had m.p. 210–212 °C (Found: C, 53.1; H, 3.75; F, 20.5. $C_{32}H_{27}F_8N_3NiO_4$ requires C, 52.78; H, 3.74; F, 20.87%); $[\alpha]_D^{25}$ (*c* 0.4, $CHCl_3$) +2580; $\delta_H(CDCl_3)$ 8.16–6.60 (14 H, m, ArH), 6.08 (1 H, tt, *J* 51.4 and 5.8, CHF_2), 5.69 (1 H, d, *J* 10.4, OH), 4.32 (1 H, d, J_{HH} 5.6, α-H), 4.24 and 3.63 (2 H, AB, *J* 12.6, benzyl CH_2), 3.87 (1 H, ddd, *J* 5.6, J_{HH} 10.4, J_{HF} 25.6, β-H), 3.53–2.05 (7 H, m, Pro).

Complex **4q** (1.0 g, 1.37 mmol) was decomposed to give syn-(2S)-**q** (0.39 g, 95%), m.p. 135–138 °C (Found: C, 27.6; H, 2.3; F, 49.8. $C_7H_7F_8NO_3$ requires C, 27.56; H, 2.31; F, 49.81%); $[\alpha]_D^{25}$ (*c* 10, 6 mol dm^{-3} HCl) +6.36; $\delta_H(D_2O)$ 6.45 (1 H, tt, J_{HF} 51.3, J_{HH} 5.7, CHF_2), 4.95 (1 H, dd, J_{HF} 22.8, J_{HH} 4.7, β-H) and 4.09 (1 H, m, α-H).

anti-(2*S*)-**q** [(2*S*,3*R*)-3-(1,1,2,2,3,3,4,4-Octafluorobutyl)serine] was obtained from compound **3q**. *Complex* **3q** (3.49 g, 33%) had m.p. 220–224 °C (Found: C, 53.0; H, 3.8; F, 20.6. $C_{32}H_{27}F_8N_3NiO_4$, requires C, 52.78; H, 3.74; F, 20.87%); $[\alpha]_D^{25}$ (*c* 0.4, $CHCl_3$) +2790; $\delta_H(CDCl_3)$ 8.05–6.60 (14 H, m, ArH), 6.00 (1 H, tt, J_{HF} 52.2, J_{HH} 5.7, CHF_2), 5.67 (1 H, br d, *J* 9.5, OH), 4.40 (1 H, br dd, J_{HH} 9.5, J_{HF} 21, β-H), 4.39 and 3.47 (2 H, AB, *J* 12.8, benzyl CH_2), 4.33 (1 H, br d, *J* 3.5, α-H) and 3.80–1.80 (7 H, m, Pro).

Complex **3q** (1.15 g, 1.59 mmol) was decomposed to give anti-(2S)-**q** (0.42 g, 87%), m.p. 192–197 °C (Found: C, 27.7; H, 2.3; F, 49.8. $C_7H_7F_8NO_3$ requires C, 27.56; H, 2.31; F, 49.81%); $[\alpha]_D^{25}$ (*c* 14, 6 mol dm^{-3} HCl) +14; $\delta_H(D_2O)$ 6.43 (1 H, tt, J_{HF} 51.3, J_{HH} 5.7, CHF_2), 4.90 (1 H, dd, J_{HF} 23.8, J_{HH} 4.0, β-H) and 4.04 (1 H, d, *J* 4.0, α-H).

Complex **3o** (1.96 g, 39%) had m.p. 218–220 °C (Found: C, 49.0; H, 3.2; F, 27.8. $C_{34}H_{27}F_{12}N_3NiO_4$ requires C, 49.30; H, 3.29; F, 27.52%); $[\alpha]_D^{25}$ (*c* 0.03, $CHCl_3$) +2138; $\delta_H(CDCl_3)$ 8.21–6.59 (14 H, m, ArH), 6.05 (1 H, tt, *J* 50 and 6), 5.61 (1 H, d, *J* 10, OH), 4.31 (1 H, d, *J* 5, α-H), 4.30 and 3.51 (2 H, AB, *J* 13, benzyl CH_2), 3.80 (1 H, dd, *J* 10.25 and 5, β-H) and 3.40–2.00 (7 H, m, Pro).

Complex **4o** (1.8 g, 36%) had the same set of parameters as described above (method A′).

Method B′. Synthesis of anti-(2R)-3-(*Fluorophenyl*)*serines* via *the Second-order Asymmetric Transformation of the Corresponding Precursor Complexes in Solution* (Et_3N–*MeOH* 1:1 *by Volume*).—Procedure B′ is illustrated by the synthesis of *anti*-(2*R*)-**c** [(2*R*,3*R*)-3-(4′-fluorophenyl)serine]. To a solution of complex **1** (1.5 g, 3 mmol) in $CHCl_3$ (3 cm^3) were added aldehyde **2c** (1.67 g, 13.5 mmol) and Et_3N (3 cm^3). The formation of the red precipitate of compound **6c** was detected within 24 h from the beginning of the reaction. The reaction mixture was kept at ambient temperature for 18 days until complex **1** had been consumed [as monitored by TLC [SiO_2; $CHCl_3$–Me_2CO (4:1)]. The precipitated thick, red suspension of compound **6c** was filtered. Another aliquot of Et_3N (0.5 cm^3) was added to the filtrate and the additional portion of the precipitated compound **6c** was combined with the first one. Compound **6c** was washed with Me_2CO, followed by $CHCl_3$, and dried over P_2O_5 *in vacuo* at 30–45 °C. *Complex* **6c** (1.18 g, 63%) had m.p. 210–212 °C (Found: C, 65.45; H, 4.7; F, 2.8. $C_{34}H_{30}FN_3NiO_4$ requires C, 65.62; H, 4.86; F, 3.05%); $[\alpha]_D^{25}$ (*c* 0.8, $CHCl_3$) −2083; $\delta_H(CDCl_3)$ 8.54–6.29 (18 H, m, ArH), 5.05 (1 H, dd, *J* 3.3 and 5, β-H), 4.38 and 3.71 (2 H, AB, *J* 14, benzyl CH_2), 4.17–1.80 (7 H, m, Pro), 3.04 (1 H, d, *J* 3.3, OH) and 4.15 (1 H, d, *J* 5, α-H); $\delta_F(CDCl_3)$ −118.31 (m, CF).

Compound **6c** (1.1 g, 1.8 mmol) was decomposed in the usual manner and the amino acid was recovered and recrystallized from EtOH to yield anti-(2R)-**c** (0.32 g, 89%), m.p. 204–205 °C (decomp.) (Found: C, 54.1; H, 5.2; F, 9.5. $C_9H_{10}FNO_3$ requires C, 54.27; H, 5.06; F, 9.54%); $[\alpha]_D^{25}$ (*c* 0.2, water) −12.80; $\delta_H(D_2O)$ 7.52–7.17 (4 H, m, ArH), 5.30 (1 H, d, *J* 4.5, β-H) and 4.14 (1 H, d, *J* 4.5, α-H).

anti-(2*R*)-**a** [(2*R*,3*R*)-3-Phenylserine] was obtained from compound **6a**. *Complex* **6a** (0.55 g, 30%) had m.p. 196–199 °C

(Found: C, 67.4; H, 5.1. $C_{34}H_{31}N_3NiO_4$ requires C, 67.57; H, 5.17%); $[\alpha]_D^{25}$ (*c* 0.03, $CHCl_3$) −2012; $\delta_H(CDCl_3)$ 8.64–6.25 (19 H, m, ArH), 4.29 (1 H, dd, *J* 3 and 5.1, β-CH), 4.19 (1 H, d, *J* 5.1, α-H), 3.03 (1 H, d, *J* 3, OH), 4.35 and 3.70 (2 H, AB, *J* 14, benzyl CH_2), 4.10–1.83 (7 H, m, Pro).

Compound **6a** (0.55 g, 0.9 mmol) was decomposed to give anti-(2R)-**a** (0.12 g, 83%), m.p. 206–208 °C (Found: C, 59.8; H, 6.3. $C_9H_{11}NO_3$ requires C, 59.66; H, 6.12%); $[\alpha]_D^{25}$ (*c* 0.1, water) −4.98; $[\alpha]_D^{25}$ (*c*. 0.1, 6 mol dm^{-3} HCl) −68.91; $\delta_H(D_2O)$ 7.31–7.10 (15 H, m, ArH), 5.31 (1 H, d, *J* 4.5, β-H) and 4.10 (1 H, d, *J* 4.5, α-H).

anti-(2R)-**b** [(2*R*,3*R*)-3-(2′-Fluorophenyl)serine] was obtained from compound **6b**. Complex **6b** (1.21 g, 65%) had m.p. 195–197 °C (Found: C, 65.6; H, 4.6. Calc. for $C_{34}H_{30}FN_3NiO_4$· C, 65.62; H, 4.86%); $[\alpha]_D^{25}$ (*c* 0.03, $CHCl_3$) −2100; $\delta_H(CDCl_3)$ 8.57–6.31 (18 H, m, ArH), 5.08 (1 H, dd, *J* 3.2 and 5, β-H), 4.33 and 3.68 (2 H, AB, *J* 14, benzyl CH_2), 4.15–1.80 (7 H, m, Pro), 4.12 (1 H, d, *J* 5, α-H) and 3.07 (1 H, d, *J* 3.2, OH); $\delta_F(CDCl_3)$ −114.50 (m, CF).

Complex **6b** (1.2 g, 2 mmol) was decomposed to give anti-(2R)-**b** (0.34 g, 85%), m.p. 188–190 °C (decomp.) (Found: C, 54.1; H, 5.0; F, 9.6. $C_9H_{10}FNO_3$ requires C, 54.27; H, 5.06; F, 9.54%); $[\alpha]_D^{25}$ (*c* 0.3, water) −10.9; $\delta_H(D_2O)$ 7.53–7.15 (4 H, m, ArH), 5.29 (1 H, d, *J* 4.5, β-H) and 4.15 (1 H, d, *J* 4.5, α-H).

anti-(2*R*)-**e** {(2*R*,3*R*)-3-[4′-(Difluoromethoxy)phenyl]serine} was obtained from compound **6e**. *Complex* **6e** (1.15 g, 57%), m.p. 168–171 °C (Found: C, 62.9; H, 4.6. $C_{35}H_{31}F_2N_3NiO_5$ requires C, 62.71; H, 4.66%); $[\alpha]_D^{25}$ (*c* 0.06, $CHCl_3$) −1706; δ_H-($CDCl_3$) 8.61–6.33 (18 H, m, ArH), 6.46 (1 H, t, *J*73.6, CHF_2O), 5.05 (1 H, dd, *J* 3.3 and 5, β-H), 4.45 and 3.71 (2 H, AB, *J* 13.5, benzyl CH_2), 4.13 (1 H, d, *J* 5, α-H) and 4.11–1.84 (7 H, m, Pro).

Compound **6e** (1.1 g, 1.64 mmol) was decomposed to give anti-(2R)-**e** 0.34 g, 85%), m.p. 210–212 °C (Found: C, 48.3; H, 4.5. $C_{10}H_{11}F_2NO_4$ requires C, 48.61; H, 4.49%); $[\alpha]_D^{25}$ (*c* 0.2, water) −9.65; $\delta_H(D_2O)$ 7.49–7.19 (4 H, m, ArH), 6.81 (1 H, t, *J* 73.2, CHF_2O), 5.31 (1 H, d, *J* 4.5, β-H) and 4.14 (1 H, d, *J* 4.5, α-H).

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