AUSTRALIA

Patents Act 1990

REQUEST FOR A STANDARD PATENT

AND NOTICE OF ENTITLEMENT

The Applicant identified below requests the grant of a patent to the nominated person identified below for an invention described in the accompanying standard complete patent specification.

[70,71]Applicant and Nominated Person:
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2110 East Galbraith Road, Cincinnati, Ohio, 45215, UNITED STATES OF AMERICA

[54]Invention Title:
CHIRAL LACTIC ACID DERIVATIVES

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This application is to be made by virtue of Section 39; being a divisional of application no. 89635/91.

Applicant states the following:

The nominated person is the assignee of the actual inventor(s):

The nominated person(s) is are the applicant(s) of the original application(s):

The nominated person is not an opponent or eligible person described in Section 33-36 of the Act.

21 January 1994

Merrell Dow Pharmaceuticals Inc.
By PHILLIPS ORMONDE & FITZPATRICK
Patent Attorneys
By

Our Ref: 354560

6000q
1. A compound of the formula

\[
\begin{array}{c}
\text{H} \\
\mid \\
\text{Y} \quad \text{CH} \quad \text{C} \quad \text{C} \quad \text{Cl}
\end{array}
\]

in which X and Y are each simultaneously represented by
2. A compound of the formula

\[
\begin{align*}
Y & - \text{CH}_2 - \text{C} - \text{C} - \text{C} - \text{C} - \text{Cl} \\
& \downarrow \text{OX}
\end{align*}
\]

in which \(X\) and \(Y\) are each simultaneously represented by
AUSTRALIA
Patents Act

COMPLETE SPECIFICATION
(ORIGINAL)

Application Number:  
Lodged:  

Complete Specification Lodged:  
Accepted:  
Published:  

Priority  

Related Art:  

Name of Applicant:  
Merrell Dow Pharmaceuticals Inc.  

Actual Inventor(s):  
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Invention Title:  
CHIRAL LACTIC ACID DERIVATIVES  

Our Ref : 354560  
POF Code: 1432/120371  

The following statement is a full description of this invention, including the best method of performing it known to applicant(s):  

- 1 -
The present application is a divisional of Australian Patent Application 89635/91, the entire disclosure of which is incorporated herein by reference.

The present invention is directed to a new class of chiral lactic acid derivatives. These derivatives may be used as intermediate compounds in the stereospecific synthesis of (S)-vinyl-GABA, (S)-allenyl-GABA, (S)-5-allenylpyrrolidinone, and (S)-5-vinyl-pyrrolidinone.

BACKGROUND OF THE INVENTION

4-Amino-5-hexenoic acid is known in the art as an antiepileptic agent and is described in United States Patent No. 3,960,927. It is also known as vinyl-GABA and is currently available from Merrell Dow Pharmaceuticals, Inc. United States Patent No. 4,621,145 (hereby incorporated by reference) describes one method for synthesizing this compound. The last step in the reaction sequence is depicted below:

In this reaction 5-vinyl-2-pyrrolidinone (structure A) is subjected to an acidic hydrolysis thereby producing the desired compound, 4-amino-5-hexenoic acid (structure B).
This acidic hydrolysis is carried out using techniques known in the art. Typically, the 5-vinyl-2-pyrrolidinone is contacted with a strong acid such as hydrochloric acid or trifluoroacetic acid at a temperature above 60°C in an aqueous solvent system.

Co-pending United States Patent Application 432,707, filed November 7, 1989 (which is hereby incorporated by reference) discloses that vinyl-GABA can be produced by subjecting 5-vinyl-2-pyrrolidinone to a basic hydrolysis as well. This hydrolysis is typically carried out by contacting the 5-vinyl-2-pyrrolidinone with a molar excess of potassium hydroxide. Typically from about 1.1 to about 1.5 equivalents are utilized. The basic hydrolysis is carried out at a temperature ranging from about 60°C to 140°C. The reaction is typically carried out for a period of time ranging from about 0.5 hours to about 24 hours.

4-Amino-hepta-5,6-dienoic acid is also known in the art as an anti-epileptic agent and is described in United States Patent No. 4,454,156. This compound is also known as allenic-GABA and is under development by Merrell Dow Pharmaceuticals, Inc. Castelhano et al. discloses that allenic-GABA (Structure E) can be produced by a hydrolysis similar to that discussed above utilizing of 5-allenyl-2-pyrrolidinone (Structure D) as the starting material, J. Am. Chem. Soc. Vol. 106, pages 1877-1879 (1984). This reaction may be depicted as:

\[
\begin{align*}
\text{HO}_2CCH_2CH_2CHCH=CH_2 & \quad \text{ACIDIC HYDROLYSIS} \\
\text{E} & \quad \text{NH}_2
\end{align*}
\]
United States Patent Nos. 4,621,145 and 4,454,156 disclose that the S-enantiomer of 4-amino-5-hexenoic acid and 4-amino-hepta-5,6-dienoic acid are the preferred isomers.

Recent efforts have focused on developing a commercially viable method for synthesizing the S-enantiomer of these compounds. The following synthetic procedure was developed as depicted by Reaction Scheme I and utilizes as an intermediate compound a chiral auxiliary according to the present invention:
REACTION SCHEME I

STEP A: Acylation

STEP B: Separation

STEP C: Hydrolysis
In Step A, a racemic pyrrolidinone derivative as described by structure 1 in which A is represented by -CH=CH=CH₂ or -CH=CH₂, is acylated with a chiral auxiliary of the present invention as described by structure 2 in which X and Y are simultaneously represented by the following substituents:
This acylation reaction produces the diastereomers described by structure 3 and 3' in which A, X, and Y are as defined above. In Step B the diastereomers are separated and the desired S,S isomer depicted by structure 3 is recovered. In Step C, this diastereomer is subjected to a hydrolysis reaction. Depending on the manner in which the hydrolysis is carried out, this reaction produces either the S-pyrroldinone derivative described by structure 4 or the (S)-amino acid derivative described by structure 5 in which A is as defined above.

The acylation reaction of Step A can be carried out using techniques known in the art. Typically the
pyrrolidinone derivative of structure 1 is contacted with an approximately equivalent amount of a base such as sodium hydride, butyllithium, lithium diisopropylamine, potassium t-butoxide and potassium carbonate for a period of time ranging from 15 minutes to 3 hours. The reactants are typically contacted at a depressed temperature in the range of -40°C to 25°C in an aprotic solvent such as toluene, tetrahydrofuran, toluene/mineral oil, etc. The reaction medium is then warmed to approximately room temperature and an equivalent amount of the chiral auxiliary of structure 2 is added to the reaction. The reactants are typically stirred together for a period of time ranging from 1 minute to 3 hours. The reaction is then quenched by the addition of water and the diastereomers of structure 3 and 3' are recovered by extraction.

In Step B, the diastereomers are separated by techniques known in the art. One suitable method is flash chromatography on silica gel. Suitable eluants include hexane/ethyl acetate, t-butylmethyl ether/hexane and toluene. Another suitable separation method is recrystallization. Suitable solvent systems include polar solvents such as hexane/ethyl acetate or tetrahydrofuran.

In Step C, the (S,S)-diastereomer produced above is subjected to a hydrolysis reaction. Depending upon the manner in which the reaction is carried out, the product will either be the (S)-pyrrolidinone derivative of structure 4 or the (S)-amino acid derivative of structure 5. The pyrrolidinone derivative of Structure 4 can be produced by subjecting the diastereomer to a basic hydrolysis with a weak base such as K₂CO₃. This hydrolysis is typically carried out in methanol at a temperature range of from 25°C to 65°C for a period of time ranging from 1 to 4 hours. The amino acid derivative can be produced by subjecting the diastereomer to a hydrolysis with a stronger base such as...
potassium hydroxide in a solvent such as water. This hydrolysis is typically carried out at a temperature ranging from 50°C to 140°C for a period of time ranging from 1 to 24 hours. Alternatively, the amino acid derivative of structure 5 can be produced via an acidic hydrolysis in which hydrochloric acid is used.

An alternative method of producing either the (S)-pyrrolidinone of structure 4 or the (S)-amino acid of structure 5 is depicted below in Reaction Scheme II. This Reaction Scheme also utilizes as an intermediate compound a chiral auxiliary of the present invention.
The initial step is to carry out an acylation reaction between the pyrrolidinone of structure 1 in which A is as defined above and the chiral auxiliary of the present invention represented by structure 6 in which X and Y are simultaneously represented by

<table>
<thead>
<tr>
<th>Y</th>
<th>X</th>
</tr>
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<tbody>
<tr>
<td>H</td>
<td>-O-</td>
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<tr>
<td>H</td>
<td>-O-</td>
</tr>
<tr>
<td>H</td>
<td>-S-</td>
</tr>
</tbody>
</table>
This acylation produces the diastereomers of structure 7 and 7'. This acylation can be carried out in the same manner discussed above for Step A of Reaction Scheme I. In Step B these diastereomers are separated and the (S,R)-diastereomer (7') is recovered for further processing. This separation can be carried out in the same manner as the separation of Step B in Reaction Scheme I. In Step C the diastereomer of structure 7 is subjected to a hydrolysis reaction thereby producing the (S)-pyrrolidinone derivative of structure 4 or the amino acid derivative of structure 5. This hydrolysis can be carried out in the same manner as above.

Methods for producing the chiral auxiliaries of the present invention as depicted by structures 2 and 6 are known in the art. Specific methods are disclosed in Examples 1-5. Method for producing the pyrrolidinones of structure 1 are known in the art.

The following examples are being presented in order to further illustrate the invention and the use of the chiral auxiliaries of the present invention in further synthetic procedures. They should not be construed as limiting the invention in any manner.
EXAMPLE 1

Step A
Sililation

\[
\text{Ph} \quad \text{OH} \quad \text{ClSiMe}_2\text{-t-Bu} \quad \text{imidazole} \quad \text{DMF} \quad \text{Ph} \quad \text{OH} \quad \text{OTBDMS}
\]

\[
\text{Ph} \quad \text{O} \quad \text{Cl} \quad \text{CH}_2\text{Cl}_2, \text{cat. DMF} \quad \text{Ph} \quad \text{O} \quad \text{Cl}
\]

\[
\text{Step B}
\]

Chlorination

\[
\text{Ph} \quad \text{Cl} \quad \text{OTBDMS}
\]

\[
\text{Ph} \quad \text{Cl} \quad \text{OTBDMS}
\]

\[
\text{Step C}
\]

Acylation and Separation

\[1. \text{NaH, THF, O}\degree\text{C} \quad 2. \text{Ph} \quad \text{O} \quad \text{Cl} \quad \text{OTBDMS} \quad \text{Ph} \quad \text{O} \quad \text{Cl} \quad \text{OTBDMS} \]

\[0\degree\text{C} \text{to} 25\degree\text{C} \]

\[\text{K}_2\text{CO}_3, \text{MeOH} \quad \text{K}_2\text{CO}_3, \text{MeOH} \]

\[\text{Step D}
\]

Hydrolysis

\[5a (S,S) \quad 5b (R,S) \]

\[5a (S,S) \quad 5b (R,S) \]
STEP A SILYATION

(1,1-Dimethylethyl)dimethylsilyl (2S)-1-((1,1-Dimethylethyl)dimethylsilyloxy)-3-phenylpropanoate

To a solution of 10.04 g (60 mmol) of (2S)-3-phenyllactic acid and 18.10 g (270 mmol) of imidazole in N,N-dimethylformamide (200 mL) was added 19.95 g (130 mmol) of t-butyldimethylchlorosilane at 25°C. The reaction mixture was stirred at room temperature for 18 hours under an argon atmosphere. To the reaction mixture was then added hexane (400 mL). The bi-phasic solution was stirred for 15 minutes prior to the addition of water (300 mL). The solution was stirred for 1 minute before the phases were separated. The organic phase was dried over magnesium sulfate. Concentration and vacuum distillation afforded 22.2 g (93%) of (1,1-dimethylethyl)dimethylsilyl (2S)-2-((1,1-dimethylethyl)dimethylsilyloxy)-3-phenylpropanoate (3) as a clear liquid: bp 123-125°C (0.5 mm Hg); 1H NMR (CDCl₃) δ = 0.206-0.074 (s, 3H), 0.273 (s, 3H), 0.812 (s, 9H), 0.942 (s, 9H), 2.85-2.92 (m, 1H), 3.05-3.11 (m, 1H), 4.27-4.31 (m, 1H), 7.21-7.31 (m, 5H); 13C NMR (CDCl₃) δ 173.2, 137.6, 129.8, 128.3, 126.5, 74.5, 41.7, 25.7, 25.6, 18.2, 17.7, -4.89, -5.19, -5.73.

STEP B CHLORINATION

(2S)-2-((1,1-Dimethylethyl)dimethylsilyloxy)-3-phenylpropanoyl chloride (4)

To a solution of 21.0 g (53 mmol) of (1,1-dimethylethyl)dimethylsilyl (2S)-2-((1,1-dimethylethyl)dimethylsilyloxy)-3-phenylpropanoate (3) and five drops of N,N-dimethylformamide in methylene chloride at 0°C was added 29.3 mL (59 mmol) of a 2.0 M solution of oxalyl chloride in methylene chloride over a 30 min period. The cooling bath was removed and the reaction mixture was allowed to stir at room temperature for 18 hours. The solvent and excess oxalyl chloride were removed by rotary evaporation resulting in a yellow liquid. Purification by vacuum distillation...
afforded 12.7 g (80%) of (2S)-2-((1,1-dimethylethyl)dimethylsilyloxy)-3-phenylpropanoyl chloride (4) as a clear liquid: bp 88-90°C (0.2 mm Hg); 1H NMR (CDCl₃) δ -0.215 (s, 3H), -0.0339 (s, 3H), 0.840 (s, 9H), 2.94-3.01 (m, 1H), 3.23-3.29 (m, 1H), 4.52-4.56 (m, 1H), 7.25-7.35 (m, 5H); 13C NMR (CDCl₃) δ 175.7, 135.9, 129.8, 128.4, 127.1, 81.1, 40.8, 25.5, 18.0, -5.40, -5.76.

STEP C ACYLATION AND SEPARATION

N-Acylation of 5-Vinylpyrrolidin-2-one with (2S)-2-((1,1-dimethylethyl)dimethylsilyloxy)-3-phenylpropanoyl chloride (4)

To 60% sodium hydride (336 mg, 10 mmol, in mineral oil) in tetrahydrofuran (20 mL) at 0°C was added dropwise a solution of 5-vinylpyrrolidin-2-one (1.0 g, 9.0 mmol) in tetrahydrofuran (10 mL) over a 5 min period. The cooling bath was removed and the solution was allowed to warm to 25°C to ensure complete anion generation. To the anion at 25°C was added dropwise a solution of (2S)-2-((1,1-dimethylethyl)dimethylsilyloxy)-3-phenylpropanoyl chloride (4, 2.98 g, 10 mmol) in tetrahydrofuran (10 mL) over a 5 min period. TLC indicated that the reaction was complete upon addition of the acid chloride (silica gel plates; hexane and ethyl acetate, 9:1). The solvent was removed by rotary evaporation affording a thick slug. The slug was dissolved in methylene chloride (75 mL) and washed with water (1x50 mL), a saturated aqueous sodium bicarbonate solution (1x50 mL) and dried (MgSO₄). Concentration and purification by flash chromatography on silica gel (EM 60, 0.040-0.063 partical size, 230-400 Mesh, column size: 4.5 cm diameter x 15 cm length) using hexane and ethyl acetate (19:1) afforded 1.54 g (46%) of (5S)-N-((2S)-2-((1,1-dimethylethyl)dimethylsilyloxy)-3-phenylpropanoyl)-5-ethenylpyrrolidin-2-one (5a) as a white crystalline material: mp 92-93.5°C; 1H NMR (CDCl₃) δ -0.316 (s, 3H), -0.217 (s, 3H), 0.703 (s, 9H), 1.94 (t, J=9.6 Hz, 1H), 2.29 (p, J=11.7 Hz, 1H), 2.50-2.75
(m, 3H), 3.11 (d, J=12.8 Hz, 1H), 4.97-5.13 (m, 1H), 5.12-5.18 (m, 2H), 5.45 (d, J=9.8 Hz, 1H), 5.75-5.86 (m, 1H); $^{13}$C NMR (CDCl$_3$) δ 175.1, 174.1, 137.9, 135.4, 130.0, 128.0, 126.4, 115.8, 74.2, 58.1, 41.2, 31.7, 25.5, 24.3, 18.1, 5.50, -5.76.

**STEP D HYDROLYSIS**

(5S)-5-Ethenylpyrrolidin-2-one (6) From (5S)-N-((2S)-2-((1,1-dimethylethyl)dimethylsilyloxy)-3-phenylpropanoyl)-5-ethenylpyrrolidin-2-one (5a)

To a solution of 500 mg (1.0 mmol) of (5S)-5-ethenylpyrrolidin-2-one (Sa) in methanol (20 mL) and water (5 mL) was added 152 mg (1.1 mmol) of potassium carbonate. The resulting reaction mixture was stirred at 25°C for 1 hour before a sample was removed for TLC analysis. TLC was carried out on silica gel plates and eluted with hexane and ethyl acetate (2:1). An additional 20 mL of water was added and the solution was extracted with methylene chloride (2x15 mL). The aqueous layer was acidified to pH ~4 with dilute hydrochloric acid (1.0 M) and extracted with methylene chloride (2x20 mL). The combined organic phases were dried over magnesium sulfate. Concentration and purification by flash chromatography on silica gel (EM 60, 0.040-0.063 particle size, 230-400 Mesh, column size: 3.5 cm diameter x 12 cm length) using hexane and ethyl acetate (9:1) afforded (67%) of (5S)-5-ethenyl-2-pyrrolidinone (6) as a clear thick oil: $^1$H NMR (CDCl$_3$) δ 1.77-1.88 (m, 1H), 2.22-2.42 (m, 2H), 4.13-4.19 (m, 1H), 5.11 (d, J=10.0 Hz, 1H), 5.22 (d, J=17.0 Hz, 1H), 5.75-5.86 (m, 1H), 7.16-7.32 (b, NH, 1H); $^{13}$C NMR (CDCl$_3$) δ 178.5, 138.6, 115.3, 56.6, 29.8, 27.8.
EXAMPLE 2

**Step A**
Substitution

\[
\text{OCH}_3 \xrightarrow{\text{PhSO}_2\text{Cl, Et}_3\text{N}} \text{OSO}_2\text{Ph}_3 \text{N} \xrightarrow{\text{toluene, 25°C}} \text{OCH}_3
\]

**Step B**
Displacement

1. \( \text{K}_2\text{CO}_3/\text{DMSO} \)
2. \( \text{OH} \) t-Bu

**Step C**
Saponification

\[
\text{OCH}_3 \xrightarrow{\text{KOH/H}_2\text{O}} \text{OCH}_3 \xrightarrow{\text{THF}} \text{OCH}_3
\]

**Step D**
Chlorination

\[
\text{OCl} \xrightarrow{\text{Cl}_2\text{Cl}_2} \text{OCl}
\]
STEP A SUBSTITUTION
Methyl (2S)-2-(Phenylsulfonyl)oxypropanate (12)

To a solution of 200 g (1.92 mol) of methyl (2S)-lactate (5) and 295 g (2.11 mol) of triethylamine in toluene (1 L) at 0°C was added 270 mL, 2.11 mol) of benzenesulfonyl chloride dropwise over a 2 hour period under a nitrogen atmosphere. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature and stir there overnight. The reaction was worked-up by washing with water (3x1 L) and dried (MgSO₄). Filtration, concentration and purification by vacuum distillation afforded 440 g (94%) of methyl (2S)-2-(phenylsulfonyl)oxypropanate (12) as a pale yellow liquid: bp 140-142°C (0.1 mm Hg); ¹H NMR (CDCl₃) δ 1.51-1.56 (d, 3H), 3.66 (s, 3H), 4.95-5.01 (q, 1H), 7.54-7.59 (m, 2H), 7.65-7.70 (m, 1H), 7.93-7.95 (d, 2H); ¹³C NMR (CDCl₃) δ 169.3, 133.9, 129.1, 127.7, 112.3, 74.2, 52.5, 18.3; IR (neat) 2958 (w), 1762 (s), 1586 (m), 1451 (s), 1190 (vs), 1084 (s), 926 (m), 753 (m) cm⁻¹.
STEP B DISPLACEMENT

Methyl (2R)-2-(3,5-di-t-butylphenyloxy)propanate (13)

To a solution 8.87 g (43 mmol) of 3,5-di-t-butylphenol in dimethyl sulfoxide (150 mL) was 26.9 mL (43 mmol) of a 1.6 M n-butyllithium/hexane solution dropwise over a 15 min period under a nitrogen atmosphere. The solution was allowed to stir at room temperature for an additional 15 min resulting in the precipitation of the lithium salt of 3,5-di-t-buthylphenol. A solution of 10.0 g (40 mmol) of methyl (2S)-2-(phenylsulfonyl)oxypropanate (12) in dimethyl sulfoxide (50 mL) was added dropwise to the suspension over a 10 min period. The reaction mixture was stirred overnight at room temperature. To the reaction solution was added water (300 mL) and the product was extracted with perchloroethylene (3x200 mL). The combined organic extracts were washed with water (1x200 mL), an aqueous saturated sodium chloride solution (1x200 mL) and dried (MgSO₄). Filtration, concentration and purification by flash chromatography on silica gel (EM silica gel 60, 0.040-0.063 particial size, 230-400 Mesh, column size: 7 cm diameter X 18 cm length) using hexane and ethyl acetate (19:1) afforded 11.75 g (89%) of methyl (2R)-2-(3,5-di-t-butylphenyloxy)propanate (13) as a thick oil: ¹H NMR (CDCl₃) δ 1.29 (s, 18H), 1.61-1.63 (d, 3H), 3.76 (s, 3H), 4.75-4.82 (q, 1H), 6.73 (s, 2H), 7.04 (s, 1H); ¹³C NMR (CDCl₃) δ 173.1, 157.2, 152.3, 115.8, 114.7, 109.7, 109.5, 72.7, 52.1, 34.9, 31.4, 18.6.

STEP C DEPROTECTION

(2R)-2-(3,5-Di-t-butylphenyloxy)propanoic Acid (14)

To a solution of 2.0 g (36 mmol) of potassium hydroxide in water (100 mL) and tetrahydrofuran (100 mL) was added 11.48 g (36 mmol) of methyl (2R)-2-(3,5-di-t-butylphenyloxy)propanate (13). The reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was acidified to pH 2 with concentrated hydrochloric acid and
the resulting solution was extracted with diethyl ether (3x200 mL). The combined extracts were washed with an aqueous saturated sodium chloride solution (1x300 mL) and dried (MgSO₄). Filtration and concentration resulted in a yellowish sludge. The crude product was purified by precipitation from hexane at -78°C to afford 8.2 g (75%) of (2R)-2-(3,5-di-t-butylphenyloxy)propanoic acid (14) as an off-white crystalline material: ¹H NMR (CDCl₃) δ 1.29 (s, 18H), 1.64-1.66 (d, 3H), 4.56-4.82 (q, 1H), 6.75 (s, 2H), 7.06 (s, 1H); ¹³C NMR (CDCl₃) δ 177.7, 156.8, 152.5, 116.2, 109.7, 72.3, 35.0, 31.4, 18.4.

STEP D CHLORINATION
(2R)-2-(3,5-Di-t-butylphenyloxy)propanoyl chloride (11)
To a mixture of 3.0 g (9.8 mmol) of (2R)-2-(3,5-di-t-butylphenyloxy)propanonic acid (14) and 4 drops of N,N-dimethylformamide in methylene chloride (50 mL) at 0°C under a nitrogen atmosphere was added 5.4 mL (10.8 mmol) of a 2M solution of oxalyl chloride in methylene chloride dropwise over a 20 min period. The reaction mixture was allowed to stir at room temperature overnight. The solvent and any excess oxalyl chloride was removed by rotary evaporation and dried (under vacuum) to afford 3.15 g (99%) of crude (2R)-2-(3,5-di-t-butylphenyloxy)propanoyl chloride (11) as yellowish liquid: ¹H NMR (CDCl₃) δ 1.30 (s, 18H), 1.73-1.76 (d, 3H), 4.92-4.98 (q, 1H), 6.72 (s, 2H), 7.10 (s, 1H); ¹³C NMR (CDCl₃) δ 175.0, 156.5, 152.7, 116.7, 109.7, 79.8, 35.0, 31.4, 18.1.

STEP E ACYLATION AND SEPARATION
N-Acylation of 5-Vinylpyrrolidin-2-one with (2R)-2-(3,5-Di-t-butylphenyloxy)propanoyl chloride (11)
To 60% sodium hydride (336 mg, 10 mmol) in toluene (20 mL) at 0°C was added dropwise a solution of 5-vinylpyrrolidin-2-one (1.0 g, 9.0 mmol) in toluene (10 mL) over a 5 min period. The cooling bath was removed and the
solution was allowed to warm to 25°C to ensure complete generation of the anion. To the anion at 25°C was added dropwise a solution of (2R)-2-(3,5-di-t-butylphenyloxy)-propanoyl chloride (11, 3.20 g, 9.8 mmol) in toluene (10 mL) over a 5 min period. TLC indicated that the reaction was complete upon addition of the acid chloride (silica gel plates; hexane and ethyl acetate, 2:1). Water (60 mL) was added to the reaction mixture and the phases were separated. The aqueous phase was extracted with ethylene chloride (1x40 mL). The combined organic phases were washed with a saturated aqueous sodium bicarbonate solution (1x70 mL) and dried (MgSO₄). Concentration and purification by flash chromatography on silica gel (EM silica gel 60, 0.040-0.063 partical size, 230-400 Mesh, column size: 6.5 cm diameter X 18 cm length) using hexane and ethyl acetate (19:1) afforded 1.65 g of (5S)-N-((2R)-2-(3,5-di-t-butylphenyloxy)propanoyl)-5-ethenylpyrrolidin-2-one (15a) as an oil: ¹H NMR (CDCl₃) δ 1.20 (s, 18H), 1.60-1.62 (d, 3H), 1.92-2.04 (m, 1H), 2.21-2.32 (m, 1H), 2.52-2.80 (m, 2H), 4.9-4.96 (q, 1H), 5.11-5.21 (m, 2H), 5.77-5.88 (m, 1H), 5.98-6.04 (g, 1H), 6.71 (s, 2H), 7.00 (s, 1H); ¹³C NMR (CDCl₃) δ 175.2, 172.7, 157.1, 152.1, 135.2, 115.9, 115.6, 109.6, 72.3, 58.0, 34.9, 31.6, 31.4, 24.4, 18.1; IR (neat) 2966 1740 1715 1593 2513 1380 1229 706 cm⁻¹.

**STEP F HYDROLYSIS**

(5S)-5-Ethenyl-2-pyrrolidin-2-one (6) from (5S)-N-((2R)-2-(3,5-Di-t-butylphenyloxy)propanoyl-5-ethenylpyrrolidin-2-one (15a)

A solution of diastereomer 15a (1.5 g, 3.8 mmol), potassium carbonate (233 mg, 1.7 mmol), and methanol (20 mL) is stirred at room temperature for 1.5 hours. The solvent is removed by rotary evaporation to afford a thick yellow oil. This oil is dissolved in methylene chloride (10 mL) and filtered through a silica gel plug (20 g, EM-60, 70-230...
mesh) to remove any salts. The plug is rinsed with hexane/ethyl acetate (4:1), discarding the initial eluent which contains the chiral auxiliary, to give (5S)-5-ethenylpyrrolidin-2-one (6).
EXAMPLE 3

Step A
Displacement

1. K$_2$CO$_3$/DMSO
2. OH

Step B
Saponification

KOH/H$_2$O

Step C
Chlorination

Oxalyl chloride

CMF (cat.)

CH$_2$Cl$_2$

(99%)

Step D
Acylation and Separation

1. NaH, Toluene, 0°C
2.

KOH/H$_2$O

Step E
Hydrolysis

S,R
STEP A DISPLACEMENT
Methyl (2R)-2-(2,4-Di-t-butylphenyloxy)propanate (17)
Potassium carbonate (5.66 g, 41 mmol) and 2,4-di-t-butyphenol (8.87 g, 43 mmol) were dissolved in dimethyl sulfoxide (175 mL) at 25°C and allowed to stir overnight under a nitrogen atmosphere to ensure complete anion formation. A solution of 10.0 g (41 mmol) of methyl (2S)-2-(phenylsulfonyl)oxypropanate (12) in dimethyl sulfoxide (50 mL) was added to the anion at 25°C and the reaction mixture was allowed to stir overnight. The reaction was quenched with water (200 mL) and the phases were separated. The aqueous phase was extracted with perchloroethylene (3x200 mL). The combined organic extracts were washed with water (3x300 mL), a saturated aqueous sodium chloride solution (1x300 mL) and dried (MgSO₄). Concentration and purification by flash chromatography on silica gel (EM silica gel 60, 0.040-0.063 partical size, 230-400 Mesh, column size: 7 cm diameter x 18 cm length) using hexane and ethyl acetate (29:1) afforded 10.1 g (77%) of methyl (2R)-2-(2,4-di-t-butylphenyloxy)propanate (17) as a thick oil: ¹H NMR (CDCl₃) δ 1.29 (9H), 1.43 (9H), 1.60-1.65 (d, 3H), 1.73 (s, 3H), 4.75-4.82 (q, 1H), 6.54-6.57 (d, 1H), 7.08-7.12 (d, 1H), 7.33 (s, 1H); ¹³C NMR (CDCl₃) δ 172.9, 153.7, 143.0, 137.2, 124.2, 123.1, 110.5, 71.7, 52.0, 5.0, 34.2, 31.5, 29.9, 18.6; IR (neat) 2962 (vs), 1764 (w), 1740 (s), 1497 (s), 1235 (vs) cm⁻¹.

STEP B DEPROTECTION
(2R)-2-(2,4-Di-t-butylphenyloxy)propanoic Acid (18)
To a solution of 5.98 mg (11 mmol) of potassium hydroxide in water (75 mL) and tetrahydrofuran (75 mL) was added 3.34 mg (10 mmol) of methyl (2R)-2-(2,4-di-t-butylphenyloxy)propanate (17). The reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was acidified to pH 2 with concentrated hydrochloric acid and the resulting solution was extracted with diethyl ether (3x200 mL). The

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combined extracts were washed with an aqueous saturated sodium chloride solution (1x300 mL) and dried (MgSO₄). Filtration and concentration afforded a thick crude oil. Purification by precipitation from hexane at -78°C afforded 2.65 g (83%) of (2R)-2-(2,4-di-t-butylphenyloxy)propanoic acid (18) as a white crystalline material: ¹H NMR (CDCl₃) δ 1.29 (s, 9H), 1.42 (s, 9H), 1.68-1.70 (d, 3H), 4.77-4.85 (q, 1H), 6.58-6.61 (d, 1H), 7.11-7.15 (d, 1H), 7.34 (s, 1H); ¹³C NMR (CDCl₃) δ 177.2, 153.5, 143.3, 137.3, 124.4, 123.3, 110.7, 71.4, 35.0, 34.3, 31.6, 30.0, 18.5.

STEP C CHLORINATION
(2R)-2-(2,4-Di-t-butylphenyloxy)propanoyl chloride (16)
To a mixture of 675 mg (2.2 mmol) of (2R)-2-(2,4-di-t-butyloxy)propanoic acid (18) and 4 drops of N,N-dimethylformamide in methylene chloride (20 mL) at 0°C under a nitrogen atmosphere was added 1.21 mL (2.4 mmol) of a 2M solution of oxalyl chloride in methylene chloride dropwise over a 10 min period. The reaction mixture was allowed to stir at room temperature overnight. The solvent and any excess oxalyl chloride was removed by rotary evaporation and dried (under vacuum) to afford 715 mg (99%) of (2R)-2-(2,4-di-t-butyloxy)propanoyl chloride (16) as a crude yellow liquid: ¹H NMR (CDCl₃) δ 1.29 (s, 9H), 1.42 (s, 9H), 1.76-1.79 (d, 3H), 4.94-5.00 (q, 1H), 6.50-6.60 (d, 1H), 7.12-7.16 (d, 1H), 7.36 (s, 1H); ¹³C NMR (CDCl₃) δ 175.0, 152.8, 144.1, 137.4, 124.6, 123.4, 110.6, 78.6, 35.1, 34.3, 1.5, 30.0, 18.0.

STEP D ACYLATION AND SEPARATION
N-Acylation of 5-Vinylpyrrolidin-2-one with (2R)-2-(2,4-Di-t-butyloxy)propanoyl chloride (16)
To 60% sodium hydride (74 mg, 2.2 mmol) in toluene (10 mL) at 0°C was added dropwise a solution of 5-vinylpyrrolidin-2-one (222 mg, 2.0 mmol) in toluene (5 mL) over a 5 min period. The cooling bath was removed and the solution was
allowed to warm to 25°C to ensure complete generation of the anion. To the anion at 25°C was added dropwise a solution of (2R)-2-(2,4-di-t-butylphenyloxy)propanoyl chloride (16, 716 mg, 2.2 mmol) in toluene (5 mL) over a 5 min period. TLC indicated that the reaction was complete upon addition of the acid chloride (silica gel plates; hexane and ethyl acetate, 4:1). Water (30 mL) was added to the reaction mixture and the phases were separated. The aqueous phase was extracted with methylene chloride (1x25 mL). The combined organic phases were washed with a saturated aqueous sodium bicarbonate solution (1x50 mL) and dried (MgSO₄). Concentration and purification by flash chromatography on silica gel (EM silica gel 60, 0.040-0.063 partical size, 230-400 Mesh, column size: 4.5 cm diameter X 15 cm length) using hexane and ethyl acetate (19:1) afforded 360 mg (45%) of (5S)-N-((2R)-2-(2,4-di-t-butylphenyloxy)propanoyl)-5-ethenylpyrrolidin-2-one (19a) as a thick oil: ¹H NMR (CDCl₃) δ 1.28 (s, 9H), 1.42 (s, 9H), 1.77-1.80 (d, 3H), 1.95-2.10 (m, 1H), 2.23-2.33 (m, 1H), 2.52-2.82 (m, 2H), 4.91-4.97 (q, 1H), 5.10-5.19 (m, 2H), 5.80-5.90 (m, 1H), 5.97-6.03 (m, 1H), 6.49-6.53 (d, 1H), 7.12-7.16 (d, 1H), 7.35 (s, 1H); ¹³C NMR (CDCl₃) δ 175.4, 172.9, 157.3, 153.4, 143.1, 137.2, 135.6, 124.3, 123.2, 115.8, 71.6, 57.9, 35.2, 34.2, 31.9, 31.4, 29.9, 24.3, 18.2; IR (neat) 2965 (vs), 1741 (vs), 1715 (vs), 1590 (s), 1230 (vs), 710 (w) cm⁻¹.

STEP E HYDROLYSIS

(4S)-Amino-5-hexenoic Acid (B) from (5S)-N-((2R)-2-(2,4-Di-t-butylphenyloxy)propanoyl)-5-ethenylpyrrolidin-2-one (19a)

A solution of (5S)-N-((2R)-2-(2,4-di-t-butylphenyloxy)propanoyl)-5-ethenylpyrrolidin-2-one (19a, 1.0 g, 2.5 mmol) and 87% potassium hydroxide (317 mg, 5.7 mmol) in water (2 mL) is refluxed for 1.5 hours. The solution is allowed to cool to room temperature. Water is added (15 mL) and the solution is acidified to pH 7 with concentrated hydrochloric acid and extracted with diethyl ether (3 x 10 mL) to remove
the chiral auxiliary. The aqueous solution is then acidified to pH 5.5 with concentrated hydrochloric acid and extracted with diethyl ether (3 x 15 mL). The second series of organic extracts are combined and dried (MgSO₄).

Concentration by rotary evaporation affords (4S)-4-amino-5-hexenoic acid (B).
EXAMPLE 4

Step A
Etherification

1. NaH, THF, 25°C
2. N-Bu₄NI

\[
\text{OCH}_2\text{CH}_3
\]

(55%)

26

Step B
Saponification

KOH/H₂O
THF

(96%)

Step C
Chlorination

Oxalyl chloride
DMF (cat.)

\[
\text{CH}_2\text{Cl}_2
\]

(84%)

27

Step E
Acetylation and Separation

\[
\text{O}
\]

28a

Step F
Hydrolysis

KOH/H₂O

\[
\text{HO}
\]

B
STEP A ETHERIFICATION

Ethyl (2S)-2-(α-(1-Methylnaphthlenyloxy)propanate (26)

To a slurry of 3.7 g (110 mmol) of sodium hydride (60% in mineral oil) in tetrahydrofuran (100 mL) at 25°C was added a solution of 12.0 g (102 mmol) of (S)-ethyl lactate (20) in tetrahydrofuran (50 mL) dropwise over a 30 min period under a nitrogen atmosphere. The resulting solution was then allowed to stir at 25°C for an additional 1 h to ensure complete anion formation. To the anion was added 40.6 g (110 mmol) of tetra-n-butylammonium iodide. A solution of 25.0 g (113 mmol) of 1-(α-bromomethyl)naphthalene in tetrahydrofuran (100 mL) was added dropwise to the reaction mixture over a 5 min period. The reaction was complete within 72 h (over the weekend) at 25°C, during which time a solid precipitate formed. The reaction mixture was filtered through a coarse sintered glass funnel containing Celite®. The solid was washed with diethyl ether (50 mL). The filtrate was washed with a saturated aqueous sodium chloride solution (2x300 mL) and dried (MgSO₄). Concentration and purification by flash chromatography on silica gel (EM silica gel 60, 0.040-0.063 partical size, 230-400 Mesh, column size: 7 cm diameter X 20 cm length) using hexane and ethyl acetate (9:1) afforded 14.5 g (55%) of ethyl (2S)-2-(α-(1-methylnaphthlenyloxy)propanate (26) as an oil: ¹H NMR (CDCl₃) δ 1.31-1.36 (t, J=7.2 Hz, 3H), 1.48-1.51 (d, J=6.7 Hz, 3H), 4.13-4.20 (q, J=6.7 Hz, 1H), 4.24-4.31 (q, J=7.1 Hz, 2H), 4.85-4.88 (d, J=11.5 Hz, 1H), 5.25-5.29 (d, J=11.5 Hz, 1H), 7.39-7.62 (m, 4H), 7.83-7.90 (m, 2H), 8.32-8.35 (d, J=8.3 Hz, 1H); ¹³C NMR (CDCl₃) δ 173.1, 133.8, 133.1, 131.9, 128.8, 128.4, 126.7, 126.2, 125.7, 125.1, 124.3, 74.1, 70.5, 60.7, 18.7, 14.1; IR (neat) 3051 (w), 2985 (w), 2940 (w), 1744 (vs), 1200 (s), 1144 (vs), 1021 (s), 777.6 (vs) cm⁻¹.
STEP B DEPROTECTION

(2S)-2-(a-(1-Methylnaphthlenyloxy)propanonic Acid (27)

To a solution of 4.2 g (74 mmol) of potassium hydroxide in water (150 mL) and tetrahydrofuran (150 mL) was added 13.5 g (52 mmol) of ethyl (2S)-2-(a-(1-methylnaphthlenyloxy)-propanate (26). The reaction mixture was allowed to stir overnight at room temperature. The reaction solution was acidified to pH 2 with concentrated hydrochloric acid and and extracted with diethyl ether (3x200 mL). The combined extracts were washed with an aqueous saturated sodium chloride solution (1x300 mL) and dried (MgSO₄). Filtration and concentration afforded 11.6 g (96%) of crude (2S)-2-(a-(1-methylnaphthlenyloxy)propanonic acid (27) as an orange oil: 1H NMR (CDCl₃) δ 1.45-1.48 (d, J=6.9 Hz, 3H), 4.11-4.18 (d, J=6.9 Hz, 1H), 4.84-4.88 (d, J=11.6 Hz, 1H), 5.21-5.25 (d, J=11.6 Hz, 1H), 7.38-7.55 (m, 4H), 7.79-7.85 (m, 2H), 8.19-8.21 (d, J=8.2 Hz, 1H); 13C NMR (CDCl₃) δ 176.9, 133.8, 132.7, 131.8, 128.9, 128.4, 126.9, 126.3, 125.8, 125.1, 124.0, 73.6, 70.5, 67.8, 25.4, 18.4; IR (neat) 3660-2600 cm⁻¹.

STEP C CHLORINATION

(2S)-2-(a-(1-Methylnaphthlenyloxy)propanoyl Chloride (25)

To a mixture of 10.0 g (43 mmol) of (2S)-2-(a-(1-methylnaphthlenyloxy)propanonic acid (27) and 5 drops of N,N-dimethylformamide in methylene chloride (150 mL) at 0°C under a nitrogen atmosphere was added 32.6 mL (65 mmol) of a 2M solution of oxalyl chloride in methylene chloride dropwise over a 1 h period. The reaction mixture was allowed to stir at room temperature overnight. The solvent and any excess oxalyl chloride was removed by rotary evaporation and dried (under vacuum) to afford 9.1 g (84%) of (2S)-2-(a-(1-methylnaphthlenyloxy)propanoyl chloride (25) as a crude yellow liquid: 1H NMR (CDCl₃) δ 1.58-1.60 (d, J=6.8 Hz, 3H), 4.38-4.44 (q, J=6.8 Hz, 1H), 4.87-4.91 (d,
STEP D ACYLATION AND SEPARATION

N-Acylation of 5-Vinylpyrrolidin-2-one with (2S)-2-(α-(1-Methylnaphthlenyloxy)propanoyl Chloride (25)

To a solution of 60% sodium hydride (336 mg, 10.0 mmol) and toluene (20 mL) at 0°C was added dropwise a solution of 5-vinylpyrrolidin-2-one (1.0 mg, 9.0 mmol) in toluene (10 mL) over a 10 min period. The cooling bath was removed and the solution was allowed to warm to 25°C to ensure complete generation of the anion. To the anion at 25°C was added dropwise a solution of (2S)-2-(α-(1-methylnaphthlenyloxy)-propanoyl chloride (25, 2.5 g, 10.0 mmol) in toluene (20 mL) over a 10 min period. TLC indicated that the reaction was complete upon addition of the acid chloride (silica gel plates; hexane and t-butyl methyl ether, 1:1). Water (50 mL) was added to the reaction mixture and the phases were separated. The aqueous phase was extracted with diethyl ether (2x40 mL). The combined organic phases were washed with a saturated aqueous sodium bicarbonate solution (1x100 mL) and dried (MgSO4). Concentration and purification by flash chromatography on silica gel (EM silica gel 60, 0.040–0.063 partical size, 230–400 Mesh, column size: 6.5 cm diameter X 20 cm length) using hexane and t-buthyl methyl ether (10:1) afforded 1.1 g (38%) of (5S)-N-{(2S)-2-(α-(1-methylnaphthlenyloxy)propanoyl)-5-ethenylpyrrolidin-2-one (28a) as a thick oil: 1H NMR (CDCl3) δ 1.49–1.51 (d, J=6.6 Hz, 3H), 1.89–1.96 (m, 1H), 2.19–2.30 (m, 1H), 2.51–2.54 (m, 1H), 2.61–2.68 (m, 1H), 4.88–4.84 (d, J=10.3 Hz, 1H), 4.93–4.97 (t, J=6.4 Hz, 1H), 5.12–5.30 (m, 4H), 5.80–5.87 (m,
1H), 7.41-7.60 (m, 4H), 7.82-7.88 (m, 2H), 8.29-8.31 (d, J=8.3 Hz, 1H); 13C NMR (CDCl3) δ 174.9, 173.6, 135.4, 133.6, 133.4, 131.8, 128.6, 128.6, 126.7, 126.1, 125.6, 125.0, 124.3, 115.3, 74.8, 70.2, 57.7, 31.5, 42.1, 18.3; IR (neat) 3051 (w), 2985 (w), 1737 (vs), 1702 (vs), 1457 (w), 1229 (s), 1108 (s), 803 (s), 780 (s) cm⁻¹.

STEP E HYDROLYSIS

(4S)-4-Amino-5-hexenoic Acid (B) from (5S)-N-((2S)-2-(α-(1-Methylnaphthlenyloxy)propanoyl)-5-ethenylpyrrolidin-2-one (28a)

A solution of diastereomer 28a (1.0 g, 3.1 mmol) and 87% potassium hydroxide (392 mg, 7.0 mmol) in water (2 mL) is refluxed for 2 hours. The solution is allowed to cool to room temperature. Additional water is added (15 mL) and the solution is acidified to pH 7 with concentrated hydrochloric acid. Extraction with diethyl ether (3 x 15 mL) removes the cleaved chiral auxiliary. The aqueous phase is acidified to pH 5.5 with concentrated hydrochloric acid and extracted with diethyl ether (3 x 15 mL). The second series of organic extracts is combined and dried (MgSO₄). Concentration by rotary evaporation affords (4S)-4-amino-5-hexenoic acid (B).
EXAMPLE 5

Step A
Displacement

1. NaH, CH₃CN

2. OSO₂Ph

Step B
Deprotection

KOH, H₂O

THF

Step C
Chlorination

oxalyl chloride
cat. DMF

CH₂Cl₂

Step D
Acylation & Separation

1. 1

Step E
Hydrolysis

K₂CO₃, MeOH

H₂O

33a (32%)
STEP A DISPLACEMENT
Methyl (2R)-2-(3,5-Di-t-butyl-4-hydroxyphenyl)thiopropanoate (31)
To a solution of 60% sodium hydride in mineral oil (7.0 g, 0.20 mol) and acetonitrile (200 mL) under a nitrogen atmosphere was added dropwise a solution of 2,6-di-t-butyl-4-mercaptophenol (A) (53.7 g, 0.23 mol, 90%) in acetonitrile (100 mL) over a 1 h period. The reaction mixture was stirred at 25°C for an additional hour to ensure complete anion generation. To the mercaptophenol anion was added a solution of methyl (2S)-2-(phenylsulfonyloxy)propanoate (50 g, 0.20 mol, 12) in acetonitrile (100 mL) dropwise over a 1 hour period. Upon addition of methyl (2S)-2-(phenylsulfonyloxy)propanoate a white precipitate was observed. The reaction mixture was allowed to stir at 25°C overnight. The mixture was worked-up by filtration through a coarse sintered glass funnel containing Celite®. The solvent was removed by rotary evaporation to afford a smelly yellow oil. Purification by flash chromatography on silica gel (EM silica gel 60, 0.040-0.063 particle size, 230-400 Mesh, column size: 10 cm diameter X 30 cm length) using hexane and ethyl acetate (9:1) afforded 51.3 g (81%) of methyl (2R)-2-(3,5-di-t-butyl-4-hydroxyphenyl)thiopropanoate (31) as a thick oil: 1H NMR (CDCl3) δ 1.42-1.45 (m, 21 H), 3.60-3.68 ppm (q, J=7.2 Hz, 1H), 3.67 (s, 3H), 5.33 (s, -OH, 1H), 7.29 (s, 2H); 13C NMR (CDCl3) δ 173.3, 154.6, 136.6, 131.8, 122.0, 52.0, 46.0, 34.3, 30.2, 17.4; IR (neat) 3635 (s), 2958 (vs), 2875 (s), 1737 (vs), 1426 (vs), 1237 (vs), 1160 (vs), 855 (w), 774 (w) cm⁻¹.

STEP B DEPROTECTION
(2R)-2-(3,5-Di-t-butyl-4-hydroxyphenyl)thiopropanoic Acid (32)
To a solution of 4.5 g (80 mmol) of potassium hydroxide in water (200 mL) and tetrahydrofuran (200 mL) was added 21.46 g (70 mmol) of methyl (2R)-2-(3,5-di-t-butyl-4-hydroxy-
phenyl)thiopropanoate (31). The reaction mixture was allowed to stir overnight at room temperature. The reaction solution was acidified to pH 1.2 with concentrated hydrochloric acid and and extracted with t-butyl methyl ether (3x100 mL). The combined extracts were washed with an aqueous saturated sodium chloride solution (1x300 mL) and dried (MgSO₄). Filtration, concentration and recrystallization from hexane and ethyl acetate afforded 18.35 g (90%) of (2R)-2-(3,5-di-t-butyl-4-hydroxyphenyl)-thiopropanoic acid (32) as a white crystalline material: m.p. 111-112°C; ¹H NMR (CDCl₃) δ 1.33-1.46 (m, 21H), 3.58-3.65 (q, J=7.1 Hz, 1H), 5.34 (s, -OH, 1H), 7.33 (s, 2H), 9.12 (b, -CO₂H, 1H); ¹³C NMR (CDCl₃) δ 178.8, 154.8, 136.7, 131.8, 121.6, 46.0, 34.4, 30.2, 17.1; IR (KBr) 3608 (s), 3570 (s), 2960 (vs), 1692 (vs), 1424 (vs), 1287 (s), 1239 (vs), 1121 (vs), 884 (s), 774 (w) cm⁻¹.

**STEP C CHLORINATION**

(2R)-2-(3,5-Di-t-butyl-4-hydroxyphenyl)thiopropanoyl Chloride (29)

To a mixture of 10.0 g (43 mmol) of (2R)-2-(3,5-di-t-butyl-4-hydroxyphenyl)thiopropanoic acid (32) and 7 drops of N,N-dimethylformamide in methylene chloride (150 mL) at 0°C under a nitrogen atmosphere was added 34.0 mL (68 mmol) of a 2M solution of oxalyl chloride in methylene chloride dropwise over a 1 h period. The reaction mixture was allowed to stir at room temperature overnight. The solvent and any excess oxalyl chloride was removed by rotary evaporation and dried (under vacuum) to afford 11.15 g (99.8%) of (2R)-2-(3,5-di-t-butyl-4-hydroxyphenyl)-thiopropanoyl chloride (29) as a thick yellow liquid: ¹H NMR (CDCl₃) δ 1.43 (s, 18H), 147-1.49 (d, J=7.0 Hz, 3H), 3.83-3.90 (q, J=7.7 Hz, 1H), 5.29 (s, -OH, 1H), 7.32 (s, 2H); IR (neat) 3631 (vs), 2962 (vs), 2875 (s), 1773 (vs), 1426 (vs), 1239 (s), 1156 (s), 1123 (s), 918 (vs), 888 (w), 774 (w) cm⁻¹.
STEP D ACYLATION AND SEPARATION

N-Acylation of 5-Vinylpyrrolidin-2-one with (2R)-2-(3,5-Di-t-butyl-4-hydroxyphenyl)thiopropanoyl chloride (29)

To a solution of 60% sodium hydride (665 mg, 19.0 mmol) and toluene (40 mL) at 0°C was added dropwise a solution of 5-vinylpyrrolidin-2-one (2.0 g, 18.0 mmol) in toluene (20 mL) over a 30 min period. The cooling bath was removed and the solution was allowed to warm to room temperature and stir there for a 30 min period to ensure complete anion generation. To the anion at 25°C was added dropwise a solution of (2R)-2-(3,5-di-t-butyl-4-hydroxyphenyl)thiopropanoyl chloride (29, 6.21 g, 19.0 mmol) in toluene (20 mL) over a 20 min period. TLC indicated that the reaction was complete upon addition of the acid chloride (silica gel plates; hexane and ethyl acetate, 2:1). Water (100 mL) was added to the reaction and the phases were separated. The aqueous phase was extracted with t-butyl methyl ether (2x100 mL). The combined organic phases were washed with a saturated aqueous sodium bicarbonate solution (1x250 mL) and dried (MgSO₄). Concentration and purification by flash chromatography on silica gel (EM 60, 0.040-0.063 partical size, 230-400 Mesh, column size: 4.5 cm diameter X 24 cm length) using hexane and ethyl acetate (10:1) afforded 2.32 g (32%) of (5S)-N-(2R)-2-(3,5-di-t-butyl-4-hydroxyphenyl)thiopropanoyl)-5-ethenylpyrrolidin-2-one (33a) as a white crystalline material: mp 105-106°C; ¹H NMR (CDCl₃) δ 1.37-1.42 (m, 21H), 1.79-1.86 (m, 1H), 1.97-2.05 (m, 1H), 2.32-2.41 (m, 1H), 2.57-2.67 (m, 1H), 4.71-4.75 (t, J=6.8 Hz, 1H), 5.03-5.17 (m, 3H), 5.33 (s, -OH, 1H), 5.78-5.87 (m, 1H), 7.23 (s, 2H); ¹³C NMR (CDCl₃) δ 174.7, 172.6, 154.7, 136.3, 135.7, 132.7, 120.9, 115.3, 58.8, 44.1, 34.3, 31.9, 30.2, 23.9, 16.4; IR (KBr) 3581 (s), 2964 (s), 1748 (vs), 1684 (vs), 1426 (s), 1345 (s), 1227 (vs), 1198 (s), 917 (w), 885 (w) cm⁻¹.
STEP E HYDROLYSIS

(5S)-5-Ethenylpyrrolidin-2-one (6) from (5S)-N-((2R)-2-(3,5-Di-t-butyl-4-hydroxyphenyl)thiopropanyl)-5-ethenylpyrrolidin-2-one (33a)

To a solution of 1.5 g (3.7 mmol) of (5S)-N-((2R)-2-(3,5-di-t-butyl-4-hydroxyphenyl)thiopropanyl)-5-ethenylpyrrolidin-2-one (33a) in methanol (25 mL) and water (5 mL) is added 257 mg (1.9 mmol) of potassium carbonate. The reaction mixture is allowed to stir at room temperature for 1.5 hours. Additional water (20 mL) is added and the solution is extracted with methylene chloride (3 x 40 mL). The combined organic extracts should be dried over magnesium sulfate. Concentration and purification by flash chromatography on silica gel (EM 60, 230-400 mesh) using hexane and ethyl acetate (9:1) affords (5S)-5-ethenylpyrrolidin-2-one (6).
The claims defining the invention are as follows:

1. A compound of the formula

\[
\begin{align*}
\text{H} & \quad \text{O} \\
\downarrow & \quad \downarrow \\
\text{Y} - \text{CH} - \text{C} - \text{C} - \text{Cl} & \quad \text{X}
\end{align*}
\]

in which \(X\) and \(Y\) are each simultaneously represented by

\[
\begin{array}{c|c}
\text{Y} & \text{X} \\
\hline
\text{H} & \text{o-} \\
\text{H} & \text{o-} \\
\text{H} & \text{s-} \\
\end{array}
\]

2. A compound of the formula

\[
\begin{align*}
\text{H} & \quad \text{O} \\
\downarrow & \quad \downarrow \\
\text{Y} - \text{CH}_2 - \text{C} - \text{C} - \text{Cl} & \quad \text{O} \text{X}
\end{align*}
\]
in which \(X\) and \(Y\) are each simultaneously represented by

\[
\begin{array}{c|c}
Y & X \\
\hline
\text{H} & \text{H} \\
\text{CH}_3 & \text{-CH}_2- \\
\text{-Si-} & \text{-CH}_2- \\
\text{CH}_3 & \text{CH}_3 \\
\end{array}
\]

DATED: 20 January 1994

PHILLIPS ORMONDE & FITZPATRICK
Attorneys For:
MERRELL DOW PHARMACEUTICALS INC.

[Signature]

63251
ABSTRACT

The present invention is directed to a new class of chiral lactic acid derivatives. These derivatives may be used as intermediate compounds in the stereospecific synthesis of (S)-vinyl-GABA, (S)-allenyl-GABA, (S)-5-allenylpyrrolidinone, and (S)-5-vinyl-pyrrolidinone.