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SUPRAMOLECULAR ASYMMETRIC INDUCTION : A NEW CONCEPT APPLIED TO THE SUPPORTED ENANTIOSELECTIVE SYNTHESIS OF α-AMINO ACIDS

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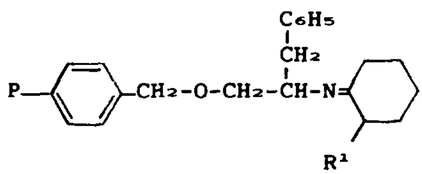
Abstract : A polyacrylic resin with pendant chirality has been used as a chiral auxiliary. The prochiral ester enolate, reversibly linked to the polymer chain via a Schiff base, is surrounded by chiral pendants, allowing supramolecular asymmetric induction to occur. Amino acids with enantiomeric excesses up to 88-89% could be synthesized from supported glycine t-butyl ester enolate by reaction with alkyl halides. Enantioselective protonation depends on the initial configuration of the supported aminoacid. Alanine was obtained in 90% ee by repetitive asymmetric protonation.

Proteinic and non-proteinic α-amino acids are important building blocks both in peptide synthesis and in the construction of chiral molecules[1]. Accordingly, many different synthetic methods have been devised, some of them affording these chirons[2] with high to very high enantioselectivities[3,4]. In view of this, the opportuneness of a supported strategy, using a chiral polymer, might be questionable. It is however possible to foresee three specific advantages of a supported asymmetric synthesis :

1/ The solid chiral auxiliary should be easily recovered and reused. This might appear trivial, but it is of importance with a view to industrial development.

2/ The second factor is apparent if we consider one of the main methods of asymmetric carbon-carbon bond formation, using enolates as reaction intermediates. Experimental evidence has established that, even in solution, lithium enolates are solvated aggregates[5-11]. These supramolecules are the actual reactants with electrophiles[11-12], and the aggregation state has been used to account for the regio- and enantioselectivity of enolate reaction products[6,11,13-16]. Moreover the chemical reactivity is known to be higher when the aggregate size decreases[*,11]. Due to site isolation in a polymeric network[18], a supported Li enolate will, in all probability, be monomeric and therefore increased reactivity can be expected in comparison to that for the corresponding n-meric species in solution.

3/ In solution, low temperatures, of the order of -78°C, are routinely used in reactions of anions with electrophiles and are essential for high stereoselectivities[**]. It was anticipated that with supported asymmetric synthesis, the steric bulk of the polymer backbone and the reduced mobility of the polymer-bound substrate could mimic enzyme reactions and give high enantioselectivities even at room temperature[23]. This was actually sustained by Leznoff et al[24] who compared two syntheses of chiral 2-methylcyclohexanone starting respectively from the chiral supported Schiff base 1a and the analogous system 1b in solution.



1a P = polystyrene, R^1 = H
1b P = R^1 = H
1c P = polystyrene, R^1 = CH_3

With 1a, the enantiomeric excess of 98% at -78°C was only slightly decreased (94%) at 20°C. With 1b, 85% and 49% ee were respectively obtained at -78°C and 20°C. With regard to the chemical yields, the polymeric system afforded better values both at -78°C and at 20°C[***].

However another problem is likely to arise if ester enolates are to be used in amino acid synthesis. Ester enolates are less stable than ketone or amide enolates[11] and, even at low temperature, fragmentation into ketenes and alkoxides can occur[8,26-28]. In that event, the above advantageous possibility of operating at room temperature would be lost. It was our working hypothesis

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*) Identical results have been observed with C-Li compounds[17].

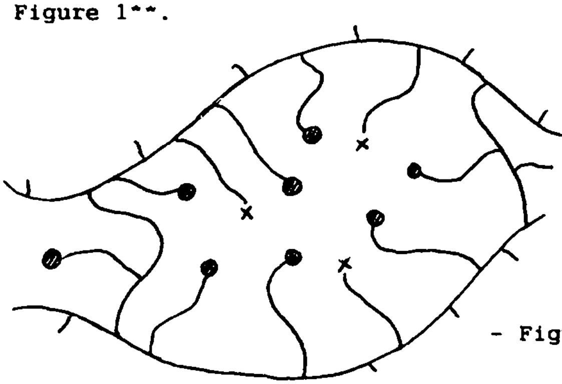
**) This can be illustrated with two examples. A temperature decrease from -78°C to -105°C has been shown to increase the enantiomeric excess from 57% to 70% in the deracemization of methyl phenylglycinate p-anisylidene imine[19]. Likewise methylation of the lithio-enamine corresponding to a chiral cyclohexanone imine afforded 2-methyl cyclohexanone with an ee of 81% at -78°C, 85% at -100°C and 20% at 65°C[20]. However Oppolzer et al.[21] have recently observed a high enantioselectivity (ee 90.6%) in the alkylation of a chiral sultam derived from a N-[bis(methylthio)methylene] glycinate anion prepared at 0°C by phase-tranfer catalysis. This could be the result of the higher stability of amide enolates as compared to ester enolates. Other stereoselective syntheses of amino acids by phase-transfer catalysis were less successful[22].

***) Lower enantiomeric excess were obtained in other supported syntheses of 2-methylcyclohexanone using different chiral arms[25].

that anchoring ester enolates to a polymer could increase their thermal stability*.

Leznoff's[24] asymmetric supported synthesis discussed above is based on a very general principle : asymmetric induction is the result of the presence of a chiral center closely bound to the prochiral carbon atom. Few examples of similar supported synthesis can be found in the literature, all of them using polystyrene derivatives and affording only moderate enantiomeric excesses[29-31].

We have tried a totally different approach, which is shown in Figure 1**.



● = chiral pendant
X = prochiral ester enolate

- Figure 1 -

The idea was to design a polymer with pendant chirality. These pendants would surround the prochiral lithium ester enolate, the latter being covalently and reversibly linked to the polymer chain via an achiral arm. In this way, the whole polymer should act as a chiral auxiliary and, if the concept works, then supramolecular asymmetric induction is likely to occur. Moreover proximity effects[33] and complexation between lithium and the pendant functional group could also reinforce the stereoselectivity by providing transition-state rigidity***.

A convenient polyacrylic cross-linked polymer was prepared by radical copolymerisation of three monomers :

- 65% (by weight) of the N-acryloyl derivative of an (S)-amine as

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*) Further arguments in support of this hypothesis will also be presented in a forthcoming paper.

**) A preliminary report on the subject has already appeared[32].

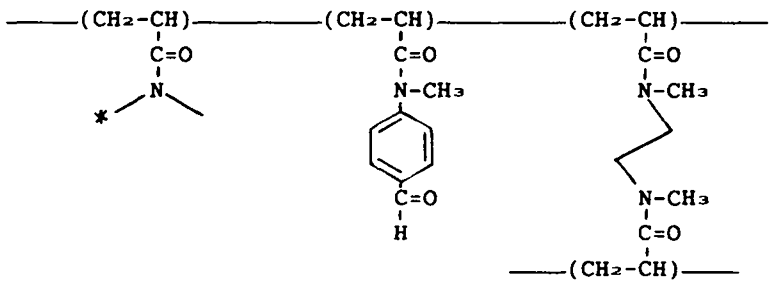
***) Participation of an oxyanion[34-38], a methoxy group[39] or the lone electron pair of a nitrogen atom[21,40] to the transition state has been considered to be responsible for the face-selective reaction of Schiff base aminoester enolates with electrophiles. Schiff bases derived asymmetric syntheses lacking this factor led only to low ee%[41]. Steric influences operate with rigid bicyclic imines[42-45].

chiral matrix; we tried successively N-methyl α-phenylethylamine, prolinol methyl ether and prolinol.

- 10% of N,N'-dimethylethylenebisacrylamide[63] as cross-linking agent.

- 25% of N-acryloyl N-methyl p-aminobenzaldehyde as functionalizing agent*.

With our former experience of polyacrylic resins usable in solid phase peptide synthesis[46], we have chosen 10% cross-linking, which assures good mechanical properties for the support. A loading of 1 meq of aldehyde function per gram was used. In this way, each aldehyde function is statistically surrounded by three to four chiral pendants**. An idealized structure of the polymer, which is obtained in 90% yield, is shown in Figure 2.



- Figure 2 -

Acid-catalysed condensation of t-butyl glycinate with the above polymer (represented by 2) in the usual way afforded Schiff base 3. Deprotonation with LDA in THF*** gave anion 4**** of probable (E)-configuration*****. Subsequent reaction with an alkyl halide followed by non-racemizing hydrolysis at room temperature with dilute HCl afforded the

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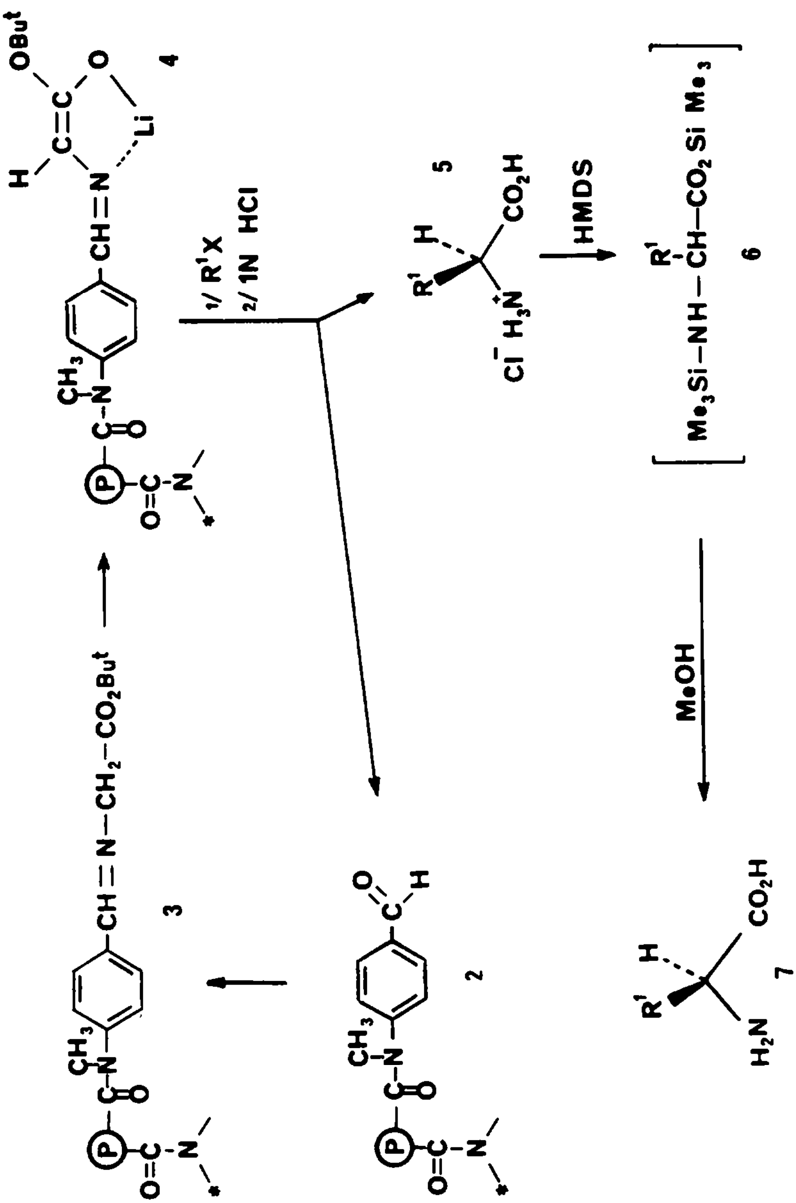
*) Protection of the aldehyde function during the polymerization step, that we used formerly[32], can be avoided.

**) It appears likely that the polymer structure is quite homogeneous, the three monomers having broadly the same polymerization rate. Some main-chain chirality[47] induced by the chiral monomer during the polymerisation step cannot be excluded.

***) Apparently metalation of the polyamide support did not occur with our experimental conditions, and an excess of LDA was not needed. See on the contrary the metalation of poly(methyl acrylate) with LDA[48].

****) Classified as a type of azaallyl anion[44].

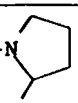
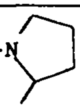
*****) It is generally granted that the C=N group coodinates with lithium to form a 5-membered ring[35,36,44,49]. (Z)-Non-stabilized enolates are formed with LDA[8,50]. An (E)-configuration has been suggested for differently stabilized Schiff base enolates[21,39,40].



1/ R¹X
2/ 1N HCl
HMDS
MeOH
2
3
4
5
6
7

crude amino acid hydrochloride 5 with quantitative recuperation of 2. Reaction with hexamethyldisilazane (HMDS) to give the bis-trimethylsilyl derivative 6, and then treatment with an excess of methanol[31], allowed final isolation of the pure amino acid 7 with predominant (S)-configuration. Conversely (R)-pendants gave rise to (R)-amino acids.

Enantiomeric excesses* depend on the nature of the chiral pendant (Table 1). Poor values were obtained even at -78°C with N-methyl α-phenylethylamine (entries 1 and 2), probably as the result of its limited interaction with the lithium enolate. However these preliminary results were encouraging enough, as they attested the validity of our concept of supramolecular asymmetric induction. As anticipated, better results were obtained with prolinol methyl ether (entries 3 and 5). Deprotonation and alkylation at room temperature resulted in an increase in chemical yield with only a slight decrease of enantioselectivity (entries 4 and 6). Finally prolinol itself was the best choice**, giving enantiomeric excesses as

Chiral pendant	Entry	Alkylating agent	Temp.(°C)	Yields %	7 ee%(S)
CH_3 $-N-CH-C_6H_5$ CH_3	1	CH_3I	-78	68	21
	2	iC_3H_7I	-78	67	20
-N 	3	CH_3I	-78	58	61[32]
	4		20	87	55
	5	iC_3H_7I	-78	62	63[32]
CH_2OCH_3	6		20	83	56
-N  ***	7	CH_3I	-78	75	88
	8		20	85	82
	9	iC_3H_7	-78	77	89
CH_2OH	10		20	84	84

*** An excess of LDA was used in order to transform all the primary alcohol functions into lithium alcoholates.

- Table 1 -

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*) Our main goal at that time was to demonstrate the validity of the concept of supramolecular asymmetric induction. We were satisfied then merely with measuring optical rotations. In a forthcoming paper, a more refined method will be used for the determination of enantiomeric excess.

**) A similar enhancement of enantioselectivity has already been observed[34]. However the oxyanion was less effective than the methoxy group with a different type of substrate[32] high as 88-89% at -78°C (entries 7 and 9) and 82-84% at 20°C (entries 8 et 10). The addition of titanium tetraisopropoxide[53] did not improve the enantioselectivity. We also replaced LDA with potassium t-butoxide, but reaction with methyl iodide produced a large amount of dialkylated derivative*.

Finally, it was possible to reuse the polymer in ten successive operations without any loss of chemical yield or enantioselectivity.

We were also eager to apply the concept of supramolecular asymmetric induction to enantioselective protonation[49] (or deracemization reaction). Schiff bases 8 were prepared by reacting 2 with racemic alanine and phenylalanine t-butyl ester**.

The following steps were routinely applied : deprotonation at -78°C with LDA in THF, addition of water at the same temperature***, hydrolysis at 20°C with dilute HCl, and successive treatment with HMDS and methanol. The enantiomeric excesses for the (S)-prolinol methyl ether pendant are given in table 2 (entries 1 and 2). Yields of 7 (R^1 = CH_3 and CH_2-C_6H_5) amounted to 90%.

Entry	Initial supported aminoacid	7 ee% (R)
1	(R,S)-Phe	49
2	(R,S)-Ala	55
3	(S)-Ala	11
4	(R)-Ala	100

- Table 2 -

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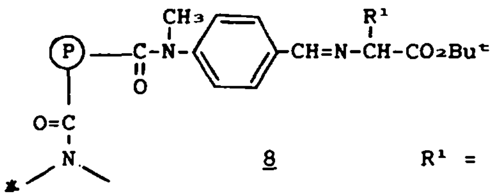
*) The extent of competition between mono and dialkylation is determined by the relative pKs of the parent acid and its monoalkyl derivative[54]. However, solvation and chelation can invert the normal order of acidity[55].

**) Leznoff et al[56] have observed a significant kinetic resolution in the preparation of Schiff base 1c starting from racemic 2-methyl cyclohexanone. Unfortunately there is no experimental part in this publication. However if conditions identical to those of Leznoff's former paper[24] were used, a large excess of ketone was employed. In our case, equimolar quantities of 2 and amino acid t-butyl ester were reacted. Nevertheless we checked that hydrolysis of 8 with dilute hydrochloric acid at room temperature reformed racemic alanine and phenylalanine. Moreover the preparation of (S)-phenylalanine methyl ester supported Schiff base was devoid of racemization.

***) In the enantiomeric protonation of 2-methylcyclohexanone Schiff base 1c, Leznoff et al[56] obtained a high enantiomeric excess (90% ee) only with ethanol amongst five other proton sources. The transition state must therefore imply a tight association between the enolate and the proton source, as has been also observed in solution[49,53,57].



8 R^1 = CH_3 and C_6H_5-CH_2

(R)-Alanine and (R)-phenylalanine were predominantly formed with a (S)-pendant. As a result, both alkylation and protonation occurred preferentially from the same diastereotopic face of the ester enolates. This has already been observed in some literature examples[55,58], but one exception has been noted[59].

Unexpected results were obtained when the deracemization procedure was applied at -78°C to each enantiomer of alanine. With (S)-Ala (entry 3), an 11% enantiomeric excess of (R)-Ala was formed; which means that a 55.5% inversion of the starting (S)-epimer has occurred, in good agreement with the value of entry 2. On the contrary, the (R)-Ala precursor was recovered unchanged (entry 4); however 90% incorporation of deuterium by treatment with LDA and D_2O proved that an ester enolate was an intermediate. Results already obtained in solution by our research group[60] also showed a relationship between the overall stereochemical result and the initial configuration.

Epimeric precursors thus give rise, in a kinetically controlled step, to non-identical enolates that behave differently with electrophiles.

The results in Table 3 were obtained with (S)-prolinol as the chiral pendant. A sufficient excess of LDA was used in order to ensure complete metalation of the alcohol functions. The chemical yields amounted to 95%. Enantioselectivities (entries 1 and 2) are only slightly higher when compared to the corresponding values in Table 2. Stereochemical results identical to those in Table 2 were observed when starting with each alanine epimer

Entry	Supported Aminoacid	Reaction temperature (°C)	7 ee% (R)
1	(R,S)-Phe	-78	54
2	(R,S)-Ala	-78	61
3	(S)-Ala	-78	16
4	(S)-Ala	20	11
5	(R)-Ala	-78 or 20	100

- Table 3 -

(entries 3 and 5). Increasing the reaction temperature to 20°C decreased the ee from 16% to 11% with (S)-Ala (entry 4), and did not modify the stereochemical result with (R)-Ala (entry 5).

Finally, starting with supported racemic alanine t-butyl ester, the cycle of two steps including deprotonation with LDA and protonation with water, both performed at -78°C, was repeated four times before hydrolysis of the Schiff base. In these conditions (R)-Ala was isolated in 95% yield and with 90% ee, as compared to 61% (Table 3, entry 2).

In conclusion, an inexpensive, easily prepared and reusable polyacrylic resin with pendant chirality has been successfully applied to the asymmetric synthesis of α-amino acids. In a forthcoming paper, the same principle of supramolecular asymmetric induction will be applied to the synthesis of enantiomerically pure amino acids.

- EXPERIMENTAL PART -

Microanalyses were performed by the CNRS Analytical Department, melting points were determined with a Buchi apparatus and are uncorrected, optical rotations were measured with a Perkin-Elmer 241 polarimeter and NMR spectra were recorded on a 250 MHz Bruker spectrometer

<u>N-Acryloyl N-methyl p-aminobenzaldehyde</u>
A solution of acryloyl chloride (10.9 g, 0.12 mole) in 20 mL of anhydrous toluene was slowly added at -5°C to a stirred solution of N-methyl p-aminobenzadehyde[61] (13.5 g, 0.10 mole) and of triethylamine (12.2 g, 0.12 mole) in 150 mL of anhydrous toluene. Stirring was continued 12 hr at room temperature and the solution was evaporated under vacuum. The residual yellow oil was purified by chromatography on silica gel (CH_2Cl_2 as eluant).
Yield = 95%, Rf (CH_2Cl_2) = 0.44
NMR ($CDCl_3$) δ ppm : 3.43 (s, 3H, N-CH_3); 5.4-6.7 (m, 3H, CH_2=CH); 7.2-8.1 (q, 4H, Ar); 9.2 (s,1H,CHO)
Analysis calc. for $C_{11}H_{11}NO_2$: C 69.82, H 5.86; found C 69.68, H 5.72

<u>N-Acryloyl-N-methyl-α-phenylethylamine</u>
This was performed according to the above procedure with N-methyl-α-phenyl ethylamine in place of N-methyl p-amino benzaldehyde. The residual oil was distilled. Bp_4 =123-125°C Yield=95% $[\alpha]_D$ = -227° (C=1.245, toluene)
NMR ($CDCl_3$) δ ppm : 1.54 (d,3H,CH_3); 2.74 (s,3H,N-CH_3); 5.6-6.7 (m,3H, CH_2=CH); 7.34 (s,5H,Ar)
Analysis calc. for $C_{12}H_{15}NO$: C 76.15, H 7.99, N 7.40; found C 76.37, H 7.83, N 7.20

N-Acryloyl prolinol

A solution of chlorotrimethylsilane (24 mL, 0.18 mole) in 45 mL of anhydrous toluene was slowly added to a stirred slurry of (S)-prolinol (9.33 g, 0.092 mole) and of triethylamine (26 mL, 0.18 mole) in 120 mL of anhydrous toluene. Stirring was continued for 2 hr. Triethylammonium chloride was filtered. A solution of acryloyl chloride (7.7 mL, 0.092 mole) in 20 mL of anhydrous toluene was added under N_2 at 0°C. After 3 hr stirring at room temperature, the solvent was evaporated under vacuum. Methanol (50 mL) was slowly added to the residual oil, the solution was stirred for 15 minutes then evaporated under vacuum and the residual oil was distilled.
Bp_6=145-147°C, Yield=70%, $[\alpha]_D$ = -48° (C=1, benzene)
NMR ($CDCl_3$) δ ppm : 1.98 (m,4H,CH_2); 3.44-3.90 (m,5H); 4.1-4.6 (m,1H,CH); 5.6-6.7 (m,3H,CH_2=CH)
Analysis calc. for $C_8H_{13}NO_2$: C 61.91, H 8.44; found C 62.13, H 8.28

Preparation of the chiral resin : typical copolymerization

A solution of N-acryloyl derivative of (S) or (R)-amine (N-methyl-α-phenylethylamine, prolinol methyl ether[32] or prolinol) (0.065 mole), of N,N'-dimethylethylene-bisacrylamide (1.3 g, 0.0066 mole), of N-acryloyl N-methyl p-aminobenzaldehyde (3.6 g, 0.019 mole), and of azoisobutyronitrile (1.5 g) in 30 mL of tetrahydrofuran was heated under reflux during 1 hr, then cooled to room temperature. The polymer was filtered, washed successively with anhydrous tetrahydrofuran, dichloromethane and ether, ground, then dried over P_2O_5 at room temperature and sifted in order to retain only particles of a diameter between 0.08 and 0.25 mm (yield 90-95%). The loading of 1.1 meq CHO/g was measured by the method of Bryant and Smith[62].

Supported amino acid Schiff bases

A slurry of resin (7 g) and amino acid t-butyl ester (0.008 mole) in 100 mL of anhydrous toluene was heated 1 hr under reflux in the presence of 3 drops of $BF_3(C_2H_5)_2O$, the water being removed by means of a Dean-Stark trap; the resin was then filtered, washed successively with toluene, THF, CH_2Cl_2 and dried under vacuum at room temperature.

Alkylation reaction

A 1.7 N solution of LDA (4.6 mL, 7.8 mmole) in THF (22 mL, 37.3 mmole of the LDA solution when prolinol pendants are used) were added at -78°C to a stirred slurry of the supported Schiff base (7.3 g) in 150 mL of anhydrous THF; after stirring 15 minutes at the same temperature, the alkylating agent (1.2 mmole) was added at -78°C; stirring was carried on first for 1 hr at the same temperature, then 12 hr at room temperature. The resin was filtered, washed successively with anhydrous THF, CH_2Cl_2 and ether, and then dried under vacuum. The over-all operation was also carried out at room temperature.

Protonation reaction

This was performed according to the above procedure, with water in place of the alkylating agent.

Hydrolysis of the supported Schiff base

A slurry of the supported Schiff base in 170 mL of HCl solution (1 N) was stirred 4 hr at room temperature. The resin was filtered, washed with water, ethanol and CH_2Cl_2. All the collected filtrates were evaporated to dryness under vacuum. The residue was dissolved in 10 mL of hexamethyldisilazane (HMDS) and the solution refluxed for 30 minutes. After cooling to room temperature, the inorganic salts were filtered and 200 mL of methanol were slowly added to the filtrate. Stirring was continued for 10 minutes, then the solution was evaporated and the pure amino acid was dried under vacuum at room temperature.

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