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Polymer Attached Cyclic Dipeptides as Catalysts for Enantioselective Cyanohydrin Formation

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Abstract. Derivatives of cyclo-[(S)-Tyr-(S)-His], related to the 'Inoue' catalyst, cyclo-[(S)-Phe-(S)-His] have been attached to chloromethylated polystyrene and to polysiloxane polymers *via* spacer groups coupled to the tyrosine phenolic residue. These polymer-attached dipeptides have been shown to be efficient catalysts for the conversion of aromatic aldehydes to cyanohydrins but enantioselectivities are low. The loss of enantioselectivity relative to the Inoue catalyst has been attributed to steric effects from the substituents on the tyrosyl phenolic group. Some mechanistic comments regarding the preferred conformation of the active dipeptide are made.

Introduction

There has been much interest in the use of the 'Inoue' dipeptide as a catalyst for the enantioselective formation of cyanohydrins.[1,2,3] The resulting cyanohydrins have been used in syntheses for the preparation of agrochemicals[2,4] and pharmaceuticals, e.g. ephedrine.[5] The mechanism of action of the dipeptide catalyst is not well known and at least three transition states have been proposed.[1,2,6] Several key points have arisen from studies by a variety of workers. Firstly, the Shell group of workers showed by X-ray studies that the dipeptide was most effective when in its amorphous form and they suggested that intermolecular hydrogen bonds were minimised in this form.[7] The reactions are apparently heterogeneous in nature as reactions can be carried out using solvents, e.g. ether in which the dipeptide is virtually insoluble. Danda has also come to the conclusion that it is essential to obtain the catalyst in an amorphous form to achieve high enantioselectivity.[8] In a recent paper Danda and his co-workers have shown that these reactions exhibit enantioselective autoinduction in that the values of ee's for cyanohydrin formation were shown to increase with conversion and were influenced by the addition of small amounts of preformed, enantiomerically enriched, cyanohydrins.[9] These workers suggest that a complex of the dipeptide and one enantiomer of the cyanohydrin is the active catalyst.

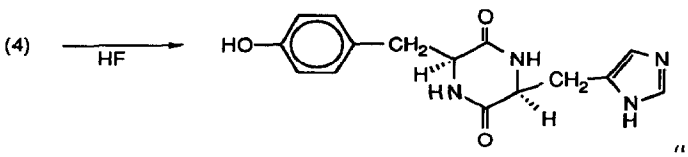
Activation of the catalyst has involved several different procedures. Inoue and Danda[8] have suggested rapid precipitation methods as a means of obtaining an active, gelatinous form of the dipeptide. The Shell workers described the preparation of an active form of the catalyst either by freeze-drying or by spray drying solutions of the dipeptide.[7] If generation of the active form of the dipeptide involves obtaining it in an amorphous form with a minimal number of intermolecular hydrogen bonds it appeared to us that this could be achieved by anchoring the dipeptide by attachment to a polymer resin *via* a spacer group attached to the *para*-position of

the phenylalanine residue. This paper describes the preparation of such polymer-attached dipeptides and their evaluation as catalysts for enantioselective hydrocyanation.

RESULTS

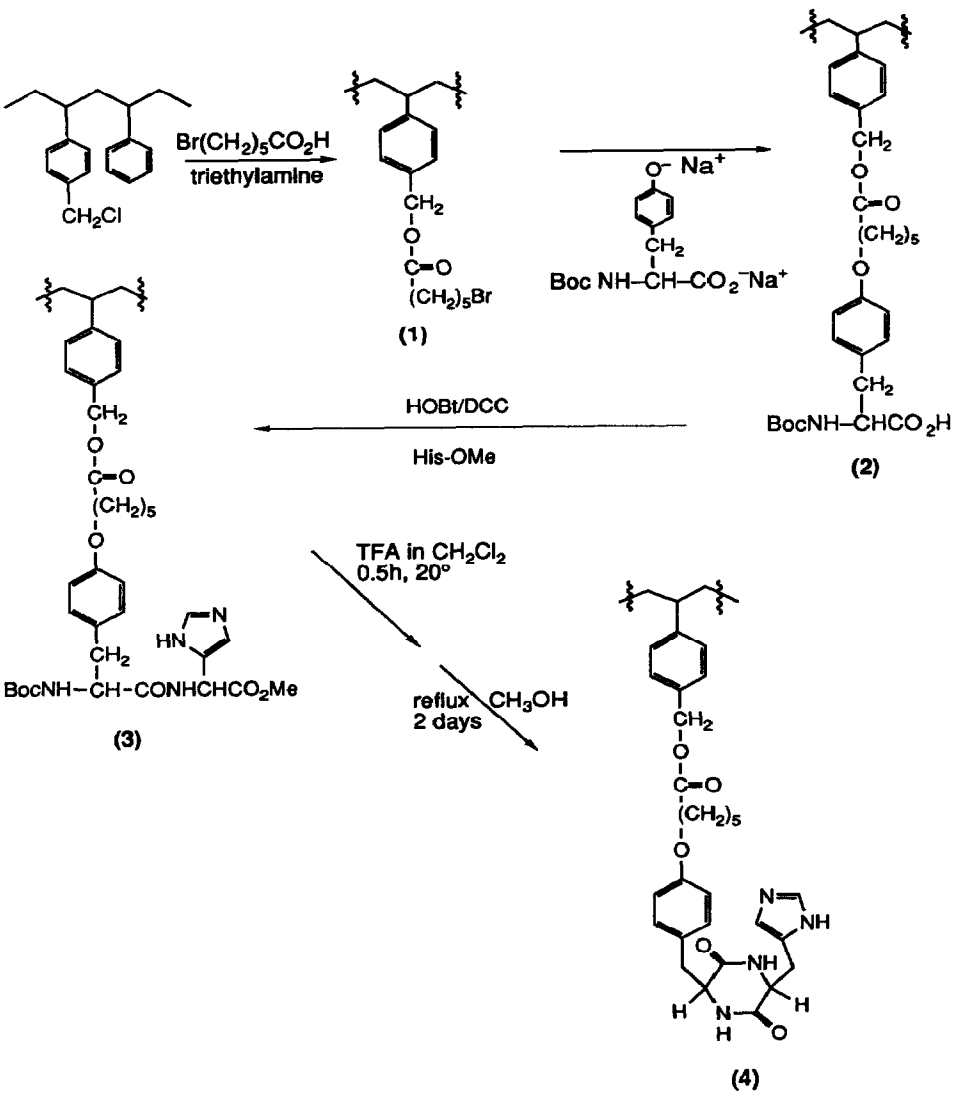
Synthesis of polymer-attached dipeptides

A synthetic scheme leading to the preparation of an analogue of cyclo-[(S)-phenylalanyl-(S)-histidyl] which is attached to a polystyrene resin *via* a spacer unit is outline in Scheme 1. A chloromethylated polystyrene resin (1% cross linked, 1.2 mequiv of CH_2Cl/g) was reacted with 6-bromohexanoic acid to form the bromoester (1). The bromoester (1) was reacted with the sodium salt of N-Boc-(S)-Tyr to give the anchored tyrosine (2). The free carboxyl group of the tyrosine was coupled with His-OMe under standard conditions to give the anchored linear dipeptide (3) which was deprotected and cyclised to give the anchored cyclic dipeptide (4). Evidence for the structure of (4) came from i.r. and ^1H n.m.r. spectroscopy and cleavage of the dipeptide (5) from the resin by treatment with hydrogen fluoride.

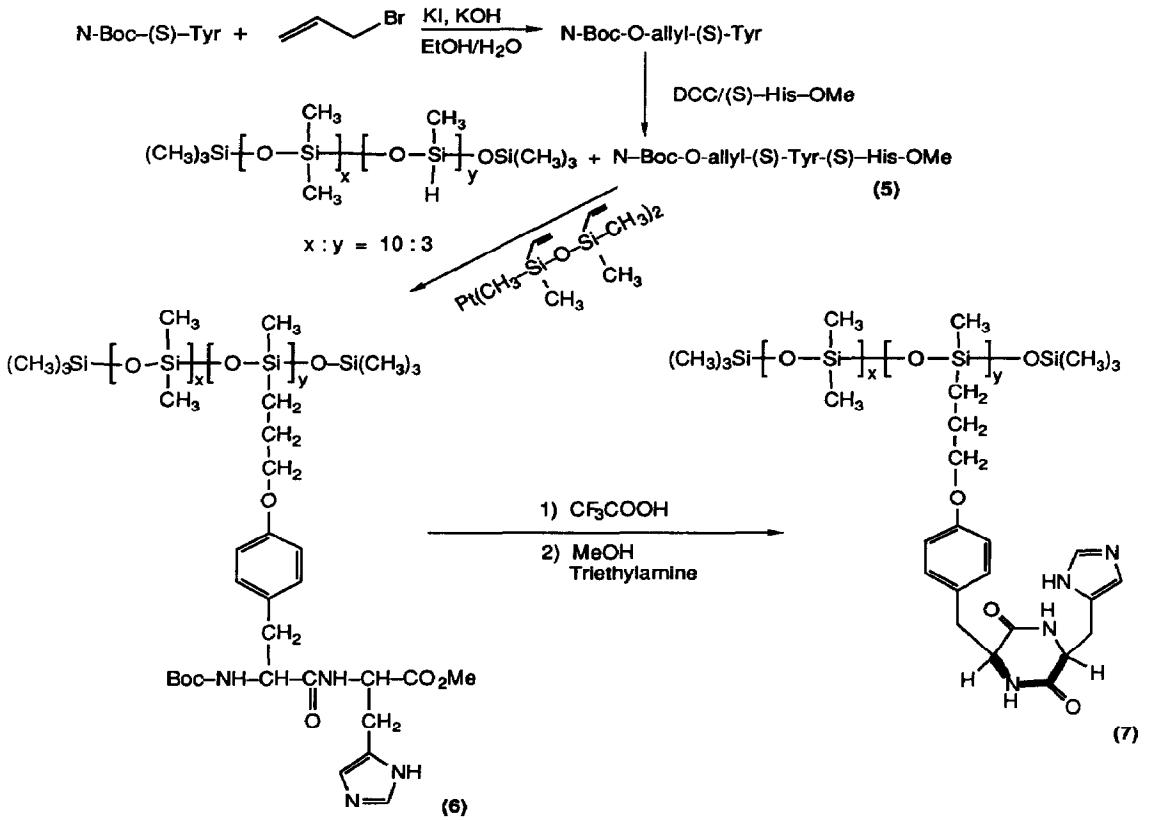


An alternative scheme (Scheme 2) was developed in which the dipeptide was attached to a poly(hydrogen, methyl)(dimethyl)siloxane copolymer *via* a C_3-spacer group. The polysiloxane was a Petrach 123 formulation with average formula as shown in Scheme 2. Although the polysiloxane backbone is flexible it was thought that the possibility of intermolecular hydrogen bonding between dipeptide residues would be minimised.

Histidine methyl ester was coupled to N–Boc–O-allyl–(S)–Tyr to give the dipeptide (5). This dipeptide was reacted with the poly(hydrogen, methyl)(dimethyl)siloxane copolymer using the Petrach catalyst, divinyltetramethyldisiloxane platinum.[10] This reaction proved to be difficult to drive to completion and the resulting product (6) contained some of the unreacted dipeptide (5). Any remaining Si-H bonds were removed by a subsequent reaction with 1-octene.[11] The polymer-attached dipeptide (6) was deprotected and cyclised to give the polymer-attached cyclic dipeptide (7) which contained some cyclo-[O-allyl-(S)-Tyr-(S)-His] as a contaminant.



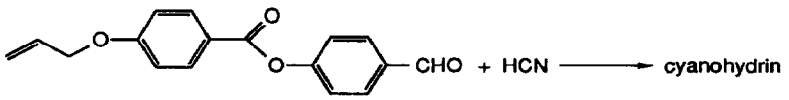
Scheme 1 Synthesis of polystyrene - attached dipeptide.



Scheme 2 Synthesis of polysiloxane - attached dipeptide

Hydrocyanation reactions

Hydrocyanation reactions were carried out using 4-(4-allyloxyphenylcarboxy)benzaldehyde (8). The cyanohydrin resulting from this reaction is an important intermediate for the synthesis of chiral side chain liquid crystal polymers.[12] Reactions were carried out in toluene at –5° using the polymer-attached dipeptides.



(8) (9)

In addition, reactions were carried out with samples of cyclo[(S)–Phe–(S)–His], cyclo[O-methyl-(S)-Tyr-(S)-His] and cyclo [O–benzyl–(S)–Tyr-(S)-His] which had been activated by the method described by Danda[8] involving rapid precipitation of the dipeptide from a solution in methanol by addition of ether. The results obtained from these reactions are summarised in the Table.

Table Hydrocyanation reactions of (8) using polymer-attached dipeptides†

Catalyst	Reaction time h	Conversion %	Enantiomeric Excess %‡
Cyclo[(S)-Phe-(S)-His]	24 48	85 95	78 75
Cyclo[O-methyl-(S)-Tyr-(S)-His]	24 48	82 99	70 65
Cyclo[O-benzyl-(S)-Tyr-(S)-His]	24	60	20
Polystyrene-attached dipeptide (4)	24	83	10
Polysiloxane-attached dipeptide (7)	24	70	10

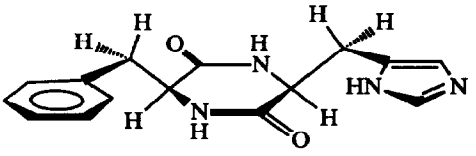
†Reactions carried out for solutions of the aldhyde (8) in toluene at –5°.

‡Determined from ^{1}H n.m.r. spectra of esters formed by reaction with (R,R)-cyhalothrin acid.[5]

Hydrocyanation using the standard 'Inoue' dipeptide gave the cyanohydrin (9) in good yield and with e.e.'s of 75 and 78% for reactions of 48 and 24 hours duration. A reaction using the O-benzyl ether of cyclo[(S)-Tyr-(S)-His] gave both a lower yield and a dramatically lower e.e. value. Similarly, both polymer-attached dipeptides (4) and (7) gave very low e.e. values (10%), though both gave high yields of cyanohydrin for reactions at -5° for 24h. A hydrocyanation reaction of benzaldehyde using the polystyrene-attached dipeptide (4) under similar conditions gave benzaldehyde cyanohydrin in 70% yield with 30% e.e. Use of the 'activated' 'Inoue' dipeptide under similar conditions gave the cyanohydrin in yields of 85± 5% with 90± 5% e.e.

Mechanistic Comments

Prevention of intermolecular hydrogen bonds by polymer attachment of the 'Inoue' dipeptide as shown in the polystyrene (4) and the polysiloxane (7) does not lead to further improvements in enantioselectivity but rather a dramatic decrease. It appears that substitution of a group other than a *p*-methoxy group on the phenylalanine ring of the original 'Inoue' dipeptide leads to a dramatic loss in the ee of the resulting cyanohydrin but with little decrease in yield. Similar decreases in ee values occur irrespective of whether the substituent is O-benzyl or a complex side-chain attached polymer. The adverse effects of a bulky para-substituent are not consistent with our previous proposal for a non-folded conformation (10) in which the aromatic rings are displaced to one side of the diketopiperazine ring.



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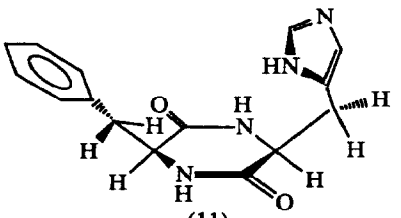

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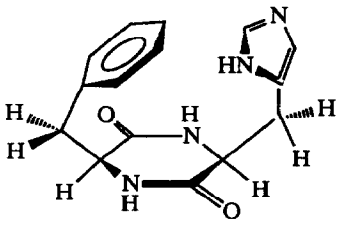

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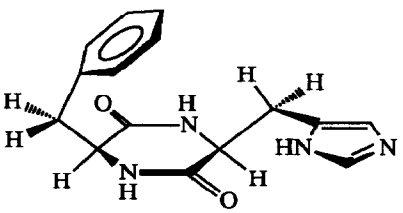

(13)

Similarly, the alternative half-folded conformation (11) proposed by Dutch-workers[6] would also appear to be relatively insensitive to substituent effects from the para-position. It is easier to conceive that adverse interactions could be important if the the phenyl ring were folded over the diketopiperazine ring whether in a fully folded conformation (12) proposed by Inoue or in the half-folded conformation (13) which is thought to be the preferred conformation of the dipeptide in dimethyl sulfoxide solution.[5] This latter conformation has been calculated to be the most stable using the Macromolecules MM2 Programme.[12] In addition, a recent paper has confirmed by ^{1}H n.m.r. experiments that conformation (13) is the most favoured for solutions of the dipeptide in DMSO.[13] The same author reports that calculations using the Macromodel programme predict that (13) is the preferred conformation of the dipeptide in aqueous solution.[13]

It should be noted however that the dipeptide is not catalytically active when in solution but apparently only functions as a catalyst as a gelatinous suspension in solvents, e.g. ether or toluene, in which it is not significantly soluble. Also, a more detailed analysis of the transition states of these reactions is complicated by the presence of a molecule of cyanohydrin in the transition state as is suggested by the work of Danda[9] as discussed above.

EXPERIMENTAL

General

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Infrared (i.r.) spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer (cm^{-1} scale). ^{1}H n.m.r. spectra were recorded at 200 MHz with Bruker AC-200 and at 300 MHz with Bruker AM-300 spectrometers in $CDCl_3$ (unless otherwise stated) containing TMS as an internal standard. Low temperatures for hydrocyanation reactions were maintained using a Hetrofridge cryostat (Model CB 10).

Materials

(S)-Phenylalanine was obtained from Fluka. All other acids and amino acid derivatives were purchased from Sigma. Chloromethylated polystyrene (1% cross linked, 200-400 mesh, 1.2 mequiv CH_2Cl/g) was obtained from Bio-Rad. All solvents were redistilled and stored over molecular sieves. Poly(hydrogen, methyl)(dimethyl)siloxane copolymer (PS 123) and divinyltetramethyldisiloxane platinum were purchased from Petrach.

Preparation of cyclic dipeptides

Cyclo[(S)-Phe-(S)-His], cyclo-[O-benzyl-(S)-Tyr-(S)-His], and cyclo[O-methyl-(S)-Tyr-(S)-His] were prepared by the procedure of Jackson et. al.[5]

Preparation of cyclo-[(S)-tyrosyl-(S)-histidyl] on a polystyrene resin (4)

Esterification of a chloromethylated polystyrene with 6-bromohexanoic acid

The chloromethylated polystyrene (1g, 1.2 mmol/g) from Bio-Rad was esterified by refluxing in ethyl acetate (50 ml) with 6-bromo-hexanoic acid (0.257g, 1.32 mmol) and triethylamine (0.13g, 0.18 mL, 1.32 mmol) for 48h. The resin (1) was filtered and washed with ethyl acetate, ethanol, water, and ethanol and dried in a vacuum at 25°. I.r. (KBr) 1727(s) cm^{-1}.

N-Boc-O-resin-(S)-tyrosine (2)

To a solution of the esterified resin (1) (1.15 g) in DMF (20 mL) was added a solution of N-Boc-(S)-Tyr (0.505g, 1.8 mmol) and sodium hydride (0.086g, 3.6 mmol). The solution was stirred for 24 h at 50° under N_2. The resin was filtered and washed with DMF, ethyl acetate, water, and ethyl acetate and dried under a vacuum at room temperature.

N-Boc-O-resin-(S)-Tyr-(S)-His-OMe (3)

Triethylamine (1.68 mL, 12 mmol) was added to a stirred suspension of (S)-histidine methyl ester dihydrochloride (1.452g, 6.0 mmol) in dichloromethane (50 mL) and the mixture stirred for 3 h at room temperature. A solution of the N-Boc-O-resin-(S)-Tyr (2) (1.36 g), 1,3-dicyclohexylcarbodiimide (1.246g, 6.0 mmol) and 1-hydroxybenzotriazole (0.81g, 6.0 mmol) in dichloromethane (50 mL) was prepared by stirring for 20 mins and then added to the mixture which was then stirred for a further 18 h. The resin was filtered and washed with dichloromethane until 1,3-dicyclohexylurea was removed. It was then washed thoroughly with water, and ethyl acetate and dried under a vacuum at ambient temperature.

Deprotection of N-Boc-O-resin-(S)-Tyr-(S)-His-OMe (3)

The N-Boc-O-resin-(S)-Tyr-(S)-His-OMe (1.45g) was added to a mixture of trifluoroacetic acid (20 mL) and dichloromethane (20 mL) and stirred for 30 min at ambient temperature. The resin was washed with water, 10% triethylamine in dichloromethane, dichloromethane and dried under vacuum at ambient temperature.

O-Resin-cyclo-[(S)-Tyr-(S)-His] (4)

O-Resin-(S)-tyrosine-(S)-histidine-OMe (1.40g) was added to methanol (50 mL) and the solution was refluxed for 48 h. The resin was filtered and washed with methanol, water, ethyl acetate and dried in a vacuum at room temperature. I.r. (KBr) 1727(s), 1683(s) cm^{-1}.

Proof of structure of (4) by hydrogen fluoride cleavage

A sample of the resin (4) (1.0g) was dried overnight under high vacuum. Hydrogen fluoride (9 mL) and anisole (1 mL) were added to the reaction vessel which had been cooled to -78°. The temperature was raised to 0° and maintained for 60 min, after which it was allowed to rise slowly to 20° over a period of 30 min. After removal of HF (oil pump), residual anisole and its derivatives were extracted with ether. The cleaved dipeptide was dissolved in methanol, filtered, evaporated to dryness and treated with sodium bicarbonate (pH. 7.5). After 2 h, the solution was dialyzed and lyophilized, to afford cyclo-[(S)-tyrosyl-(S)-histidyl] (5). The ^1H n.m.r. spectrum was identical with that of an authentic sample.[5]

Preparation of cyclo[(S)-tyrosyl-(S)-histidyl] on a polysiloxane resin (7)

N-Boc-O-allyl-(S)-Tyr

N-Boc-(S)-Tyr (5g) and allyl bromide (2.15g, 1.54 mL) were added to a solution of potassium hydroxide (2.61g), in ethanol (50 ml) and water (6 mL) The solution was refluxed for 18h, then cooled, acidified (HCl) and cooled to 0°C. The viscous oil was collected by centrifugation and dried under vacuum for 4 h, to afford the product (3g) as a viscous oil. ^1H n.m.r. (200 MHz) δ 1.38 (s, 9H, $(CH_3)_3C$); 2.83 (dd, *J* 8.8 Hz, 13.9 Hz, 1H, CH_2); 3.05 (dd, *J* 5.0 Hz, 14.0 Hz, 1H, CH_2); 4.28 (dd, *J* 5.0 Hz, 8.9 Hz, 1H, CH_2); 4.51 (m, 2H, CH_2 (allyl)); 5.18-5.45 (m, 2H, $CH=CH_2$); 5.93-6.12 (m, 1H, $CH=CH_2$); 6.83 (d, *J* 8.6 Hz, 2H, ArH); 7.12 (d, *J* 8.6 Hz, 2H, ArH). I.r. (film) 3340(bs), 1716(s), 1612(s), 1512(s) cm^{-1}.

N-Boc-O-allyl-(S)-Tyr-(S)-His-OMe ester (5)

Triethylamine (1.67g, 16.6 mmol) was added to a stirred suspension of (S)-histidine methyl ester dihydrochloride (2g, 8.3 mmol) in dry acetonitrile (50 mL) and the mixture stirred for 3 h at ambient temperature. A solution of N-Boc-O-allyl-(S)-Tyr (2.65g, 8.3 mmol) and 1,3-dicyclohexylcarbodiimide (1.73g, 8.3 mmol) in acetonitrile (50 mL) was added to the mixture and stirring continued for 24 h. 1,3-Dicyclohexylurea was removed by filtration and the filtrate evaporated under reduced pressure to give a white solid. This solid was dissolved in dichloromethane and the solution washed (satd. $NaHCO_3$), water (2 x 100 mL), and dried (Na_2SO_4). The solvent was removed and the residue was recrystallized from dichloromethane and light petroleum, to afford the product as a white powder, m.p. 89-90°. I.r.(film) 3330(s), 1740(s), 1690(s), 1644(s), 1512(s) cm^{-1}. ^1H n.m.r. (200 MHz) δ 1.40 (s, 9H, $(CH_3)_3C$); 2.85-3.20 (m, 4H, Ar-CH_2 and Im-CH_2); 3.69 (s, 3H, OMe); 4.22, (m, 1H, CH (Tyr)); 4.49 (m, 2H, OCH_2); 4.75 (m, 1H, CH(His)); 5.20-5.45 (m, 2H, CH_2=CH); 5.95-6.12 (m, 1H, $CH=CH_2$); 6.72 (s, 1H, Im); 6.82 (d, *J* 8.6 Hz, 2H, ArH); 7.10 (d, *J* 8.6 Hz, 2H, ArH); 7.49 (s, 1H, Im). $[\alpha]_D^{25} = 35$ (c. 015, $CHCl_3$).

N-Boc-O-(propylsilylresin)-(S)-Tyr-(S)-His-OMe (6)

Poly(hydrogen, methyl)(dimethyl)siloxane copolymer (0.305g) and N-Boc-O-allyl-(S)-Tyr-(S)-His-OMe (5) (1.05g, 2.3 mmol) were dissolved in dichloromethane (50 mL) and a solution of divinyltetramethyldisiloxane platinum in xylene (4 drops) was added. The solution was refluxed for 3 days. 1-Octene (0.5 mL) was then added and the solution refluxed for a further 8 h to remove residual Si-H bonds. The solution was washed with water, dried (Na_2SO_4) and the solvent was removed, to afford the title compound, m.p. 65-70°. I.r. (film) 3330(s), 1730(s), 1694(s), 1644(s), 1605(s) cm^{-1}.

O-(Propylsilylresin)-cyclo[(S)-Tyr-(S)-His] (7)

The polymer (1.3g) was dissolved in a solution of trifluoroacetic acid (20 mL) and anisole (2 mL) at 0° and the solution stirred for 1h at 0°C. Trifluoroacetic acid and anisole were removed and the residue was dried completely under high vacuum. The dried residue was dissolved in methanol (500 ml) and triethylamine (0.32 mL, 2 equiv) added. The solution was refluxed for two days and the solvent removed. The residue was washed with ether (200 mL) and dried, to afford the product as a white powder, m.p. 175-186° I.r. (KBr) 1680(s) cm^{-1}.

Hydrocyanation Reactions

Aldehydes

Aldehyde hydrocyanation reactions were carried out with freshly distilled benzaldehyde and with 4-(4-allyloxyphenylcarboxy)benzaldehyde (8). The latter compound was prepared by dissolving 4-allyloxybenzoic acid (3.0g, 16.8 mmol) and 4-hydroxybenzaldehyde (2.06g, 16.8 mmol) in dichloromethane (30 mL). 1,3-Dicyclohexylcarbodiimide (3.81g, 16.8 mmol) and 4-dimethylaminopyridine (30 mg) were added and the solution stirred at ambient temperature for 4h. Dicyclohexylurea was removed by filtration and the resulting solution washed with water (3 x 30 mL), dried (Na_2SO_4) and the solvent removed. The residue was chromatographed (SiO_2, dichloromethane), to afford 4-(4-allyloxyphenyl)benzaldehyde as white crystals (4.50g, 16 mmol, 95%), m.p. 80-85°. (Found: C, 72.1; H, 5.3. $C_{17}H_{14}O_4$ requires C, 72.3; H, 5.0) ^1H n.m.r. (200 MHz) δ 4.56 (m, 2H, CH_2O); 5.30-5.48 (m, 2H, CH_2:CH); 6.0-6.11 (m, 1H, CH_2:CH); 7.0-8.17 (m, 8H, ArH); 10.02 (s, 1H, ArCHO).

General hydrocyanation procedure

A mixture of the aldehyde (1 equivalent) and cyclo[(S)-phenyalanyl-(S)-histidyl] or polymer attached dipeptide (2 mol %) in toluene was cooled to -5°. Hydrogen cyanide (2 equivalents) was added and the mixture held at the required temperature. The reaction was followed by ir and t.l.c. At the end of the reaction, hydrogen cyanide and toluene were removed under reduced pressure, ether was added and recovered dipeptide catalyst filtered off. The precipitate was washed thoroughly with ether. The combined filtrate and washings were evaporated under reduced pressure, to afford the cyanohydrin.

The mole fraction of cyanohydrin in the mixture was determined from the ^1H n.m.r. spectrum of the mixture. The enantiomeric excess was calculated from the ^1H n.m.r. spectrum of the corresponding (+)-cyhalothrin ester.[5]

4-(2-Hydroxy)-(4-allyoxyphenylcarboxy)phenyl acetonitrile (9) had i.r. (KBr) 3400(s), 2250(s) cm^{-1}. ^1H n.m.r. (200 MHz) δ 4.64 (m, 2H, CH_2O); 5.32-5.39 (m, 2H, CH_2:CH); 5.56 (s, 1H, CH(OH)CN); 5.98-6.17 (m, 1H, CH_2CH); 6.97-8.17 (m, 8H, ArH). (R)-(+)-Cyhalothrin ester: the α-CH resonances were used to calculate e.e. values. ^1H n.m.r. (300 MHz): (1'R, 3'R, 2R)-isomer δ 6.40 (s, CH(CN)). (1'R, 3'R, 2S)-isomer δ 6.45 (s, CH(CN)).

Reactions using the polystyrene resin involved pre-swelling of the resin by stirring a suspension of it in toluene for 30 min at ambient temperature prior to the addition of aldehyde.

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