Optically Pure (*S*)-6,7-Dimethoxy-1,2,3,4-Tetrahydro-3-Isoquinolinecarboxylic Acid and Asymmetric Hydrogenation Studies Related to Its Preparation

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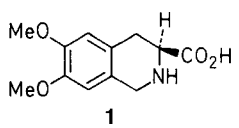
(*S*)-6,7-Dimethoxy-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid has been prepared in optically pure form as its hydrochloride. Pictet–Spengler ring closure of the optically pure (*S*)-2-amino-3-(3,4-dimethoxyphenyl)propanoic acid hydrochloride salt (L-3,4-dimethoxyphenylalanine hydrochloride) proceeded without significant racemization.

A simple and safe, asymmetric hydrogenation catalyst system has been developed which allows the rapid screening of various chiral phosphine ligands via an *in situ* ionic complex. A protocol was demonstrated which uses a statistical approach to consider the effects of changes in solvent, nitrogen substituent, oxygen substituent, and ligand in the asymmetric hydrogenation of alkyl or aryl (*Z*)-2-acylamino-3-(3,4-dimethoxyphenyl)-2-propenoate derivatives. This method was used to successfully determine the optimal substrate and conditions for the preparation of enantiomerically pure (*S*)-2-amino-3-(3,4-dimethoxyphenyl)propanoic acid hydrochloride salt.

Introduction

Tetrahydro-3-isoquinolinecarboxylic acids are of great utility in the preparation of a number of pharmaceuticals, as well as the total synthesis of natural products. The substructure is present in many naturally occurring alkaloids, such as the protoberberines,[1] berbines,[2] papaverolines,[3] yohimbines,[4] and other isoquinoline alkaloids.[5] The natural products exhibit a variety of physiological activities,[6] but many unnatural analogues have found utility in modern medicine. Examples of their physiological effects include anti-arrhythmic activity,[7] angiotensin-converting enzyme inhibition,[8] antihypertensive activity,[9] and the treatment of mental depression.[10]

Of particular interest to us was (*S*)-6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid **(1)** which has been used in its optically pure form in drug synthesis.[11,12]



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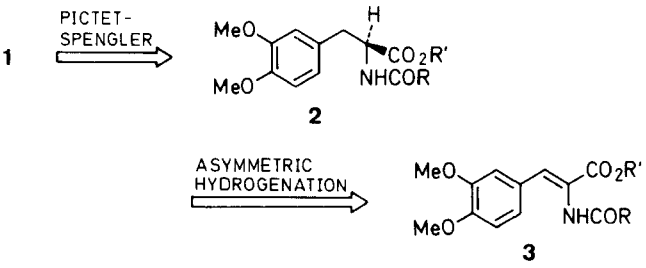
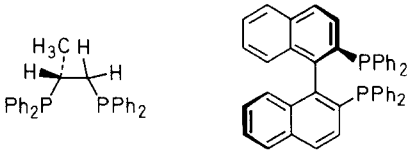
Though used in the literature, a preparation of the enantiomerically pure material has not been reported, and it is believed that previous workers must have resorted to resolution techniques.

The racemate has been prepared by Pictet–Spengler ring closure of 3,4-dimethoxyphenylalanine,[2,13] however, this closure has not been reported using the optically pure compound. Cyclization of similar compounds in the literature have given mixed results, and mechanistic studies of the racemization during this reaction have been reported.[14,15] Should the highly activated nature of this ring-system be sufficient to allow the cyclization to occur without loss of optical purity this would provide an expedient route to the pure enantiomer, from the corresponding L-amino acid.

This paper describes a convenient synthesis of optically pure **1**, which avoids resolutions, but instead makes use of an optically pure amino acid derivative, **2**, as an intermediate. This in turn is prepared enantioselectively by an asymmetric hydrogenation of the corresponding (*Z*)-2-acylamino-3-(3,4-dimethoxyphenyl)-2-propenoate **(3)**.



Much is known in the literature regarding the preparation of enantiomerically pure α-acylamino acids by asymmetric hydrogenation,[18–20] and great success has been met using chiral versions of Wilkinson's catalyst, i.e. $[Rh(Ph_3P)_3Cl]$.[19] Typically, the catalysts are used as either a neutral *in situ* catalyst (prepared from a neutral rhodium complex and a phosphine ligand), or an isolated ionic complex. The ionic complexes are often found to be superior, in terms of reaction rate and selectivity. Examples of very efficient isolated ionic complexes are $[Rh((R)\text{-PROPHOS})(NBD)]ClO_4$ (NBD = norbornadiene),[21] and $[Rh((R)\text{-BINAP})(NBD)]ClO_4$.[22]



R-PROPHOS *R*-BINAP

Because the success of these ligands has been outstanding in the field, these were the ones chosen to be used in this study. One concept we wished to apply was to combine the convenience of an *in situ* catalyst formation, with the advantages of an ionic catalyst. In this way, easy to handle precursors could be used, and a number of ligands could readily be screened, hopefully without suffering any loss in enantioselectivity. It would also be desirable to eliminate the danger associated with the perchlorate salts, almost invariably used in the literature.[23] Hexafluoro-

phosphate salts were therefore used in all the work. Finally, for ease of operation, the reaction should proceed under ambient conditions (1 atm of hydrogen at room temperature). With these constraints in mind we employed a statistically designed set of experiments, which allowed for the analysis of solvent, oxygen substituent, nitrogen substituent, and ligand effects on the efficiency of the asymmetric hydrogenation. Major dependent effects were observed, and it was possible to determine an optimal set of experimental conditions, which were then applied successfully on a larger, preparative scale. After cleavage of the protecting groups the stereochemical course of the Pictet–Spengler ring closure to the desired tetrahydroisoquinoline **1** was investigated.

Experimental Design

Using the catalyst system discussed in detail below, four discrete variables were deemed to be of prime importance in the asymmetric reduction of (*Z*)-2-acylamino-3-(3,4-dimethoxyphenyl)-2-propenoates **3**. These were varied in the following way:

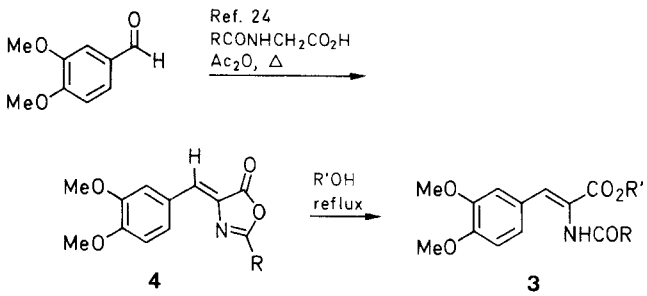
Oxygen Substituent: methyl or hydrogen.

Nitrogen Substituent: acetyl or benzoyl.

Solvent: tetrahydrofuran or methanol.

Ligand: *R*-PROPHOS or *R*-BINAP.

Each of these variations has been used in the literature in one system or another, but no clear picture has emerged as to which would be favorable in a particular case. Each also represents an extreme in its field, like the very polar solvent, methanol, and the much less polar solvent, tetrahydrofuran; the large group benzoyl and the much smaller group, acetyl. In this way, by carrying out 16 ($2^4 = 16$) experiments it should be possible to fully cover the potential for an efficient asymmetric reduction of a particular parent substrate. Furthermore, by using this symmetrical full-factorial approach, there would be a built in replication of each effect, and any secondary effects will be apparent (one effect dependent on another). Though each of the expected products, **2a**,[1] **2b**,[26] **2c**,[33] and **2d**[34] has been previously prepared in the optically pure *S*-form, to our knowledge, there has been no systematic study of this type.



4 **3**

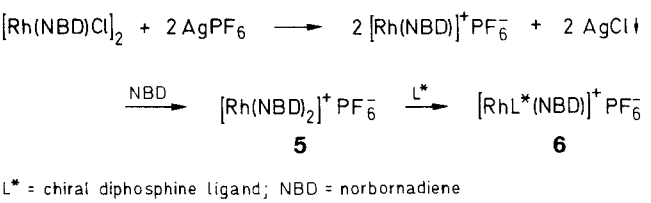
4	R	Yield (%)	3	R	R′	Yield (%)
a	Me	40	**b**	Ph	Me	84
b	Ph	68	**c**	Me	H	59
			d	Ph	H	87

Preparation of (*Z*)-2-Acylamino-3-(3,4-dimethoxyphenyl)-2-propenoates 3

A simple, and much used, route to (*Z*)-2-acylamino-3-(3,4-dimethoxyphenyl)-2-propenoates is the classical Ehrlenmeyer azlactone synthesis. The necessary azlactones **4a,b** were prepared from 3,4-dimethoxybenzaldehyde, and were then each converted to the corresponding methyl esters, **3a,b** or acids, **3c,d**, by methanolysis or hydrolysis, respectively. Ester **3a** was additionally prepared by esterification of acid **3c**.

Catalyst System

The desired cationic precursor complex, rhodium(I) bis(norbornadiene) hexafluorophosphate **(5)** was prepared by application of a generalized procedure for making cationic rhodium complexes.[31]



L* = chiral diphosphine ligand; NBD = norbornadiene

Both PROPHOS,[21] and BINAP,[22] have previously been used to prepare hydrogenation catalysts by reaction with the perchlorate salt corresponding to complex **5**. In the current reactions, the asymmetric hydrogenation catalyst **6** was formed in the reaction medium prior to the addition of the substrate. This method has the advantage that a variety of ligands can be screened without having to separately prepare and isolate the individual catalysts. The associated handling problems are therefore avoided.

Hydrogenation Results

The investigatory hydrogenation reactions were run on a 0.2 to 1.0 gram scale in the appropriate solvent by first allowing **5** and the ligand to react briefly, and then applying a blanket of hydrogen for 30 min prior to the introduction of the substrate (*Z*)-2-acylamino-3-(3,4-dimethoxyphenyl)-2-propenoates **3**. The hydrogen treatment caused a color change from the bright orange/yellow of **6**, to the dull amber of the active hydrogenation catalyst. This color was lost when the substrate was introduced, but returned upon completion of the reaction, thus acting as a self-indicator. Analysis of the crude products by chiral LC (in the case of the *N*-benzoyl series), or chiral GC (for the *N*-acetyl series) allowed the determination of both the chemical conversion and the relative proportions of the two enantiomers. For all of the substrates, the corresponding racemic products **2a–d**, were prepared by standard palladium on carbon reduction. In each case, base line separation of the enantiomers was achieved. All enriched products were of the *S*-configuration, as confirmed by analysis of an authentic sample of *S*-**2c**. This was prepared from commercial (*S*)-2-amino-3-(3,4-dihydroxyphenyl)propanoic acid by *N*-acetylation, followed by *O*-methylation using dimethyl sulfate.

In this work 0.2 mole% of catalyst was used, since when 0.1% was tested the reaction was found to be incomplete.

The reaction data is summarized in Table 1.

Table 1. Preparation of **2a–d** by the Asymmetric Hydrogenation of **3a–d**

Substrate	R′	R	L*[a]	Solvent	Time (h)	Yield[b] (%)	ee[b] (%)
3b	Me	Ph	P	THF	5	99	88.3
3a	Me	Me	P	THF	135	3	–
3d	H	Ph	P	THF	5.5	100	90.9
3c	H	Me	P	THF	1.5	98	91.6
3b	Me	Ph	P	MeOH	2	99	85.1
3a	Me	Me	P	MeOH	6.5	100	84.3
3d	H	Ph	P	MeOH	136	84	72.1
3c	H	Me	P	MeOH	3.4	100	88.6
3b	Me	Ph	B	THF	5	99	57.3
3a	Me	Me	B	THF	279	36	10.5
3d	H	Ph	B	THF	5.5	100	50.2
3c	H	Me	B	THF	243.1	~70	3.1
3b	Me	Ph	B	MeOH	21	3	–
3a	Me	Me	B	MeOH	150.3	76	6.5
3d	H	Ph	B	MeOH	136	64	27.9
3c	H	Me	B	MeOH	3.4	97	10.8

[a] L* = ligand, P = *R*-PROPHOS, B = *R*-BINAP.
[b] Determined by GC or LC internal standard analysis.

A simpler way of displaying these results is in terms of the two-factorial diagram, which also shows clearly the symmetrical nature of the experimental design, and the relationships between the various data points (Figure 1). In this diagram, each point represents the enantiomeric excess [ee = 100% × (desired isomer − undesired isomer/total)] resulting from that particular set of conditions, somewhat like a four dimensional graph.

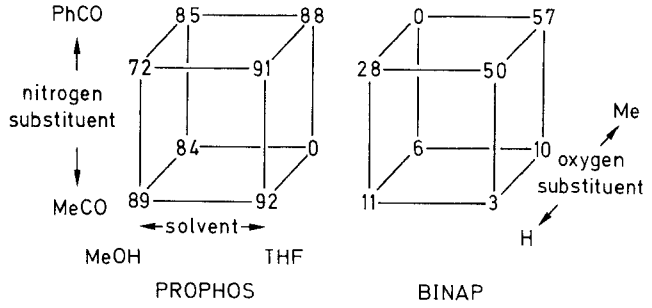


Figure 1

Simple inspection of these results reveal that in general tetrahydrofuran is the preferred solvent, PROPHOS is clearly superior to BINAP; and with BINAP, *N*-benzoyl is a better substituent. Also there is no clear difference between the acid or the ester. A more thorough analysis was carried out using a standard commercial statistics software package to analyze the data. The estimates of factor effects are given in Table 2.

Major factor effects were observed for the catalyst (*R*-PROPHOS preferred) and the nitrogen substituent (*N*-benzoyl preferred). A strong second order effect between the nitrogen substituent and the solvent was observed. The effect is such that with tetrahydrofuran the *N*-benzoyl substituent is generally preferred. However, in methanol either nitrogen substituent gives good results with the *R*-PROPHOS catalyst, and poor results with the *R*-BINAP catalyst. Tetrahydrofuran is therefore the best solvent for the BINAP catalyst system, but for greater tolerance of the nitrogen substituent when using the PROPHOS catalyst, methanol should be used. The choice of catalyst was by far the major effect.

Table 2. Computed Factor Effects of Hydrogenation Variables

Factor	Effect
A	−12.9
B	**22.1**
AB	10.3
C	**54.3**
AC	− 8.5
BC	− 4.1
ABC	16.3
D	2.1
AD	− 7.0
BD	**23.3**
ABD	11.9
CD	−16.9
ACD	−18.7
BCD	2.5
ABCD	6.0

A = Oxygen Substituent
1 = Methyl Ester (Me)
−1 = Acid (H)
B = Nitrogen Substituent
1 = Benzoyl (COPh)
−1 = Acetyl (COMe)
C = Catalyst
1 = *R*-PROPHOS
−1 = *R*-BINAP
D = Solvent
1 = THF
−1 = MeOH

Preparative Asymmetric Hydrogenation

Since the investigatory hydrogenations had defined a fairly large safe operating region, other factors were taken into consideration in the design of the preparative runs. Thus, methyl (*Z*)-2-benzoylamino-3-(3,4-dimethoxyphenyl)-2-propenoate **(3b)** was used since the *N*-benzoyl derivatives are easier to prepare and handle, and reactions of the methyl esters can easily be followed by gas chromatography, without sample derivatization. Thus, under the standard conditions with *R*-PROPHOS in tetrahydrofuran, the reaction proceeded smoothly on a 10 gram scale to give the crude product with an optical purity of 89.9% ee. A simple recrystallization from dichloromethane/hexane enriched the optical purity to 96–98% ee, with an isolated chemical yield of 88%. The optical rotation of the current material was found to be greater than that of the sole literature value, indicating a higher optical purity.[26]

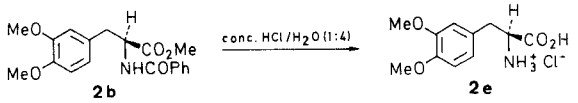
Deprotection

Hydrolysis of methyl 2-benzoylamino-3-(3,4-dimethoxyphenyl)propanoate **(2b)** in refluxing conc hydrochloric acid/water, 1:4, for 16 h using the method of Saxena and co-workers,[13] resulted in incomplete hydrolysis.

Thus 2-benzoylamino-3-(3,4-dimethoxyphenyl)propanoic acid, 2-amino-3-(3,4-dimethoxyphenyl)propanoic acid hydrochloride, and benzoic acid were isolated in 57%, 35%, and 48% yields, respectively. The use of a stronger acid was not practical, since experiments with 2-acetylamino-3-(3,4-dimethoxyphenyl)propanoic acid **(2c)** had shown that cleavage of the ring methoxy groups occurred in a refluxing mixture of conc hydrochloric acid/water, 1:1. The 1:4 mixture was therefore used, and the reflux period was extended (21.5 h).

This approach was successful and the reactions are summarized in Table 3.

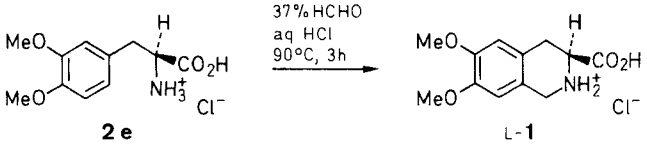
Table 3. Hydrolysis of Methyl (*S*)-2-Benzoylamino-3-(3,4-dimethoxyphenyl)propanoate **(2b)**



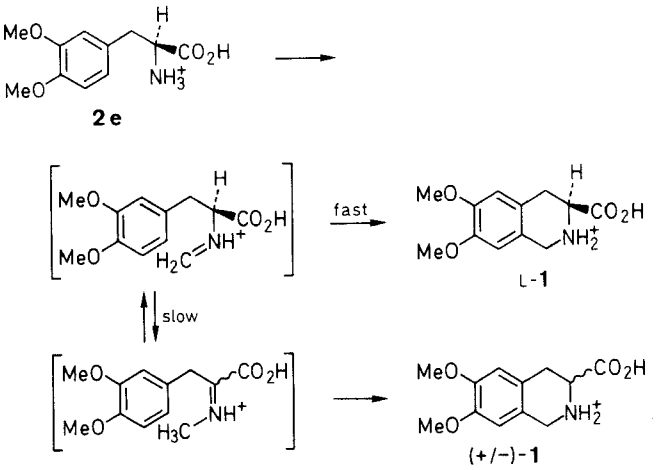
Substrate **2b** ee (%)	Amount (g)	Bath Temperature (°C)	Time (h)	Yield (%)
88	0.8	124–127	21.5	98
0	10.0	126–135	22.5	93
99	12.0	120–130	20	95

Pictet–Spengler Ring Closure

Ring closure of 2-amino-3-(3,4-dimethoxyphenyl)propanoic acid hydrochloride salt **(2e)** to the tetrahydroisoquinoline **1** was carried out using formaldehyde and aqueous hydrochloric acid following the procedure of Saxena and co-workers for the racemic compound.[13] Comparison of the optical rotation of the product with that reported[12] for the pure *S*-isomer indicated that racemization had not occurred to any significant extent when optically pure material was used. Furthermore, though the enantiomeric purity of **2e** was not determined, that of **1** indicates that minimal racemization occurred during the hydrolysis step.



Cyclization using other literature conditions, such as aqueous hydrochloric acid at a higher temperature,[2] or with sulfuric acid to give the hydrate,[14] also proceeded smoothly. These results contrast strongly with work on unsubstituted phenylalanine, which has been shown to undergo ring closure to the extent of 32%.[15] Presumably the rate of cyclization is so increased by the ring activation from the methoxy groups, that the slower racemization does not compete significantly.



Summary and Conclusions

(*S*)-6,7-Dimethoxy-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid **(1)** has been prepared in optically pure form as its hydrochloride. Pictet–Spengler ring closure of the optically pure (*S*)-2-amino-3-(3,4-dimethoxyphenyl)propanoic acid hydrochloride salt **(2e)** proceeds without significant racemization.

A simple and safe, asymmetric hydrogenation catalyst system has been developed which allows the rapid screening of various chiral phosphine ligands via an *in situ*, ionic complex. Thus, commercially available ligands can be used, but new, proprietary ligands could also be utilized without the need to isolate unique catalysts. A protocol was demonstrated which uses a statistical approach to consider the effects of changes in solvent, nitrogen substituent, oxygen substituent, and ligand in the asymmetric hydrogenation of alkyl or aryl 2-acylamino-3-(3,4-dimethoxyphenyl)-2-propenoate derivatives. This method was used to successfully determine the optimal substrate and conditions for the preparation of enantiomericall pure (*S*)-2-amino-3-(3,4-dimethoxyphenyl)-propanoic acid hydrochloride salt **(2e)**.

Melting points were determined on a Büchi 510 melting point apparatus, and are uncorrected. ^{1}H-, ^{31}P-, and ^{13}C-NMR spectra were recorded on an IBM-Bruker AC-300 spectrometer. Mass spectra were recorded on either Finnigan MAT 212 or 4500, or Hewlett Packard 5985 mass spectrometers. Enantiomeric ratios for the *N*-benzoyl amino acids were determined by HPLC analysis using a Pirkle D-Phenylglycine column eluting with isopropyl alcohol/hexane, 1:1, at 1 mL/min. For the *N*-acetyl series an Alltech Chirasil-Val capillary GC column was used. Acid samples are derivatized with $BF_3 \cdot$ MeOH prior to analysis. Optical rotations were measured using a Rudolph manual polarimeter with a sodium lamp. Reactions were followed using a combination of a DB-5 capillary column on a Hewlett Packard 5890 GC and TLC on silica coated glass plates eluting with MeOH/$CHCl_3$ mixtures, the spots being visualized by UV and iodine staining.

Chemicals were purchased from the Aldrich Chemical Company and, with the exception of norbornadiene which was distilled, were used without further purification. Solvents were J. T. Baker analytical grade. MeOH and THF were refluxed over CaH_2 in a dry N_2 atmosphere and distilled prior to use. Dry, deoxygenated THF used in the catalyst precursor preparation was distilled from Na-benzophenone ketyl. Dowex® ion-exchange resin was washed with dilute HCl and water prior to use.

All compounds possessed spectral and physical data consistent with the assigned structures and reported values.

4-(3,4-Dimethoxybenzylidene)-2-methyl-5-oxazolone (4a):
This is prepared in 40% isolated yield from 3,4-dimethoxybenzaldehyde and acetylglycine by a modification of the procedure of Buck and Ide;[24] mp 168–172°C (Lit.[25] 165–169°C).

4-(3,4-Dimethoxybenzylidene)-2-phenyl-5-oxazolone (4b):
This is prepared in 68% isolated yield from 3,4-dimethoxybenzaldehyde and hippuric acid according to the procedure of Buck and Ide;[24] mp 152–154°C (Lit.[24] 151–152°C).

Methyl 2-Acetylamino-3-(3,4-dimethoxyphenyl)-2-propenoate (3a):
This is prepared from **4a** by treatment with Na_2CO_3 in MeOH by a modification of the procedure of Saxena and co-workers.[13] Alternatively, it could be made by esterification of 2-acetylamino-3-(3,4-dimethoxyphenyl)-2-propenoic acid (**3c**). Thus, **3c** (9.62 g, 36.3 mmol) is heated under reflux for 19 h in MeOH (100 mL) containing conc HCl (1 mL). After diluting with water (500 mL), the solution is basified with a 10% aq solution of Na_2CO_3 to a pH of 8–9. The resultant solids are collected by filtration, washed with water (3 × 50 mL) and dried at the pump. The crude product is further purified by column chromatography on silica gel, eluting with a gradient of CH_2Cl_2/MeOH (99:1 thru 96:4). After stripping the solvent from the appropriate fractions, and drying at the pump the title compound is obtained; yield: 2.01 g (21%); mp 198–200°C.

$C_{14}H_{17}NO_5$	calc.	C 60.20	H 6.14	N 5.02
(279.287)	found	60.42	5.78	4.53

^{1}H-NMR ($CDCl_3$/TMS): δ = 7.42 (s, 1H), 7.10 (d, J = 8.5 Hz, 1H), 7.07 (s, 1H), 6.99 (s, 1H), 6.86 (d, J = 8.5 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 2.17 (s, 3H).

Full spectroscopic data have not been previously reported on this known compound.[26,27]

Methyl 2-Benzoylamino-3-(3,4-dimethoxyphenyl)-2-propenoate (3b):
This is prepared in 84% yield from **4b** by treatment with Na_2CO_3 in MeOH using the procedure of Saxena and co-workers.[13] mp 135–137°C (Lit.[36] 139–140°C).

2-Acetylamino-3-(3,4-dimethoxyphenyl)-2-propenoic Acid (3c):
A 1 L single-necked flask is charged with **4a** (43.68 g, 0.1767 mol), water (125 mL), and acetone (320 mL). The reaction mixture is heated under reflux for 17.5 h, then diluted with water (200 mL) and refluxed for a further 23 h. The apparatus is then adapted for distillation and the acetone is removed. After adding fresh water (300 mL), the reaction mixture is heated under reflux for a further 2 h, filtered and the collected solids washed with boiling water (2 × 50 mL). The filtrate is refluxed with activated carbon (≈ 10 g) for 15 min, then filtered and the carbon is washed with boiling water (2 × 100 mL). The filtrate is allowed to cool to r.t. overnight. The resulting white, volumous precipitate is collected by filtration and washed with iced water (2 × 50 mL). After drying at the pump the product is dried in a vacuum desiccator (yield: 18.06 g). A similar rework of the filtrate yields a second batch of product (9.75 g). The overall yield of the title compound is 27.81 g (59%); mp 212–214°C.

^{1}H-NMR (DMSO-d_6/TMS): δ = ≈ 12.5 (br, 0.5H, part. exch.), 9.42 (s, 0.7H, part exch.), 7.31 (d, J = 1.65 Hz, 1H), 7.23 (s, 1H), 7.20 (dd, J = 8.4 and 1.65 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 2.0 (s, 3H).

Full spectroscopic data have not been previously reported on this known compound.[28]

2-Benzoylamino-3-(3,4-dimethoxyphenyl)-2-propenoic Acid (3d):
This is prepared according to the method of Deuloffeu and Mendivelzua by the hydrolysis of **4b** with refluxing 2% aq NaOH over 2 h.[29] The yield is 87%, mp 198–199.5°C (Lit.[30] 196–198°C).

Rhodium(I) Bis(norbornadiene) Hexafluorophosphate (5):
This preparation is based on the generalized procedure for making cationic rhodium complexes described by Schrock and Osborn.[31] Thus, a 50 mL round-bottomed flask equipped with a magnetic stirrer is charged under a dry N_2 atmosphere with rhodium norbornadiene chloride dimer (0.4855 g, 2.11 mmol) and dried, O_2-free THF (10 mL). To this is added a solution containing silver hexafluorophosphate (0.5334 g, 2.11 mmol) in THF (10 mL). An immediate precipitate of silver chloride is formed and after stirring for 14 min this is collected by filtration in a dry-box, and washed with THF (2 × 2 mL). To the dark amber filtrate is added freshly distilled norbornadiene (0.1958 g, 2.13 mmol) in THF (2 mL), causing the color to turn deep red/maroon and gradual formation of a precipitate. The reaction mixture is stirred overnight (16 h) at r.t., after which time the maroon solids are collected by filtration and washed with THF (4 × 2 mL). Drying in vacuum (≈ 0.2 Torr) produced analytically pure material as a brick red solid; yield: 0.4049 g (47%).

$C_{14}H_{16}RhPF_6$	calc.	C 38.91	H 3.73	
432.149	found	38.56	3.63	

^{1}H-NMR (CD_2Cl_2/TMS): δ = 5.65 (dd, J = 2.1 and 4.7 Hz, 4H), 4.82 (br s, 2H), 1.66 (t, J = 1.5 Hz, 2H).

^{31}P-NMR (CD_2Cl_2/H_3PO_4): δ = −143.83 (sp, J = 711 Hz).

Preparation of Methyl (*S*)-2-Benzoylamino-3-(3,4-dimethoxyphenyl)-propanoate (2b). From Methyl (*Z*)-2-Benzoylamino-3-(3,4-dimethoxyphenyl)-2-propenoate (3b); Typical Procedure for Asymmetric Hydrogenation
Into a dry 500 mL round-bottomed, 3-neck flask equipped with a magnetic stirrer, a reflux condenser, 2 three-way stopcocks attached to rubber balloons (Aldrich Chemical Company), a septum, and a nitrogen manifold is injected a solution containing rhodium(I) bis(norbornadiene) hexafluorophosphate (**5**, 0.2579 g, 59.7 μmol, 2.6 wt%, 0.2 mole%) in dry THF (10 mL). Further THF (10 mL) is used to ensure a complete transfer. To the bright orange/red solution is then injected a solution of *R*-PROPHOS (0.2499 g, 60.6 μmol, 2.5 wt%, 0.2 mol%) in dry THF (5 mL). Further THF (2 × 5 mL) is used to complete the transfer. The addition causes an immediate color change to a bright orange/yellow. After stirring at r.t. for 15 min the flask is evacuated using a water aspirator and purged with H_2 (via the balloons). This process is repeated four more times. The reaction mixture is then stirred under a H_2 atmosphere at r.t. for 30 min after which time the color has changed to a dull orange/amber brown. At this time a solution of the title substrate **3b** (9.9998 g, 29.3 mmol) in dry THF (80 mL) is injected via the septum. Further THF (2 × 15 mL) is used to ensure a complete transfer. The addition causes the color to take on a bright deep red hue, and upon letting the mixture stir for 1 h this becomes a ruby red. The reaction mixture is stirred overnight (16 h) after which time the dull orange/amber brown color has returned and the reaction is quenched by purging with N_2 gas. Cleaned Dowex® 50X2-400 (≈ 10 g) is then added and stirring is continued for 1 h. The reaction mixture is then added to the top of a silica column and the product is eluted with THF. After drying (Na_2SO_4) the solvent is removed on a rotary evaporator to yield an oil. This is pumped at 0.02–0.05 Torr overnight (16 h) to afford the crude product as a cream/light yellow solid (11.64 g, 89.9 ee% of *S*-isomer by LC). The product is recrystallized from CH_2Cl_2/hexane and the mother liquor is stripped and reworked to yield in total 3 batches of pure product 5.69 g, 1.25 g, and 1.90 g; total yield: 8.84 g (25.7 mmol, 87.7%); 95.9–97.7 ee% of *S*-isomer by LC; mp 124–125°C, 125.5–126.5°C, and 126–126.5°C, respectively; $[\alpha]_D^{23}$ (c = 2.4, $CHCl_3$) +83–86° (Lit.[26] $[\alpha]_D$ +55.8–76.6°). The final residue from the mother liquor is found to consist of almost completely racemic material (0.59 g, 1.72 mmol, 5.9%. 1.7 ee% of *S*-isomer by LC. mp 105–107°C).

Preparation of Racemic Methyl 2-Benzoylamino-3-(3,4-dimethoxyphenyl)propanoate:
Methyl (*Z*)-2-benzoylamino-3-(3,4-dimethoxyphenyl)-2-propenoate (20 g) is treated with 10% Pd-C (2 g) in MeOH (400 mL) under a H_2 atmosphere (1 atm) for 3 d. The reaction mixture is then filtered and the solvent stripped to yield the title compound; yield: 18.90 g (95%); mp 106–107°C (Lit.[13] 105–106°C).

(*S*)-2-Amino-3-(3,4-dimethoxyphenyl)propanoic Acid Hydrochloride Salt (2e):

The procedure is based on that used by Saxena and co-workers for the hydrolysis of the racemic material.[13] Thus, a 2 L round-bottomed, 3-neck flask is charged with (*S*)-**2b** (98.8 ee%, 12.01 g, 35.2 mmol), water (1.08 L), and conc HCl (276 mL). The reaction mixture is heated under reflux for 20 h and then allowed to cool to r.t. It is then filtered and the collected solids are washed with water (2 × 25 mL). The filtrate is then extracted with CH_2Cl_2 (5 × 200 mL). The aqueous layer is stripped on a rotary evaporator, and the residue is dried at the pump to yield the title product; yield: 8.73 g (94.8%); mp 218–219 °C (Lit.[32] mp 220 °C).

IR (KBr): ν = 3612–3343m, 3290–2400s, 1740m, 1608m, 1517s, 1250s, 1144m, 1022m cm^{-1}.

^{1}H-NMR (DMSO-d_6/TMS): δ = 8.52 (s, 3 H, exch. D_2O), 6.98 (d, J = 1.5 Hz, 1 H), 6.89 (d, J = 8.2 Hz, 1 H), 6.78 (dd, J = 8.2 and 1.5 Hz, 1 H), 4.11 (m, 1 H), 3.75 (s, 3 H), 3.73 (s, 3 H), 3.11 (m, 2 H).

Preparation of Racemic 2-Amino-3-(3,4-dimethoxyphenyl)propanoic Acid Hydrochloride Salt:

Using the above procedure, racemic methyl 2-benzoyl-3-(3,4-dimethoxyphenyl)propanoate is hydrolyzed to the title compound in 93% yield.

Preparation of (*S*)-6,7-Dimethoxy-1,2,3,4-tetetrahydro-3-isoquinolinecarboxylic Acid (1):

A 50 mL, round-bottomed, single-neck flask is charged with (*S*)-2-amino-3-(3,4-dimethoxyphenyl)propanoic acid hydrochloride salt, (7.00 g, 26.9 mmol), conc HCl (5 mL), water (95 mL), and 37% aqeuous formaldehyde solution (4.2 mL). The reaction mixture is heated with a bath temperature of ≈ 90 °C for 3 h under a N_2 atmosphere. It is then allowed to cool to r.t. and stored in a refrigerator (≈ 0 °C) overnight (16 h). To further precipitate product the flask is cooled in a freezer until ice formation had just begun. The cream-colored precipitate is then collected by filtration and washed with ice-water (2 × 5 mL). After sucking dry the product is further dried in a vacuum desiccator over P_2O_5 to give the title compound as a cream colored powder; yield: 6.26 g (85%); mp 278–279 °C dec (Lit.[12] 281–282 °C dec); $[\alpha]_D^{35}$ −92.1° (c = 2.45, 1 N HCl) [Lit.[12] $[\alpha]_D^{23}$ −98° (c = 2.5, 1 N HCl)]; 94.0 ee%.

Recrystallization from hot 0.1 N aq HCl affordes an analytical sample (recovery 72%, mp 279–280 °C dec).

$C_{12}H_{16}ClNO_4$	calc.	C 52.66	H 5.89	N 5.12
(273.719)	found	52.63	5.63	5.12

IR (KBr): ν = 3561–3304s, 3256–2367s, 1734s, 1522s, 1267s, 1224s, 1121s cm^{-1}.

^{1}H-NMR (CF_3CO_2D/TMS): δ = 9.06 (acid peak), 6.90 (s, 1 H), 6.83 (s, 1 H), 4.64 (AB, J = 15.8 Hz, 1 H), 4.60 (AB, J = 15.8 Hz, 1 H), 4.57 (dd, J = 10.0 and 5.5 Hz, 1 H), 3.96 (s, 3 H), 3.94 (s, 3 H), 3.57 (dd, J = 17.0 and 5.5 Hz, 1 H), 3.44 (dd, J = 17.0 and 10.0 Hz, 1 H).

Preparation of Racemic 6,7-Dimethoxy-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic Acid:

Using the above procedure racemic 2-amino-3-(3,4-dimethoxyphenyl)propanoic acid hydrochloride salt is cyclized to the title compound in quantitative yield (mp 273–275 °C).

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(1) Kametani, T.; Takagi, N.; Toyota, M.; Honda, T.; Fukumoto, K. *Heterocycles* **1981**, *16*, 591.
Kametani, T.; Takagi, N.; Toyota, M.; Honda, T.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2830.
(2) Dean, R.T.; Rapoport, H. *J. Org. Chem.* **1978**, *43*, 2115.
(3) Davis, V.E.; Walsh, M.J. *Science* **1970**, *167*, 1005.
(4) Prasad, K.B.; Swan, G.A. *J. Chem. Soc.* **1958**, *2045*.
Julian, P.L.; Karpel, W.J.; Magnani, A.; Meyer, E.W. *J. Amer. Chem. Soc.* **1948**, *70*, 180.
(5) Czarnocki, Z.; MaClean, D.B.; Szarek, W.A. *Can. J. Chem.* **1986**, *64*, 2205.
(6) Czarnocki, Z.; MaClean, D.B.; Szarek, W.A. *J. Chem. Soc., Chem. Commun.* **1985**, 1318.
(7) Morrison, G.C.; Cetenko, W.A. *US Patent* 3836536, (1974), Warner-Lambert; *C.A.* **1975**, *82*, 16709.
(8) Suh, J.T.; Barton, J.N.; Regan, J.R. *Eur. Pat. Appl.* EP 104, 546 (1982) USV Pharmaceutical; *C.A.* **1984**, *104*, 38832.
Japanese Patent 81145274; *C.A.* **1984**, *96*, 142722 (1981) Tanabe Seiyaku;
Oka, Y.; Nishikawa; K. *Eur. Pat. Appl. EP* 18104 (1980) Takeda Chemical; *C.A.* **1981**, *95*, 42934.
(9) Suh, J.T.; Williams, B.E.; Skiles, J.W. *Eur. Pat. Appl. EP* 39, 804 (1981) USV Pharmaceutical; *C.A.* **1982**, *96*, 122647.
Japanese Patent 82235513 (1982) Tanabe Seiyaku; *C.A.* **1982**, *97*, 156523.
(10) Morrison, G.C.; Cetenko, W.A. *US Patent* 3906099 (1975), Warner-Lambert; *C.A.* **1975**, *83*, 193106.
(11) Gu, L.; Strickley, R.G. *Pharm. Res.* **1987**, *4*, 392.
(12) Hoefle, M.L.; Klutchko, S. *US Patent* 4344949 (1982), Warner-Lambert; *C.A.* **1983**, *98*, 34598.
Klutchko, S.; Blankley, C.J.; Fleming, R.W.; Hinkley, L.; Werner, A.E.; Nordin, I.; Holmes, A.; Hoefle, M.L.; Cohen, D.M.; Essenburg, A.D.; Kaplan, H.R. *J. Med. Chem.* **1986**, *29*, 1953.
(13) Saxena, A.K.; Jain, P.C.; Anand, N. *Indian J. Chem.* **1975**, *13*, 230.
(14) Brossi, A.; Focella, A.; Teitel, S. *Helv. Chim. Acta* **1972**, *55*, 15.
(15) Hayashi, K.; Ozaki, Y.; Nunami, K.-I.; Yoneda, N. *Chem. Pharm. Bull.* **1983**, *31*, 312.
(16) For detailed discussions on the use of amino acids in the synthesis of optically pure materials see:
Martens, J. *Top. Curr. Chem.* **1984**, *125*, 165.
Coppola, G.M., Schuster, H.F. *Asymmetric Synthesis. Construction of Chiral Molecules Using Amino Acids*, John Wiley & Sons, New York, 1987.
(17) Izumi, Y.; Chibata, I.; Itoh, T. *Angew. Chem. Int. Eng.* **1978**, *17*, 176.
Kirk Othmer Encyclopedia of Chemical Technology; 3rd edition, Vol. 2, 376.
(18) For comprehensive coverage of the subject see:
Morrison, J.D., Mosher, H.S. *Asymmetric Organic Reactions*, American Chemical Society, Washington, D.C., 1976.
Morrison, J.D. Ed. *Asymmetric Synthesis*, Vol. 5, Academic Press, Inc., Orlando, FL, 1985.
(19) Nogradi, M. *Stereoselective Synthesis*, VCH Publishers, New York, 1987, Chapter 2.
(20) For recent reviews see:
Caplar, V.; Comisso, G.; Sunjic, V. *Synthesis* **1981**, 85.
Apsimon, J.W.; Seguin, R.P. *Tetrahedron* **1979**, *35*, 2797.
Apsimon, J.W.; Collier T.L. *Tetrahedron* **1986**, *42*, 5157.
(21) Fryzuk, M.D.; Bosnich, B. *J. Am. Chem. Soc.* **1978**, *100*, 5491.
(22) Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245.
(23) Though rarely noted in the literature, *Extreme Caution* should be taken when using the noble-metal perchlorate complexes, due to their highly explosive nature.
(24) Buck, J.S.; Ide, W.S. *Org. Synth. Coll. Vol. 2*, **1943**, 55.
(25) Suh, J.T. *US Patent* 3882172 (1975), Colgate Palmolive; *C.A.* **1975**, *83*, 59269.
(26) Selke, R.; Pracejus, H. *Dtsch. Pat. (DDR)* 140036 (1980); *C.A.* **1981**, *94*, 66066.

(27) Glaser, R. Geresh, S.; Schöllkopf, U.; Meyer, R. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1746.
(28) Kato, T.; Higuchi, C.; Mita, R.; Yamaguchi, T. *Japanese Patent* 60 190749 (1985), Mitsui Toatsu Chemicals, Inc.; *C.A.* **1986**, *104*, 109267.
Kato, T.; Higuchi, C.; Mita, R.; Yamaguchi, T. *Japanese Patent* 60 185752 (1985), Mitsui Toatsu Chemicals, Inc.; *C.A.* **1986**, *104*, 68622.
(29) Deuloffeu, V.; Mendivelzua, G. *Z. Physiol. Chem.* **1933**, *219*, 233.
(30) Butterick, J.R.; Unrau, A.M. *Can. J. Chem.* **1974**, *52*, 2873.
(31) Schrock, R.R.; Osborn, J.A. *J. Am. Chem. Soc.* **1971**, *93*, 3089.
(32) Yamamoto, H.; Hayakawa, T. *Polymer* **1978**, *19*, 963.
(33) Nakamoto, H.; Aburatani, M.; Inagaki, M. *J. Med. Chem* **1971**, *14*, 1021.
(34) Devasia, M.; Pillai, C.R. *Tetrahedron Lett.* **1975**, 4051.
(35) Arenal, I.; Bernabe, M.; Fernandez-Alvarez, E. *An. Quim Ser. C.* **1981**, *77*, 56.