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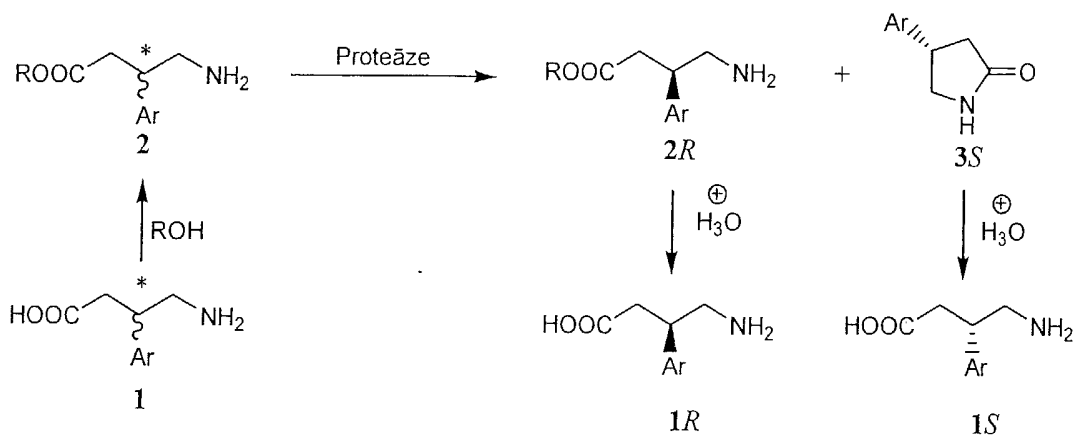
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Ivars KALVIŅŠ (LV)⑤④ Virsraksts: ENZIMĀTISKA METODE RACEMISKĀS 3-ARIL-4-AMINOSVIESTSKĀBES SADALIŠANAI
ENANTIOMĒROS

⑤⑦ Kopsavilkums: Izgudrojums attiecas uz racēmiskā 3-aril-4-aminosviestskābes estera enzimatisko sadalīšanu *R*- un *S*-enantiomēros, kur arilgrupa ir fenil- (fenibuts) vai *para*-hlorfenil- (baklofens) un estera grupa ir piesātināta vai nepiesātināta alkilgrupa ar 2 līdz 8 oglekļa atomiem. Patentējamā iegūšanas metode sastāv no sekojošiem etapiem: (1) racēmiskās 3-aril-4-aminosviestskābes estera (*S*)-enantiomēra selektīvas ciklizācijas par 4(*S*)-aril-2-pirolidinonu ūdens šķīdumā *alfa*-himotripsīna klātienē; (2) 4(*S*)-aril-2-pirolidinona un 3(*R*)-aril-4-aminosviestskābes estera atdalīšanas ar ekstrakcijas paņēmieni pēc reakcijas maisījuma paskābināšanas līdz pH<2.0; (3) 4(*S*)-aril-2-pirolidinona izolēšanas no organiskās fāzes un 3(*R*)-aril-4-aminosviestskābes estera izolēšanas no ūdens fāzes un to sekojošas konversijas 3-aril-4-aminosviestskābēs *R*- un *S*-stereoizomēros ar skābās hidrolīzes palīdzību.

IZGUDROJUMA FORMULA

1. Racemiskā 3-aril-4-aminosviestskābes estera (1) sadalīšana optiskajos izomēros, kas atšķiras ar to, ka racemāta sadalīšanu veic ar proteāžu palīdzību, kuras izvēlētas no grupas, kas sastāv no α -himotripsīna, papaiņa vai subtilizīna:



Ar ir izvēlēts no grupas, kas sastāv no fenil- vai *para*-halogēnfenil- un R ir izvēlēts no grupas, kas sastāv no piesātinātas vai nepiesātinātas alkilgrupas ar 2-8 oglekļa atomiem, kura atšķiras ar to, ka sastāv no sekojošiem etapiem:

- 10 (1) racemiskās 3-aril-4-aminosviestskābes skābes estera sastāvā esošā 3(*S*)-aril-4-aminosviestskābes estera selektīvu ciklizāciju par 4(*S*)-aril-2-pirolidinonu (3*S*);
- (2) 4(*S*)-aril-2-pirolidinona (3*S*) un 3(*R*)-aril-4-aminosviestskābes estera (2*R*) atdalīšanu ar ekstrakciju pēc reakcijas maisījuma paskābināšanas līdz pH<2.0;
- (3) 4(*S*)-aril-2-pirolidinona (3*S*) izdalīšanu no organiskās fāzes un 3(*R*)-aril-4-aminosviestskābes estera (2*R*) izdalīšanu no ūdens fāzes ar ietvaicēšanu vai kristalizāciju.
- 15 2. Process pēc p. 1., kas atšķiras ar to, ka proteāze ir α -himotripsīns.
3. Process pēc p. 1., kas atšķiras ar to, ka α -himotripsīns tiek lietots tā ūdenī šķīstošā formā.
4. Process pēc p. 1., kas atšķiras ar to, ka α -himotripsīns tiek lietots tā ūdenī nešķīstošā imobilizētā formā.
- 20 5. Process pēc p. 1., kas atšķiras ar to, ka procesu pielieto racemiskās 3-fenil-4-aminosviestskābes estera sadalīšanai (*R*) un (*S*) enantiomēros.
6. Process pēc p. 1., kas atšķiras ar to, ka procesu pielieto racemiskās 3-*p*-hlorfenil-4-aminosviestskābes estera sadalīšanai (*R*) un (*S*) enantiomēros.
- 25 7. Process pēc p. 1., kas atšķiras ar to, ka procesu pielieto racemiskās 3-aril-4-aminosviestskābes estera, tajā skaitā zemāko un vidējo alkilesteru, kā arī nepiesātināto alkilesteru sadalīšanai enantiomēros.

8. Process pēc p. 1., kas atšķiras ar to, ka procesu pielieto racēmisko 3-aril-4-aminosviestskābju etilesteru sadalīšanai enantiomēros.
9. Process pēc p. 1., kas atšķiras ar to, ka procesu pielieto racēmisko 3-aril-4-aminosviestskābju *n*-propilesteru sadalīšanai enantiomēros.
- 5 10. Process pēc p. 1., kas atšķiras ar to, ka procesu pielieto racēmisko 3-aril-4-aminosviestskābju *izo*-propilesteru sadalīšanai enantiomēros.
11. Process pēc p. 1., kas atšķiras ar to, ka procesu pielieto racēmisko 3-aril-4-aminosviestskābju *n*-butilesteru sadalīšanai enantiomēros.
12. Process pēc p. 1., kas atšķiras ar to, ka procesu pielieto racēmisko 3-aril-4-aminosviestskābju alilesteru sadalīšanai enantiomēros.
- 10 13. Process pēc p. 1., kas atšķiras ar to, ka procesu pielieto racēmisko 3-aril-4-aminosviestskābju oktilesteru sadalīšanai enantiomēros.
14. Process pēc p. 1, kas atšķiras ar to, ka etapā (1) pielietotais šķīdinātājs ir ūdens.
15. Process pēc p. 1, kas atšķiras ar to, ka etapā (1) pielietotais šķīdinātājs ir ūdens maisījums ar organisko šķīdinātāju, kas nejaucas vai vāji jaucas ar ūdeni un ir izvēlēts no grupas, kas sastāv no alifātiskajiem ogļūdeņražiem, aromātiskajiem ogļūdeņražiem, halogēnalkāniem, ēteriem, esteriem, ketoniem un to maisījumiem.
- 15 16. Process pēc p. 1., kas atšķiras ar to, ka etapu (1) veic pie 20° līdz 40°C.
17. Process pēc p. 1., kas atšķiras ar to, ka etapu (1) veic pie reakcijas vides pH no 6 līdz 7.
- 20 18. Process pēc p. 1 kas atšķiras ar to, ka etapā (3) 3(*R*)-aril-4-aminosviestskābes esteri (2*R*) ekstrahē no ūdens fāzes pēc tās neitralizācijas līdz pH 7.
19. Process pēc p. 1 kas atšķiras ar to, ka etapos (2) un (3) ekstrakcijai lieto organisko šķīdinātāju, kas ir izvēlēts no grupas, kas sastāv no heksāna, benzola, toluola, hloroforma, metilēnhlorīda, dihloretāna, etilacetāta, metilacetāta, dietilētera un metil-*terc*-butilētera.
- 25 20. Process pēc p. 1 kas atšķiras ar to, ka etapos (2) un (3) ekstrakcijai izmanto heksānu..
21. Process pēc p. 1 kas atšķiras ar to, ka etapos (2) un (3) ekstrakcijai izmanto benzolu.
22. Process pēc p. 1 kas atšķiras ar to, ka etapos (2) un (3) ekstrakcijai izmanto toluolu.
23. Process pēc p. 1 kas atšķiras ar to, ka etapos (2) un (3) ekstrakcijai izmanto hloroformu.
24. Process pēc p. 1 kas atšķiras ar to, ka etapos (2) un (3) ekstrakcijai izmanto metilēnhlorīdu.
- 30 25. Process pēc p. 1 kas atšķiras ar to, ka etapos (2) un (3) ekstrakcijai izmanto dihloretānu.
26. Process pēc p. 1 kas atšķiras ar to, ka etapos (2) un (3) ekstrakcijai izmanto etilacetātu.
27. Process pēc p. 1 kas atšķiras ar to, ka etapos (2) un (3) ekstrakcijai izmanto metilacetātu.
28. Process pēc p. 1 kas atšķiras ar to, ka etapos (2) un (3) ekstrakcijai izmanto dietilēteri.

29. Process pēc p. 1 kas atšķiras ar to, ka etapos (2) un (3) ekstrakcijai izmanto metil-*tert*-butilēteri.
30. Process pēc p. 1. kas atšķiras ar to, ka etapā (3) iegūto 3(*R*)-aril-4-aminosviestskābes esterī (2*R*) pārvērš *R*-enantiomērajā 3-aril-4-aminosviestskābē (1*R*) ar skābās hidrolīzes paņēmieni.
- 5
31. Process pēc p. 1., kas atšķiras ar to, ka etapā (3) iegūto 4(*S*)-aril-2-pirolidinonu (3*S*) pārvērš *S*-enantiomērajā 3-aril-4-aminosviestskābē (1*S*) ar skābās hidrolīzes paņēmieni.

Enzymatic resolution of racemic 3-aryl-4-aminobutyric acid

Background of the invention.

The invention relates to the isolation of pure *R*- and *S*-enantiomers from racemic 3-aryl-4-aminobutyric acids by the means of selective enzymatic resolution. For example pure *R*- and *S*-enantiomers of racemic 4-amino-3-phenylbutyric acid (fenibut) or 4-amino-3-*p*-chlorophenylbutyric acid (baclofen) can be obtained by this method. It is known that only *R*-enantiomer of fenibut is acting as mood enhancer and tranquilizer (Allan et al., *Tetrahedron*, 1990, **46**, No7, 2511-2524.). Similarly only *R*-enantiomer of baclofen is the bearer of antispastic activity (N. E. Bowery, *Trends Pharm. Sci.*, 1982, **31**, 411-413). Optical antipodes of these drugs: *S*-enantiomers of fenibut and baclofen are not only less active but even antagonistic to their *R*-antipodes and their presence in racemic mixture makes necessary to administer higher doses of drugs.

That is why the elaboration of effective process for the optical resolution of racemic 3-aryl-4-aminobutyric acids opens way to the improvement of the target therapeutic activity of fenibut and baclofen.

Description of the prior art

Several methods of racemic 3-aryl-4-aminobutyric acids resolution into *R*- and *S*-enantiomers are documented in literature. These are mainly chromatographic separations which include tedious steps of protection and subsequent deprotection of appropriate amino acid [I. Basova et al., *SU* 1432051 (1986). N. Langlois et. al. *Tetrahedron*, 1996, **52**, No 48, 15117-15126. R. D. Allan et al., *Tetrahedron*, 1990, **46**, No7, 2511-2524. R. E. Zeile, *Synthesis*, 1991, 1023.]. Direct resolution of racemic 3-aryl-4-aminobutyric acid was achieved by using columns packed with expensive chiral stationary phase [C. Vaccher, *J. Chromatogr.* 1991, **542**, 502-507]. Some methods are represented by cumbersome preferential crystallization of diastereoisomeric salts using optically active bases cinchonidine or L-(-)- α -methylbenzylamine as resolution agent [M. Soborcinska et al., *Pol. J. Chem.*, 1979, **53**, 435-446. A. F. Wildervanck, et al., (*US* 6051734, 2000.].

Optical resolution was achieved also by methods based on the combination of chemical and enzymatic transformations [R. Chenevret, M. Desjardins, *Can. J. Chem.*, 1994, **72**, 2312-2317. R. V. Muralidhar, R. R. Chirumamilla et al., *Med. Fac. Landbouww. Univ. Gent*, 2001, **66**, Nr 3a, 227-232]. *R*-Enantiomer of baclofen was also isolated from its racemic mixture by selective microbial degradation of its *S*-enantiomer therefore excluding the latter from utilization [W. Levadoux et al., *D. US* 5483765, 1998].

In general, all mentioned methods are not convenient for large-scale production of pure enantiomeric drugs, because of ignoring technological and especially economical aspects of the availability and the cost of reagents and materials.

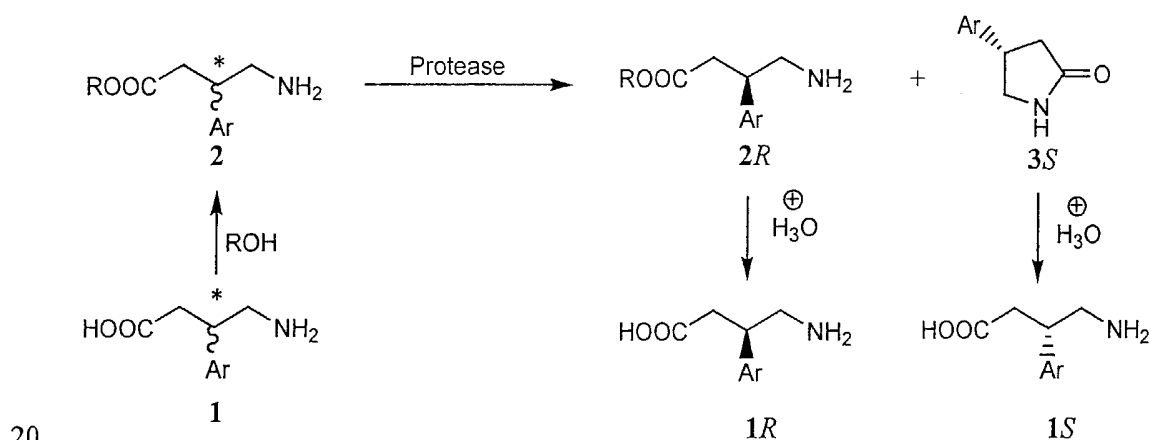
Therefore easy and effective optical resolution method of racemic 3-aryl-4-aminobutyric acids into their *R*- and *S*-enantiomers was the aim of the present invention.

Summary of the invention

Present invention provides a simple process for the cheap production of optically pure *R*- and *S*-enantiomers of 3-aryl-4-aminobutyric acid. After extensive investigations we discovered, that *R*- and *S*-enantiomers of 3-aryl-4-aminobutyric acid can be produced from easily available racemic ester of 3-aryl-4-aminobutyric acid **2** by its treatment with enzymes selected from protease family which catalyze the hydrolysis of ester group and the formation of peptide bond.

Selective cyclization of 3-aryl-4-aminobutyrate *S*-enantiomer in the presence of protease provided the formation of reaction mixture containing only two products: 4(*S*)-aryl-2-pyrrolidinone (**3S**) and 3-aryl-4-aminobutyrate **2R** in *R*-enantiomeric form. We found, that these compounds can be easily separated from each other by conventional extraction technique and then converted into target 3(*R*)-aryl-4-aminobutyric acid **1R** and 3(*S*)-aryl-4-aminobutyric acid **1S** by acidic hydrolysis (Scheme 1).

Scheme 1.



Detailed description of the invention

According to the invention, a process for the enzymatic resolution of the racemic mixture of formula **2** wherein Ar is phenyl or *p*-halo substituted phenyl, R is alkyl group and * marks chiral carbon atom, is provided by the exposing of the racemic mixture of formula **2** to the catalyzing action of protease in its free or immobilized state in suitable aqueous or aqueous-organic co-solvent medium. These enzymes react selectively only with *S*-enantiomer of **2** converting it into 4(*S*)-aryl-2-pyrrolidinone (**3S**), but do not attach the *R*-enantiomer of **2**. We found that obtained

enantiomeric products: 4(*S*)-aryl-2-pyrrolidinone (**3S**) and 3(*R*)-aryl-4-aminobutyric acid ester (**2R**), due to their different solubility in two-phase water/organic solvent system at low pH can be effectively separated by extraction and then converted into enantiomeric **1R** and **1S** 3-aryl-4-aminobutyric acids respectively by acidic hydrolysis.

5 The preferred reaction conditions for the enzymatic resolution of racemic esters of 3-aryl-4-aminobutyric acids **2** include:

1. application of α -chymotrypsin in water soluble or in water insoluble immobilized reusable state for the resolution of 3-aryl-4-aminobutyric acid esters;
2. the preferred substituents R in **2** which are represented by saturated or unsaturated alkyl
10 group containing from 2 to 8 carbon atoms;
3. the usage of aqueous or aqueous-organic co-solvent reaction medium with pH between 6.0-7.0;
4. reaction temperature between 20-40°C;
5. the stirring or shaking of reaction mixture from 1 to 72 hours.

15 Thus obtained mixture of optically active 4(*S*)-aryl-2-pyrrolidinone (**3S**) and 3(*R*)-aryl-4-aminobutyric acid ester (**2R**) can be separated by extraction. Any of not mixing with water organic solvents (hydrocarbons such as hexane, benzene, toluene; halogenated hydrocarbons such as chloroform, methylene chloride; esters such as ethyl acetate; ketones, ethers) may be employed for this purpose. Reaction products **2R** and **3S** can be isolated from water and organic
20 phases by conventional procedures such as evaporation or crystallization, if necessary. We found that 3(*R*)-aryl-4-aminobutyric acid esters **2R** are readily soluble in water in acidic conditions and can be also extracted at neutral pH 7 and isolated from organic phase by evaporation or crystallization, if necessary.

The preferred conditions for the isolation of substantially pure optically active 4(*S*)-aryl-2-pyrrolidinone (**3S**) from reaction mixture include:
25

1. the acidification of reaction mixture till pH<2.0;
 2. the extraction of 4(*S*)-aryl-2-pyrrolidinone (**3S**) with organic solvent preferably with ethyl acetate, methylene chloride, toluene or benzene and the following evaporation of organic phase.
- 30 The preferred conditions for the isolation of substantially pure optically active 3(*R*)-aryl-4-aminobutyric acid ester (**2R**) from reaction mixture, after the elimination of 4(*S*)-aryl-2-pyrrolidinone (**3S**) by extraction can be performed by two methods including:
1. the evaporation of water phase;

2. the neutralization of water phase till pH 7.0, the extraction of 3(*R*)-aryl-4-aminobutyric acid ester (**2R**) with organic solvent preferably with ethyl acetate, methylene chloride, toluene or benzene and the evaporation of organic phase.

The following examples are illustrating but not restricting the present invention.

5

General procedure for the synthesis and enzymatic resolution of racemic 3-aryl-4-aminobutyric acid ester 2.

Protocol 1.

- 10 A. Thionyl chloride (0.616 ml, 8.4 mM) was added to a cooled to -16°C mixture of 3-aryl-4-aminobutyric acid **1** (5.5 mM) in 20 ml of appropriate alcohol. Obtained solution was boiled for 4 hours, and evaporated under reduced pressure yielding hydrochloric salt of 3-aryl-4-aminobutyric acid ester **2** (98.0%-99.5% purity according to HPLC analysis).
- 15 B. Racemic 3-aryl-4-aminobutyric acid ester **2** 25 mg was dissolved in 5 ml of 0.1 M phosphate buffer with pH 6.0-7.0 with/without addition of 10% of organic co-solvent (dioxane, acetone etc.). Water soluble α -chymotrypsin¹ 5 mg (or 25 mg of α -chymotrypsin immobilized on the suspension of SiO₂ (1 g) according to the procedure [K. Watanabe, G.P. Royer, Journal of Molecular Catalysis, 1983, 22, 145]) was added to the reaction mixture and the latter was stirred at 20-40°C for 72 hours. The reaction progress leading to the formation of 4(*S*)-aryl-2-pyrrolidinone (**3S**) was monitored by HPLC.
- 20 C. After the end of enzymatic process² the reaction mixture was acidified by the addition of 2N HCl to pH <2.0 and 4(*S*)-aryl-2-pyrrolidinone (**3S**) was extracted by 3x20 ml of methylene chloride. Thus obtained organic and water phases were evaporated to dryness giving residues of 4(*S*)-aryl-2-pyrrolidinone (**3S**) and 3(*R*)-aryl-4-aminobutyric acid ester (**2R**) which were converted in hydrochloric salts of *S*- and *R*-enantiomers **1S** and **1R** of 3-aryl-4-aminobutyric acid by their treatment in boiling 2N HCl for 20 hours and
- 25 following evaporation of reaction mixture. Their optical purity was evaluated on the base of chiral HPLC analysis data³.

Protocol 2.

30 The enzymatic resolution of 3-aryl-4-aminobutyric acid (**1**) on the stages A and B was realized according to **Protocol 1**.

- C. After the end of enzymatic process² the reaction mixture was acidified by the addition of 2N HCl to pH <2.0 and 4(*S*)-aryl-2-pyrrolidinone **3S** was extracted by 3x20 ml of ethyl acetate and evaporated to dryness giving residue of 4(*S*)-aryl-2-pyrrolidinone **3S**. The water phase was treated with 5N NH₄OH to pH 7 and 3(*R*)-aryl-4-aminobutyric acid ester (**2R**) was extracted by 3x20 ml of ethyl acetate. Thus obtained organic pahse was

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evaporated to dryness giving residue of 3(*R*)-aryl-4-aminobutyric acid ester (**2R**). Both enantiomeric products were converted in hydrochloric salts of *S*- and *R*-enantiomers **1S** and **1R** of 3-aryl-4-aminobutyric acid by their treatment in boiling 2N HCl for 20 hours and following evaporation of reaction mixture. Their optical purity was evaluated on the base of chiral HPLC analysis data ³.

¹ α -chymotrypsin activity: 65-85 units/mg

² in the case of immobilized α -chymotrypsin the suspension of catalyst after the end of enzymatic conversion was filtered off, washed by distilled water and re-used repeatedly, if necessary.

³ mobil phase - HC104 (pH 1.0); stationary phase - CROWNPAK CR(+)5a

The effectiveness of enzymatic resolution and the enantiomeric excess for 3-aryl-4-aminobutyric acids *R*- and *S*-enantiomers obtained according the Protocol A and B are presented in the Table 1.

Table 1

The conditions of enzymatic resolution process, yields and the enantiomeric excess for 3-aryl-4-aminobutyric acid *R*- and *S*-enantiomers (**1R** and **1S**)

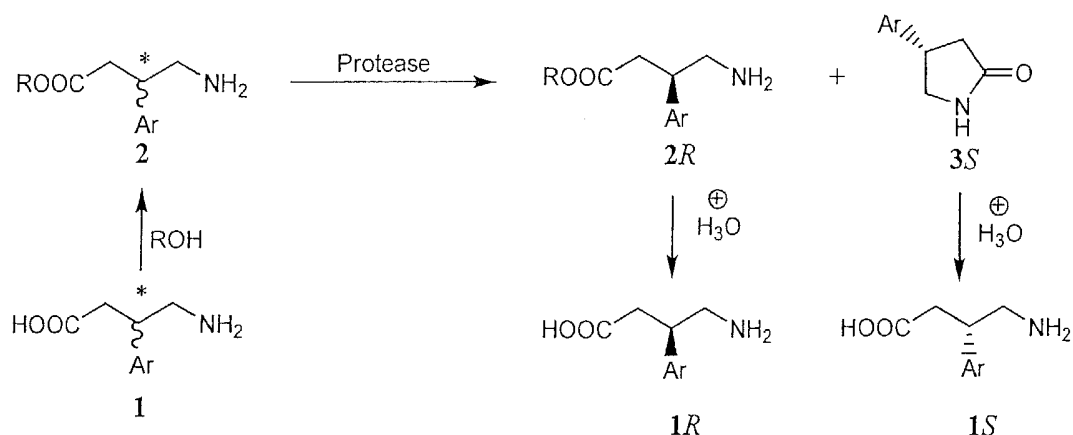
Example Nr (Protocol)	R	Ar	Time (h)	t(°C)	Medium*	Yield ** (%)	Enantiomeric excess (%, <i>ee</i>)	
							1S	1R
1 (1)	Et	Ph	72	20-22	A	66	92	64
2 (1)	<i>i</i> -Pr	Ph	72	20-22	A	54	76	53
3 (1)	<i>n</i> -Pr	Ph	72	20-22	A	78	96	76
4 (1)	Allyl	Ph	24	20-22	A	68	74	67
5 (2)	Allyl	Ph	72	20-22	A	86	96	84
6 (1)	<i>n</i> -Bu	Ph	24	20-22	A	74	90	72
7 (2)	<i>n</i> -Bu	Ph	72	20-22	A	98	98	97
8 (2)	Octyl	Ph	72	20-22	A	62	76	60
9 (1)	<i>n</i> -Bu	<i>p</i> -ClPh	72	20-22	B	98	≥98	≥97
10 (2)	<i>n</i> -Bu	<i>p</i> -ClPh	72	20-22	C	98	≥98	≥97

* A - phosphate buffer (pH 6.0-7.0); B - phosphate buffer/dioxane ratio 10:1; C - phosphate buffer/acetone ratio 10:2.

** reaction yield was calculated on the basis of decrease in the size of 3-aryl-4-aminobutyric acid ester **2** peak on HPLC chart.

We claim:

1. The process of the optical resolution of racemic 3-aryl-4-aminobutyric acid ester (1) according to the scheme:



catalyzed by protease selected from group consisting of α -chymotrypsin, papain and subtilisin, wherein, Ar is selected from group consisting of phenyl or *p*-halosubstituted phenyl and R is selected from group of substituents consisting of saturated or unsaturated alkyl group containing from 2 to 8 carbon atoms which includes following steps:

- (1) selective catalytic conversion of racemic 3(*S*)-aryl-4-aminobutyric acid ester from racemic 3-aryl-4-aminobutyric acid ester into 4(*S*)-aryl-2-pyrrolidinone (3*S*);
 - (2) acidification of reaction mixture to pH<2.0 and separation of 4(*S*)-aryl-2-pyrrolidinone (3*S*) and 3(*R*)-aryl-4-aminobutyric acid ester (2*R*) by extraction;
 - (3) isolation of 4(*S*)-aryl-2-pyrrolidinone (3*S*) from organic phase and 3(*R*)-aryl-4-aminobutyric acid ester (2*R*) from water phase by evaporation or crystallization.
2. A process according to claim 1 wherein protease is α -chymotrypsin
 3. A process according to claim 1 wherein in step (1) α -chymotrypsin is used in water soluble state.
 4. A process according to claim 1 wherein in step (1) α -chymotrypsin is used in water insoluble immobilized state.
 5. A process according to claim 1 for enantiomeric separation of racemic 3-phenyl-4-aminobutyric acid esters .
 6. A process according to claim 1 for enantiomeric separation of racemic 3-*p*-chlorophenyl-4-aminobutyric acid esters .
 7. A process according to claim 1 wherein 3-aryl-4-aminobutyric acid esters are selected from group consisting of lower and medium size saturated and unsaturated alkyl alcohols.

8. A process according to claim 1 for enantiomeric separation of racemic 3-phenyl-4-aminobutyric acid ethyl ester.
9. A process according to claim 1 for enantiomeric separation of racemic 3-phenyl-4-aminobutyric acid *n*-propyl ester.
- 5 10. A process according to claim 1 for enantiomeric separation of racemic 3-phenyl-4-aminobutyric acid *i*-propyl ester.
11. A process according to claim 1 for enantiomeric separation of racemic 3-phenyl-4-aminobutyric acid *n*-butyl ester.
12. A process according to claim 1 for enantiomeric separation of racemic 3-phenyl-4-aminobutyric acid allyl ester.
- 10 13. A process according to claim 1 for enantiomeric separation of racemic 3-phenyl-4-aminobutyric acid octyl ester.
14. A process according to claim 1 wherein in step (1) the solvent used is water.
15. A process according to claim 1 wherein in step (1) the solvent used is water-organic co-solvent medium wherein the organic solvent or mixture of them is selected from group of solvents, consisting of appropriate alkanes, haloalkanes, aralkanes, aromatic solvents, esters, ketones and ethers .
- 15 16. A process according to claim 1 wherein in step (1) reaction temperature is between 20° and 40°C.
- 20 17. A process according to claim 1 wherein in step (1) reaction medium pH is between 6 and 7.
18. A process according to claim 1 wherein in step (3) water phase is neutralized to pH 7 followed by the extraction of 3(*R*)-aryl-4-aminobutyric acid ester (2*R*).
19. A process according to claim 1 wherein in steps (2) and (3) organic solvent is used for extraction, which is selected from group consisting of hexane, benzene, toluene, chloroform, dichloromethane, dichloroethane, ethyl acetate, methyl acetate, diethyl ether, methyl *t*-butyl ether and mixtures of them.
- 25 20. A process according to claim 1 wherein in steps (2) and (3) hexane is used for extraction.
21. A process according to claim 1 wherein in steps (2) and (3) benzene is used for extraction.
- 30 22. A process according to claim 1 wherein in steps (2) and (3) toluene is used for extraction.
23. A process according to claim 1 wherein in steps (2) and (3) chloroform is used for extraction.
24. A process according to claim 1 wherein in steps (2) and (3) dichloromethane is used for extraction.
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25. A process according to claim 1 wherein in steps (2) and (3) dichloroethane is used for extraction.
26. A process according to claim 1 wherein in steps (2) and (3) ethyl acetate is used for extraction.
- 5 27. A process according to claim 1 wherein in steps (2) and (3) methyl acetate is used for extraction.
28. A process according to claim 1 wherein in steps (2) and (3) diethyl ether is used for extraction.
29. A process according to claim 1 wherein in steps (2) and (3) methyl *t*-butyl ether is used
10 for extraction.
30. A process according to claim 1 wherein in step (3) isolated 3(*R*)-aryl-4-aminobutyric acid ester (2*R*) is converted into *R*-enantiomer of 3-aryl-4-aminobutyric acid (1*R*) by acidic hydrolysis.
31. A process according to claim 1 wherein in step (3) isolated 4(*S*)-aryl-2-pyrrolidinone (3*S*)
15 is converted into *S*-enantiomer of 3-aryl-4-aminobutyric acid (1*S*) by acidic hydrolysis.