



(86) Date de dépôt PCT/PCT Filing Date: 2005/09/13  
(87) Date publication PCT/PCT Publication Date: 2006/03/23  
(45) Date de délivrance/Issue Date: 2013/05/14  
(85) Entrée phase nationale/National Entry: 2007/02/01  
(86) N° demande PCT/PCT Application No.: IB 2005/002706  
(87) N° publication PCT/PCT Publication No.: 2006/030278  
(30) Priorités/Priorities: 2004/09/13 (EP04292199.9);  
2004/09/20 (US60/611,511); 2005/09/12 (US11/224,250)

(51) Cl.Int./Int.Cl. *C07B 57/00* (2006.01),  
*C07C 317/24* (2006.01)  
(72) Inventeurs/Inventors:  
HAUCK, WILHELM, US;  
LUDEMANN-HOMBOURGER, OLIVIER, FR;  
RULAND, YVAN, CN;  
LANDMESSER, NELSON G., US;  
MALLAMO, JOHN P., US  
(73) Propriétaire/Owner:  
CEPHALON, INC., US  
(74) Agent: GOUDREAU GAGE DUBUC

(54) Titre : PROCÉDE DE SEPARATION DE MODAFINIL  
(54) Title: METHODS FOR THE SEPARATION OF MODAFINIL

(57) Abrégé/Abstract:

The present invention is directed to a process for the isolation of the enantiomeric forms of modafinil with high enantiomeric purity and high overall yields by means of a continuous chromatographic process.



## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
23 March 2006 (23.03.2006)

PCT

(10) International Publication Number  
**WO 2006/030278 A1**

(51) International Patent Classification:  
C07B 57/00 (2006.01) C07C 317/24 (2006.01)

John [US/US]; 98 Macleod Pond Road, GLENMOORE,  
PA 19343 (US).

(21) International Application Number:  
PCT/IB2005/002706

(74) Agents: COLOMBET, Alain et al.; Cabinet LAVOIX, 2,  
Place d'Estienne d'Orves, F-75441 Paris Cedex 09 (FR).

(22) International Filing Date:  
13 September 2005 (13.09.2005)

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
04292199.9 13 September 2004 (13.09.2004) EP  
60/611,511 20 September 2004 (20.09.2004) US  
11/224,250 12 September 2005 (12.09.2005) US

(71) Applicant (*for all designated States except US*):  
CEPHALON INC. [US/US]; 41 Moores road - PO  
Box 4011, FRAZER, PA 19355 (US).

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): HAUCK, Wilhelm [DE/US]; 21 Green Valley road, WALLINGFORD, PA 19086 (US). LUDEMANN-HOMBOURGER, Olivier [FR/FR]; 62 rue du Maréchal de Lattre de Tassigny, F-54340 POMPEY (FR). RULAND, Yvan [FR/CN]; Novasep Asia / Applexion - Orelis - Novasep, Hui Yin Plaza, South Tower, #1401, 2088 Huashan Road, 200030 Shanghai (CN). LANDMESSER, Nelson [US/US]; 278 Edinburgh road, EXTON, PA 19341 (US). MALLAMO,

Published:

— with international search report

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: METHODS FOR THE SEPARATION OF MODAFINIL

(57) Abstract: The present invention is directed to a process for the isolation of the enantiomeric forms of modafinil with high enantiomeric purity and high overall yields by means of a continuous chromatographic process.



WO 2006/030278 A1

## METHODS FOR THE SEPARATION OF MODAFINIL

**BACKGROUND OF THE INVENTION**

5 This invention relates to chromatographic processes for obtaining optically active modafinil compounds, including the levorotatory enantiomer, (-)-benzhydrilsulfinylacetamide ("armodafinil"), and the dextrorotatory enantiomer, (+)-benzhydrilsulfinylacetamide. Such processes include commercially viable methods for producing armodafinil on an industrial scale  
10 suitable for pharmaceutical use. Racemic modafinil is the active agent in the pharmaceutical product Provigil<sup>®</sup>, which has been approved by the United States Food and Drug Administration for use in the treatment of excessive daytime sleepiness associated with narcolepsy, and to improve wakefulness in patients with excessive sleepiness associated with obstructive sleep  
15 apnea/hypopnea syndrome and shift work sleep disorder.

The levorotatory isomer of modafinil and processes for its preparation have been described in U.S. Pat. No. 4,927,855 ("the '855 patent").

The '855 patent details the preparation of the levorotatory isomer by achiral synthesis. This process is not sufficiently  
20 robust to produce armodafinil on an industrial scale in pharmaceutically acceptable purities. It would be of significant advantage to obtain armodafinil in large quantities that meet acceptable pharmaceutical standards.

A variety of methods have been utilized to obtain compounds in stereochemically pure form. Stereoisomers can be synthesized using  
25 asymmetric synthetic techniques, however such syntheses often require expensive reagents. Alternatively, stereoisomers can be obtained by selective recrystallization of one stereoisomer, however such a process cannot be used for all compounds, and may not be useful for enantiomeric separations. In addition, the process is considered inefficient, in that product  
30 recovery is often low and purity uncertain. Stereoisomers can also be resolved chromatographically, although the large amount of solvent required for conventional batch chromatography is cost prohibitive and results in the

preparation of relatively dilute products. Limited throughput volumes also often make batch chromatography impractical for large-scale production. Moreover, the number of technical parameters required for its applicability on an industrial scale makes it difficult to select appropriate conditions for the mass production of pharmaceutically viable amounts of an enantiomeric compound. Determination of the conditions necessary for productive separation of enantiomers has been found by those of ordinary skill in the art to be a matter of trial and error. Even so, it is a common for those skilled in the art to find chiral separation of certain chiral mixtures to be inefficient or ineffective. In the instant case, these problems are heightened by the relative difficulty in solubilizing modafinil in many common solvents. The object of the present invention is to provide an efficient process for the separation of the modafinil enantiomers from racemic modafinil that provides a viable combination of selectivity and resolution at high throughput volumes or in bulk amounts.

Hence, the present invention is directed to producing optically pure armodafinil at relatively low cost and with optimized productivity on a commercially viable scale. It has been found that multi-column continuous chromatography processes are capable of providing large scale, industrial enantiomeric separation of racemic modafinil, and in particular for the preparation of armodafinil. In particular, the necessary operational parameters have been found to yield an excellent degree of separation of the stereoisomers of modafinil with sufficiently robust productivity on a large scale. These multicolumn continuous chromatographic processes overcome certain limitations in classical batch chromatography, such as having increased productivity, lower eluent composition and higher robustness, resulting in lower final purification costs.

### **SUMMARY OF THE INVENTION**

The present invention provides an improved process for the isolation of the enantiomeric forms of modafinil with high enantiomeric purity and high overall yields. Thus the present invention provides processes for obtaining an

enantiomer of modafinil, and in particular, the levorotatory isomer of modafinil, by forming a solution of racemic modafinil and separating the enantiomers of modafinil by means of a continuous chromatographic process. The continuous chromatographic process includes, but is not limited  
5 to a countercurrent chromatographic process, such as a simulated moving bed ("SMB") process, or a non-steady state system, such as the Varicol™ process, which uses at least two columns packed with an optical resolution packing material from the amylosic or cellulosic class of polysaccharides or chemically modified forms thereof.

10 In an additional embodiment of the present invention, there is provided a method for chromatographically resolving at least one enantiomer (preferably armodafinil) from a racemic mixture of modafinil using multicolumn continuous chromatography, wherein the continuous chromatographic method comprises a liquid mobile phase comprising a least  
15 one solvent and a solid chiral stationary phase comprising a derivatized polysaccharide that is selected from the amylosic, cellulosic, chitosan, xylan, curdlan, dextran, and inulan class of polysaccharides.

The invention also relates to an industrial scale method of obtaining an enantiomer of modafinil comprising the steps of:

- 20 a) forming a solution of racemic modafinil; and  
b) subjecting the racemic modafinil solution to continuous chromatography to separate the enantiomers of modafinil and obtain at least one of the enantiomers in an industrial scale quantity;

wherein the continuous chromatography is performed with:

- 25 (i) a liquid mobile phase consisting essentially of an organic solvent, which is a C<sub>1</sub>-C<sub>10</sub> alkane, a C<sub>1</sub>-C<sub>6</sub> alcohol, an acetate or a propionate of a C<sub>1</sub>-C<sub>6</sub> alcohol, a C<sub>1</sub>-C<sub>10</sub> ketone, a C<sub>1</sub>-C<sub>10</sub> ether, a halogenated C<sub>1</sub>-C<sub>10</sub> hydrocarbon, trifluoroacetic acid, dimethylformamide, dimethylacetamide, acetonitrile or a  
30 combination thereof; and  
(ii) a chiral stationary phrase consisting essentially of a derivatized polysaccharide from the amylosic, cellulosic,

3a

chitosan, xylan, curdlan, dextran or inulin class of polysaccharides, or a combination thereof.

The invention also relates to an industrial scale method for chromatographically resolving at least one enantiomer from a racemic mixture of modafinil using multicolumn continuous chromatography, the continuous chromatography comprising:

- a) a liquid mobile phase consisting essentially of at least one organic solvent; and
- b) a solid chiral stationary phase consisting essentially of a derivatized polysaccharide from the amylosic, cellulosic, chitosan, xylan, curdlan, dextran, or inulan class of polysaccharides;

wherein the method is performed at an industrial scale.

#### DETAILED DESCRIPTION

The processes of the present invention can utilize any chromatographic method for separating racemic modafinil to produce optically pure armodafinil. Such methods include, but are not limited to, traditional single column batch chromatography, continuous chromatography, or a steady state, sequential injection process (as described in, for example, U.S. Pat. No. 5,630,943 and PCT Publ. No. WO 98/51391). Continuous chromatographic methods include, but are not limited to multicolumn continuous chromatographic processes, including such countercurrent chromatographic processes as SMB, or a non-steady state continuous chromatographic method known as the "Varicol™" process.

The SMB process is a continuous system that simulates counter-current flows to perform the chromatographic separation. The separation is achieved using a set of fixed-bed columns packed with a solid stationary

30

phase; ports for the continuous introduction of solvent desorbent (mobile phase) and feed; ports for the continuous removal of raffinate (solution containing the less strongly retained enantiomer) and extract (solution containing the more strongly retained enantiomer); and a means of recycling fluid through the system, if necessary. In a closed loop system, the columns are connected such that the outlet of each column is connected to the inlet of the next column also with the outlet of the last column being connected to the inlet of the first column. Other implementations of the SMB process include an open loop system which can include 4-zone systems with external recycling or other 3-zone systems. All the inlet and outlet ports are shifted substantially simultaneously at substantially fixed time intervals in the fluid flow direction to simulate counter-current flow between the liquid phase and the solid phase. For the separation of stereoisomers, a chiral stationary phase ("CSP") capable of chiral recognition is often employed.

15       The Varicol™ process is a non-steady state continuous separation process and is more fully described in U.S. Pat. No. 6,136,198, as well as in U.S. Pat. Nos. 6,375,839; 6,413,419; and 6,712,973.

          This non-steady state process differs from the SMB process in that the inlet and outlet ports are not all shifted at the same time. The column distribution between zones does not stay the same during the period because the lines are shifted at different times, so the column allocation differs accordingly. In this process, there is no limitation on the number of configurations for a given number of columns, thereby giving the non-steady state process a greater degree of flexibility as compared to the SMB process. The potential for variation of the average length of given zones represented by column sections during the chromatographic separation can lead to an increase efficiency by using less columns, reducing the amount of the solid phase and solvent(s), and increasing higher purity yields.

30       In one aspect of the present invention, a five to six column-four variable zone Varicol™ system may be used. The zones vary in length during operation, and have an average rather than fixed length in a given operation

cycle. In another aspect, a three column-four variable zone Varicol™ system is used, a system which cannot be utilized in a SMB process, as at least four columns with four zones are necessary to simulate the true moving bed system. For the SMB process, the minimal number of columns required for the separation is equal to the number of zones of the system, whereas the number of columns can be smaller than the number of zones in the Varicol™ system

In another aspect of the present invention the chiral stationary phase is derivatized with at least one sugar derivative, and in particular is a derivatized polysaccharide that is selected from the amylosic, cellulosic, chitosan, xylan, curdlan, dextran, and inulan class of polysaccharides. In certain embodiments, the chiral stationary phase is a member of the amylosic or cellulosic class of polysaccharides. Esters and carbamates of these materials in particular are suitable. In additional embodiments, the chiral stationary phase is selected from cellulose phenyl carbamate derivatives, such as cellulose tris (3,5-dimethylphenyl) carbamate (available from Daicel Chemical Industries, Ltd. as "Chiralcel OD"); cellulose tribenzoate derivatives, such as cellulose tris 4-methylbenzoate (available from Daicel Chemical Industries, Ltd. as "Chiralcel OJ"); cellulose tricinnamate (available from Daicel Chemical Industries, Ltd. as "Chiralcel OK"); amylose phenyl and benzyl carbamate derivatives, such as amylose tris [(S)- $\alpha$ -methyl benzylcarbamate] (available from Daicel Chemical Industries, Ltd. as "Chiralpak AS"), amylose tris (3,5-dimethylphenyl) carbamate (available from Daicel Chemical Industries, Ltd. as "Chiralpak AD", or as "Chiralpak IA", wherein the carbamate derivative is bonded to the amylosic backbone), amylose 3,4-substituted phenyl carbamate, and amylose 4-substituted phenyl-carbamate; and amylose tricinnamate.

Typically, the polysaccharide derivative is bonded or coated on silica gel, zirconium, alumina, ceramics and other silicas, and preferably on silica gel. Although the average particle diameter of the packing material varies depending on the volume flow rate of the solvent flowing in the chromatographic system, it is usually 1 to 300  $\mu\text{m}$ , preferably 2 to 100  $\mu\text{m}$ ,

more preferably 5 to 75  $\mu\text{m}$  and most preferably 10 to 30  $\mu\text{m}$ . As is known in the art, the selection of the average particle diameter of the packing material will help to adjust the pressure drop in the continuous chromatographic process and the efficiency of the packing material.

5 In a further aspect of the present invention, the mobile phase an organic solvent selected from the group consisting of  $\text{C}_1\text{-C}_{10}$  alkanes, including hexane and heptane; alcohols ( $\text{C}_1\text{-C}_6$ ) such as methanol, ethanol, propanol, isopropanol, butanol; acetates and propionates of these alcohols; ketones ( $\text{C}_1\text{-C}_{10}$ ) such as acetone, butanone, isopropyl-methylketone; ethers  
10 ( $\text{C}_1\text{-C}_{10}$ ) such as diethyl ether, diisopropyl ether, tertbutylmethyl ether, tetrahydrofuran, dioxane; halogenated hydrocarbons ( $\text{C}_1\text{-C}_{10}$ ) such as methylene chloride, chloroform, chlorobenzene, fluorinated alkanes; trifluoroacetic acid; dimethylformamide; dimethylacetamide; and acetonitrile, and combinations therein. In certain aspects, the mobile phase is a polar  
15 solvent, preferably a  $\text{C}_1\text{-C}_6$  alcohol, and more preferably is methanol.

In other aspects, any of the solvents listed above can be combined to produce the desired chromatographic separations. In particular, the primary solvent can be a  $\text{C}_1\text{-C}_6$  alcohol, and more preferably is methanol. The secondary solvent can be a  $\text{C}_1\text{-C}_6$  alcohol, and in particular, can be ethanol  
20 or isopropanol. Thus, certain eluent mixtures can include methanol/isopropanol wherein the eluent preferably contains at least 50% by volume of methanol. Alternatively the eluent may contain at least 60%, 70%, 80%, or 90% by volume of methanol.

A feature of the present invention is the adjustment of the  
25 chromatographic conditions to obtain the desired enantiomer of modafinil (preferably armodafinil) in at least 95% enantiomeric excess. Alternatively, the desired enantiomer of modafinil (preferably armodafinil) is recovered in at least 96%, 97%, 98%, 99% enantiomeric excess, and preferably in greater than 98 or 99% enantiomeric excess.

30 Another feature of the present invention provides for adjusting or modifying the chromatographic conditions to obtain the desired enantiomer (preferably armodafinil) in at least 90% yield. Alternatively, the desired

enantiomer of modafinil (preferably armodafinil) is recovered in at least a 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% yield, and preferably greater than a 90 or 95% yield.

## 5        **Examples**

The following examples show representative parameters for the isolation of the levorotatory enantiomer of modafinil. Other column configurations can be utilized for the chiral separations described herein, including but not limited to 1.3 / 2.3 / 1.6 / 0.8; or 1 / 2.45 / 1.85 / 0.7.

10

### **Examples 1-4:**

#### **1 kg Scale**

	Column	Chiralpak AD
	Mobile Phase	methanol
15	Column Length	9.7 cm avg
	Column I.D.	2.5 cm
	No. of Columns	6
	Column Configuration	1.2 / 2.3 / 1.7 / 0.8
	Feed Concentration	18 g/l
20	Temperature	25 °C

Parameters	Example 1	Example 2	Example 3	Example 4
Recycling Flow Rate (ml/min)	109.5	108.8	114	114
Extract Flow Rate (ml/min)	32.33	34.52	38.8	37.2
Feed Flow rate (ml/min)	2.83	5.12	7	7
Raffinate Flow Rate (ml/min)	9.5	13.4	12.7	13.3
Switch Time (min)	0.7	0.73	0.7	0.7
Eluent Flow Rate (ml/min)	39	42.8	44.5	43.5
Purity of armodafinil	99.9%	99.3%	99.9%	99.4%
Yield of armodafinil	93%	>96%	93.4%	97.4%
Specific Productivity (kg armodafinil/kg CSP/day)	0.19	0.36	0.48	0.49

**Examples 5-6:****500 kg Scale**

5	Column:	Chiralpak AD
	Mobile Phase	methanol
	Column Length	columns 1-5: 10 cm; column 6: 7.1 cm
	No. of Columns	6
	Column Configuration	1.2 / 2.3 / 1.7 / 0.8
10	Feed Concentration	18 (g/l)
	Temperature:	25 °C

Parameters	Example 5	Example 6
Column I.D. (cm)	202	300
Recycling Flow Rate (l/h)	438	986
Extract Flow Rate (l/h)	153	344
Feed Flow rate (l/h)	26.9	60.5
Raffinate Flow Rate (l/h)	44.9	101
Switch Time (min)	0.7	0.7
Eluent ( l/h)	171	384.5
Purity of armodafinil	>99%	≥ 99%
Yield of armodafinil	93%	≥ 90%
Amt of CSP (kg)	11	25.5
Specific Productivity (kg armodafinil/kg CSP/day)	0.49	≥0.46

The scope of the claims should not be limited by the preferred embodiments set forth in the examples, but should be given the broadest interpretation consistent with the description as a whole.

**What is claimed is:**

1. An industrial scale method of obtaining an enantiomer of modafinil comprising the steps of:
  - a) forming a solution of racemic modafinil; and
  - b) subjecting the racemic modafinil solution to continuous chromatography to separate the enantiomers of modafinil and obtain at least one of the enantiomers in an industrial scale quantity;wherein the continuous chromatography is performed with:
  - (i) a liquid mobile phase consisting essentially of an organic solvent, which is a C<sub>1</sub>-C<sub>10</sub> alkane, a C<sub>1</sub>-C<sub>6</sub> alcohol, an acetate or a propionate of a C<sub>1</sub>-C<sub>6</sub> alcohol, a C<sub>1</sub>-C<sub>10</sub> ketone, a C<sub>1</sub>-C<sub>10</sub> ether, a halogenated C<sub>1</sub>-C<sub>10</sub> hydrocarbon, trifluoroacetic acid, dimethylformamide, dimethylacetamide, acetonitrile or a combination thereof; and
  - (ii) a chiral stationary phase consisting essentially of a derivatized polysaccharide from the amylosic, cellulosic, chitosan, xylan, curdlan, dextran or inulin class of polysaccharides, or a combination thereof.
2. The method of claim 1 wherein the levorotatory isomer of modafinil is obtained.
3. The method of claim 1 or 2 wherein the chromatographic method is simulated moving bed chromatography.
4. The method of claim 1 or 2 wherein the chromatographic method is multicolumn non-steady state continuous chromatography.
5. The method of any one of claims 1 to 4, wherein the chiral stationary phase is cellulose tris 4-methylbenzoate; cellulose tricinnamate; amylose tris [(S)- $\alpha$ -methyl benzylcarbamate]; or amylose tris (3,5-dimethylphenyl) carbamate.
6. The method of claim 5 wherein the chiral stationary phase is amylose tris (3,5-dimethylphenyl) carbamate.

7. The method of any one of claims 1 to 6 wherein the solvent is hexane, heptane, methanol, ethanol, propanol, isopropanol, butanol, methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, methyl propionate, ethyl propionate, propyl propionate, isopropyl propionate, acetone, butanone, isopropyl methylketone, diethyl ether, diisopropyl ether, tertbutylmethyl ether, tetrahydrofuran, dioxane, methylene chloride, chloroform, chlorobenzene, trifluoroacetic acid, dimethylformamide, dimethylacetamide, acetonitrile or a combination thereof.
8. The method of claim 7 wherein the solvent is methanol.
9. The method of claim 7 wherein the solvent is a mixture of methanol and isopropanol.
10. The method of claim 2 wherein the solvent is methanol or isopropanol, or a mixture thereof, and wherein the chiral stationary phase is cellulose tris 4-methylbenzoate; cellulose tricinnamate; amylose tris [(S)- $\alpha$ -methyl benzylcarbamate]; or amylose tris (3,5-dimethylphenyl) carbamate.
11. The method of claim 10 wherein the chiral stationary phase is amylose tris (3,5-dimethylphenyl) carbamate.
12. The method of claims 2 or 11 wherein the levorotatory enantiomer of modafinil is recovered in at least 95% enantiomeric excess.
13. The method of claim 12 wherein the levorotatory enantiomer of modafinil is recovered in at least 98% enantiomeric excess.
14. The method of claim 13 wherein the levorotatory enantiomer of modafinil is recovered in at least 99% enantiomeric excess.
15. The method of any one of claims 2 and 11 to 14 wherein the levorotatory enantiomer of modafinil is recovered in at least a 90% yield.
16. The method of claim 15 wherein the levorotatory enantiomer of modafinil is recovered in at least a 93% yield.

17. An industrial scale method for chromatographically resolving at least one enantiomer from a racemic mixture of modafinil using multicolumn continuous chromatography, the continuous chromatography comprising:
  - a) a liquid mobile phase consisting essentially of at least one organic solvent; and
  - b) a solid chiral stationary phase consisting essentially of a derivatized polysaccharide from the amylosic, cellulosic, chitosan, xylan, curdlan, dextran, or inulan class of polysaccharides;wherein the method is performed at an industrial scale.
18. The method of claim 17 wherein the resolved enantiomer is the levorotatory isomer of modafinil.
19. The method of claim 17 or 18 wherein the continuous chromatographic method is multicolumn non-steady state continuous chromatography.
20. The method of any one of claims 17 to 19 wherein the solvent is methanol or isopropanol, or a mixture thereof, and wherein the chiral stationary phase is cellulose tris 4-methylbenzoate; cellulose tricinnamate; amylose tris [(S)- $\sigma$ -methyl benzylcarbamate]; or amylose tris (3,5-dimethylphenyl) carbamate.
21. The method of claim 20 wherein the chiral stationary phase is amylose tris (3,5-dimethylphenyl) carbamate.
22. The method of claims 17 or 21 wherein the levorotatory enantiomer of modafinil is recovered in at least 95% enantiomeric excess.
23. The method of claim 22 wherein the levorotatory enantiomer of modafinil is recovered in at least 98% enantiomeric excess.
24. The method of claim 23 wherein the levorotatory enantiomer of modafinil is recovered in at least 99% enantiomeric excess.

25. The method of any one of claims 17 and 22 to 24 wherein the levorotatory enantiomer of modafinil is recovered in at least a 90% yield.
26. The method of claim 25 wherein the levorotatory enantiomer of modafinil is recovered in at least a 93% yield.