

(19) AUSTRALIAN PATENT OFFICE

- (54) Title
Intermediate halophenyl derivatives and their use in a process for preparing azole derivatives
- (51)⁶ International Patent Classification(s)
C07C 29/42 (2006.01) **OBMJP** **C07C**
C07B 61/00 (2006.01) 33/48
C07C 33/48 (2006.01) 20060101ALI2005100
C07C 59/115 **8BMEP** **C07C**
(2006.01) 59/115
C07D 249/08 20060101ALI2005122
(2006.01) **OBMJP** **C07D**
C07D 417/06 249/08
(2006.01) 20060101ALI2006052
C07D 521/00 **1BMUS** **C07D**
(2006.01) 417/06
20060101ALI2005122
C07C 29/42 **OBMJP** **C07D**
20060101AFI2005122 521/00
OBMJP **C07B** 20060101ALI2005100
61/00 **8BMEP**
20060101ALI2005122 PCT/EP02/06644
- (21) Application No: 2002321068 (22) Application Date: 2002 .06 .17
- (87) WIPO No: W003/002498
- (30) Priority Data
- (31) Number (32) Date (33) Country
01115355.8 2001 .06 .26 EP
- (43) Publication Date : 2003 .03 .03
(43) Publication Journal Date : 2003 .05 .15
- (71) Applicant(s)
Basilea Pharmaceutica AG
- (72) Inventor(s)
Soukup, Milan
- (74) Agent/Attorney
Spruson & Ferguson, Level 35 St Martins Tower 31 Market Street, Sydney, NSW, 2000
- (56) Related Art
Chem Pharm Bull 40(3), 661-665 (1992)

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

(19) World Intellectual Property Organization
International Bureau



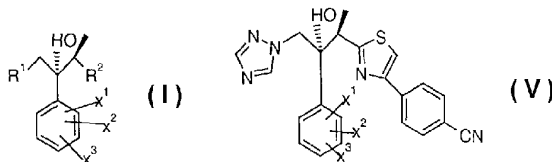
(43) International Publication Date
9 January 2003 (09.01.2003)

PCT

(10) International Publication Number
WO 03/002498 A1

- (51) International Patent Classification⁷: C07C 29/34, 33/48, 57/58, 51/285, 51/29, C07D 249/08, 417/06
- (21) International Application Number: PCT/EP02/06644
- (22) International Filing Date: 17 June 2002 (17.06.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 01115355.8 26 June 2001 (26.06.2001) EP
- (71) Applicant (for all designated States except US): BASILEA PHARMACEUTICA AG [CH/CH]; Rudolf Maag, 11 Neuhofweg, CH-4102 Binningen (CH).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): SOUKUP, Milan [CZ/CH]; 5 Efeuweg, CH-4103 Bolltingen (CH).
- (74) Agent: F. HOFFMANN-LA ROCHE AG; 124, Grenzacherstrasse, CH-4070 Basle (CH).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- 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: INTERMEDIATE HALOPHENYL DERIVATIVES AND THEIR USE IN A PROCESS FOR PREPARING AZOLE DERIVATIVES

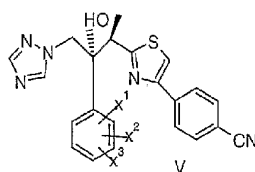


(57) Abstract: Novel halophenyl derivatives of the general formula (I), wherein R¹ is halogen, a leaving group or 1H-1,2,4-triazol-1-yl and R² is ethynyl or carboxy, X¹ is halogen and X² and X³ are each independently hydrogen or halogen, and their manufacture are described. They are intermediates for manufacturing azole derivatives of the general formula (V) which are valuable medicaments useful for treating systemic mycoses.

WO 03/002498 A1

Intermediate Halophenyl Derivatives and their use in a Process for preparing Azole Derivatives

Azole derivatives of the general formula

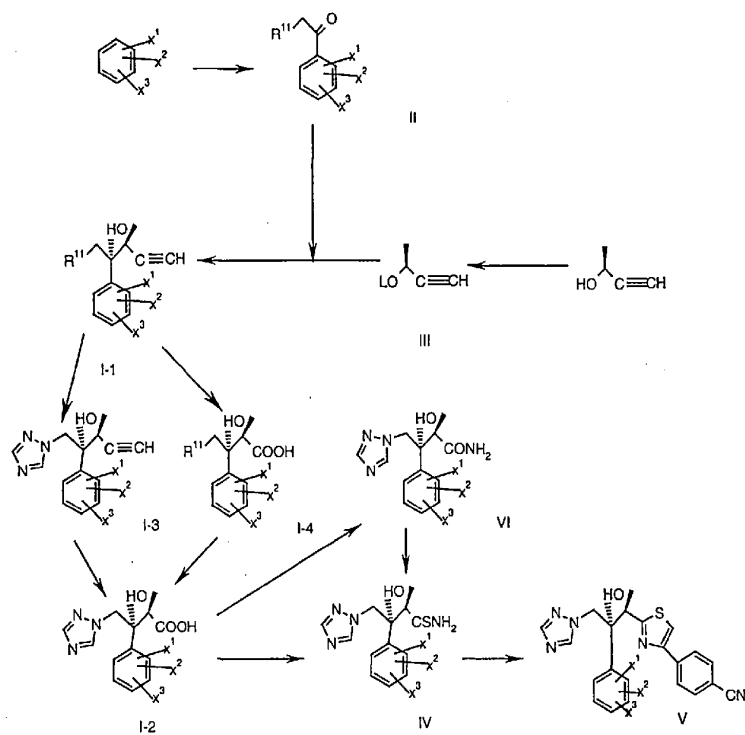


- 5 wherein X^1 is halogen and X^2 and X^3 are each independently hydrogen or halogen,
- are valuable medicaments useful for treating systemic mycoses and possess a broad antifungal spectrum. However, heretofore they have been available only by multistep linear synthesis with low overall yield and low diastereoselectivity with respect to the
- 10 (1R,2R)-propyl moiety of the molecule (EP 0667 346 A2, South African Patent 99/1763, WO 01/32652).

It has now surprisingly been found that the azole derivatives aforesaid can be manufactured in a much simplified manner using considerably less process steps and with considerably improved yield and diastereoselectivity. The process which offers these

15 advantages can be depicted by the following Scheme 1:

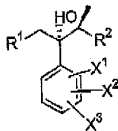
Scheme 1



wherein the symbols have the significance given below.

- 2a -

According to a first aspect of the present invention, there is provided halophenyl derivatives of the general formula



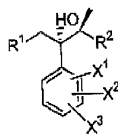
wherein R¹ is halogen, a leaving group or 1H-1,2,4-triazol-1-yl and R² is ethynyl, X¹ is halogen and X² and X³ are each independently hydrogen or halogen.

According to a second aspect of the present invention, there is provided a process for the manufacture of (2R,3S)-1-chloro-2-(2,5-difluorophenyl)-3-methyl-pent-4-yne-2-ol according to formula (I) as claimed in claim 1, wherein it comprises reacting 2-chloro-1-(2,5-difluorophenyl)-ethanone with (R)-methanesulfonic acid 1-methyl-prop-2-ynyl ester in the presence of palladium (II)-dichloride-diacetonitrile as palladium catalyst and diethylzinc as organometallic reagent in tetrahydrofuran as apolar organic solvent.

According to a third aspect of the present invention, there is provided a process for the manufacture of (2R,3S)-1-chloro-2-(2,4-difluorophenyl)-3-methyl-pent-4-yne-2-ol according to formula (I) as claimed in claim 1, wherein it comprises reacting 2-chloro-1-(2,4-difluorophenyl)-ethanone with (R)-methanesulfonic acid 1-methyl-prop-2-ynyl ester in the presence of palladium(II)-dichloride-diacetonitrile as palladium catalyst and diethylzinc as organometallic reagent in tetrahydrofuran as apolar organic solvent.

According to a fourth aspect of the present invention, there is provided a compound prepared by the process of the second or third aspects.

There is disclosed herein novel intermediates of the general formula



25

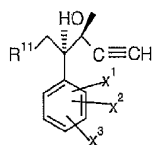
A112:(670893_1).JIF

- 3 -

wherein R^1 is halogen, a leaving group or 1H-1,2,4-triazol-1-yl and R^2 is ethynyl or carboxy, X^1 is halogen and X^2 and X^3 are each independently hydrogen or halogen.

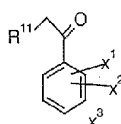
In the above scheme 1, formulas I-1, I-2, I-3 and I-4 are comprised by the above
5 formula I.

In a second embodiment, the invention concerns the diastereoselective synthesis of halophenyl derivatives of the general formula



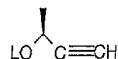
I-1

wherein R^{11} is halogen or a leaving group, X^1 is halogen and X^2 and X^3 are each
10 independently hydrogen or halogen,
which is characterized in that it comprises reacting a halophenyl derivative of the general formula



II

wherein R^{11} , X^1 , X^2 and X^3 are as above,
15 with an alkyne of the general formula



III

wherein L is halogen or a leaving group,
in the presence of a palladium catalyst and an organometallic reagent in an apolar organic solvent.

In this process R¹¹ and L signify halogen, preferably chloro or bromo, particularly chloro, or a leaving group such as lower alkylsulphonyl, phenylsulfonyl or lower alkylsulfonyl, e.g. methylsulfonyl (mesyl), phenylsulfonyl or p-tolylsulfonyl (tosyl). R¹¹ is preferably chloro, L is preferably mesyl.

5 The reaction between compounds II and III is carried out in the presence of a palladium catalyst in an apolar organic solvent. This catalyst is preferably a Pd(0)organic complex, a Pd(II)salt or an organic complex thereof. Examples of these catalysts are tetraphosphinyl palladium, palladium dichloride, palladium diacetate or an organic complex thereof, e.g. the diacetonitrile complex. Preferably the reaction is carried out in
10 the presence of a phosphine ligand such as triphenylphosphine. The reaction proceeds in the presence of an organometallic reagent, preferably an excess of a di-(lower alkyl)-metal reagent in which the metal is selected from Li, Mg, Zn, Sn and Al. The preferred metal is zinc; the preferred reagent is diethylzinc. The preferred apolar organic solvent for the reaction is n-hexane, toluene and tetrahydrofuran. The temperature of the reaction
15 preferably lies in the range of -40°C to +40°C, particularly +25°C to +30°C. The reaction product is subsequently worked up in usual manner and extracted with an organic solvent such as ethyl acetate.

In the resulting compound I-1 R¹¹ is replaced by the 1H-1,2,4-triazole group and the ethynyl group is oxidized to carboxy; while these reaction steps can be carried out in any
20 order, it is preferred to introduce the 1H-1,2,4-triazole group first, leading to compounds I-3, followed by oxidation to yield compounds I-2.

The reaction of compounds I-1 and I-4 with 1H-1,2,4-triazole is carried out in a polar or apolar organic solvent, e.g. dimethyl sulfoxide, dimethyl formamide, tetrahydrofuran or a lower alkanol such as methanol, ethanol or isopropanol in the
25 presence of a base. As base preferably an alkali metal hydroxide or hydride is used, most preferably sodium hydroxide. The temperature lies advantageously in the range of 40-80°C. The reaction products of formulas I-3 and I-2 are preferably recovered as water-soluble N-quaternary salts by the addition of acid such as hydrochloric acid or oxalic acid.

Compounds I-1 and I-3 are oxidized to introduce carboxy in lieu of ethynyl. The
30 oxidation is carried out in a solvent, e.g. water, acetic acid or ethyl acetate and is preferably effected by treatment with an alkali metal periodate (e.g. sodium(meta)periodate) or hypochlorite in the presence of a catalyst such as ruthenium dioxide. Another oxidation agent is alkali metal permanganate. The oxidation is preferably carried out at a temperature of about 40-70°C and in the presence of a phase transfer reagent for
35 oxidations, such as trialkyl(C₈/C₁₀)methylammonium chloride (ADOGEN® 464).

The carboxylic acids of formulas I-2 are converted to the thioamides IV e.g. by reaction with a dithiophosphoric acid 0,0-di-(lower-alkyl)ester and either of ammonia or hexamethyldisilazane in an organic solvent, e.g. with 0,0-diethyldithiophosphate and hexamethyldisilazane in toluene. Preferred temperature range is 60-80°C. An alternative
5 thioamidation process is conversion of the carboxylic acid I-2 to the acid amide VI with carbonyldiimidazole to yield the corresponding β -lactone, subsequently with aqueous ammonia and subsequent reaction of the acid amide VI obtained with 2,4-bis-(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetan-2,4-dithion (Lawesson reagent) in an inert organic solvent, e.g. tetrahydrofuran, at a temperature of room temperature to about 80°C.

10 Another possibility is to dehydrate the acid amide VI into the nitrile with phosphoroxychloride at about 30 to 50°C and subsequently transformation of the nitrile into thioamide by standard methods such as HSPS(OEt)₂ in water or aqueous (NH₄)₂S at about 70°C.

Compounds IV are finally reacted with 2-bromo-4'-cyanoacetophenone to yield the
15 desired end products of formula V, preferably in an inert organic solvent such as acetonitrile, ethanol or methanol at a temperature between room temperature and about 80°C. This reaction is described also in EP 0667 346 A2, South African Patent 99/1763 and WO 01/32652.

The significance of X¹, X² and X³ in the above formulas is dictated by the therapeutic
20 activity of the compounds V as antifungal agents; preferably X¹ is 2-fluoro, X² is hydrogen and X³ is 4-fluoro or 5-fluoro.

The following examples illustrate the invention in more detail.

Example 1

1.062 g (4.092 mmol) of palladium(II)-dichloride diacetonitrile were dissolved in
25 380 ml of tetrahydrofuran. 2.710 g (10.23 mmol) of triphenylphosphine were added at room temperature. The reaction mixture turned yellow and, after about 5 minutes, turbid. Stirring was continued at room temperature for 10 minutes whereafter 27.29 g (184.1 mmol) of (R)-methanesulfonic acid 1-methyl-prop-2-ynylester and 19.50 g (102.3 mmol) of 2-chloro-1-(2,5-difluoro-phenyl)-ethanone were added. About 30 ml of a solution of
30 279.0 ml (306.9 mmol) of diethylzinc solution in toluene (1.1 M; 100 %) were added dropwise so as to enable the temperature to rise to 36°C. The rest of said diethylzinc solution was added dropwise within 13 minutes at 37 – 38°C, whereafter the temperature was maintained below 39 °C by cooling. Stirring was continued for 40 minutes

- 6 -

(temperature 26 °C). The reaction mixture was poured onto a mixture of 80.00 ml (614.4 mmol) of 25 % aqueous hydrochloric acid and 800 ml of deionized water (with ice):

The reaction mixture was extracted three times with each 400 ml of ethyl acetate, the organic phases washed twice with each 250 ml of 5 % aqueous sodium chloride solution, combined, dried over sodium sulfate, evaporated, again dissolved in about 100 ml of ethyl acetate, dried over sodium sulfate and evaporated to dryness. 31.45 g of (2R,3S)-1-chloro-2-(2,5-difluoro-phenyl)-3-methyl-pent-4-yne-2-ol were obtained as a yellow oil containing 86.5 % of the stated diastereomer. Purity 67.4%. Yield 84.7 %.

NMR (CDCl₃): 1.20 (d, 3H), 2.2 (s, 1H), 2.70 (bd, 1H), 3.20 (q, 1H), 4.20 (m, 2H), 6.9-7.4 (m, 3H).

The 2-chloro-1-(2,5-difluoro-phenyl)-ethanone used as starting material was prepared as follows:

100.0 g (876.5 mmol) of 1,4-difluorobenzene and 90.83 ml (1139 mmol) of chloroacetyl chloride were cooled to 10 °C. Within 5 minutes at 10 – 17 °C 153.5 g (1139 mmol) of aluminium chloride (99 %) were added and the mixture warmed to room temperature. The mixture was heated for 30 minutes to 60 °C and the heating continued at this temperature for another 70 minutes. The reaction mixture was cooled to room temperature and poured onto a mixture of 0.8 l of ice and 400 ml of concentrated aqueous hydrochloric acid, extracted twice with each 500 ml of ethyl acetate, and the organic phases were washed once with 200 ml of water, three times with 400 ml of half-saturated aqueous sodium bicarbonate solution, dried over sodium sulfate, dissolved for 1 hour at 80 °C in 400 ml of n-hexane and, after the addition of 4 g of active carbon, filtered hot, stirred at room temperature and cooled to 0 °C; the crystals formed were dried at room temperature under reduced pressure to give 104 g (69 %) of 2-chloro-1-(2,5-difluoro-phenyl)-ethanone.

NMR (CDCl₃): 4.72 (d, 2H), 7.10-7.30 (m, 2H), 7.60-7.70 (m, 1H).

The (R)-methanesulfonic acid 1-methyl-prop-2-ynyl ester used above was prepared as follows:

25.30 g (353.7 mmol) of (R)-(+)-butyn-2-ol in 190 ml of methylene chloride were cooled to -78 °C and 99.09 ml (707.4 mmol) of triethylamine and 41.23 ml (530.5 mmol) of methanesulfochloride added carefully within 1 hour at -78 °C with stirring. The reaction mixture was poured onto 200 ml of half-saturated aqueous sodium bicarbonate,

- 7 -

extracted twice with each 100 ml of methylene chloride, the organic phase washed with water, dried over sodium sulfate, filtered and evaporated. 76.2 g of raw product was obtained which was filtered on 50 g of silica gel with 2 l of methylene chloride and the 2 first fractions (2x500ml) collected. After evaporation of the solvent 52.4 g (100%) of (R)-methanesulfonic acid 1-methyl-prop-2-ynyl ester were obtained as a slightly yellow liquid.

NMR (CDCl₃): 1.66 (d,3H), 2.71 (s,1H), 3.13 (s,3H), 5.29 (q,1H).

Example 2

887.3 mg (3.423 mmol) of palladium(II)-dichloride-diacetonitrile were dissolved in 325.0 ml of tetrahydrofuran. 2.243 g (8.530 mmol) of triphenylphosphine were added. The reaction mixture turned yellow and, after 6 minutes, turbid. The reaction mixture was stirred for 10 minutes at room temperature, whereafter 22.81 g (153.9 mmol) of (R)-methanesulfonic acid 1-methyl-prop-2-ynylester and 16.30 g (85.52 mmol) of 2-chloro-1-(2,5-difluoro-phenyl)-ethanone were added together with about 25 ml of totally 233.3 ml (256.6 mmol) of diethylzinc solution in toluene (1.1 M) dropwise. The temperature was permitted to rise to 36 °C. The remaining diethylzinc solution was added dropwise within 12 minutes at 37 – 38 °C, whereafter the temperature was prevented from rising over 39 °C. After 40 minutes (temperature about 27 °C) the reaction mixture was poured onto 350 ml of ice-cold half-saturated aqueous sodium chloride solution, 500 ml of ethylacetate were added, the mixture was stirred for 5 minutes at room temperature, and 70 ml of 25 % aqueous hydrochloric acid were added (everything in solution). The aqueous phase was washed once with 250 ml of ethyl acetate and the organic phases once with 150 ml of quarter-saturated aqueous sodium bicarbonate solution and once with 50 ml of 0.1N aqueous hydrochloric acid. The organic phases were combined, dried over sodium sulfate and evaporated to dryness. 24.85 g of (2R,3S)-1-chloro-2-(2,5-difluoro-phenyl)-3-methyl-pent-4-yne-2-ol were obtained, which were 70.5 % pure and contained 86 % of the stated diastereomer. Yield 83.1 %.

The NMR spectrum was identical to that described in Example 1.

Example 3

16.33 mg (0.0630 mmol) of palladium(II)-dichloride-diacetonitrile were dissolved in 6.00 ml of tetrahydrofuran. 41.29 ml (0.157 mmol) of triphenylphosphine were added. The reaction mixture turned yellow and was stirred for 10 minutes at room temperature. 419.8

- 8 -

mg (2.833 mmol) of (R)-methanesulfonic acid 1-methyl-prop-2-ynylester and 300.0 mg (1.574 mmol) of 2-chloro-1-(2,4-difluorophenyl)-ethanone were added, also 4.293 ml (4.722 mmol) of diethylzinc solution in toluene (1.1 M) within 5 min. at 25 – 35 °C, the latter dropwise with intermittent cooling of the reaction mixture. Stirring was continued
5 for 45 min. at room temperature. The reaction mixture was added to 10 ml of ice-cold water and 5 ml of 25 % aqueous hydrochloric acid, extracted twice with each 25 ml of ethyl acetate, the organic phases washed once with 15 ml of water, combined, dried over sodium sulfate and evaporated to dryness. 444 mg of (2R,3S)-1-chloro-2-(2,4-difluoro-phenyl)-3-methyl-pent-4-yne-2-ol were obtained as a yellow oil with purity 78.6%, which contained
10 77% of the stated diastereomer. Yield 90.6%.

NMR (CDCl₃): 1.22 (d,3H), 2.2 (6d,1H), 2.7 (vbs,1H), 3.20 (q,1H), 4.20 (dxd,2H), 6.70-6.90 (1m,2H), 7.20-7.70 (m,1H).

Example 4

163.3 mg (0.630 mmol) of palladium(II)-dichloride-diacetonitrile were dissolved in
15 60.00 ml of tetrahydrofuran, and 412.9 mg (1.570 mmol) of triphenylphosphine were added. The reaction mixture turned yellow and was stirred for 10 min. at room temperature. 4.198 g (28.33 mmol) of (R)-methanesulfonic acid 1-methyl-prop-2-ynylester and 3.00 g (15.74 mmol) of 2-chloro-1-(2,4-difluorophenyl)-ethanone were added as well as 42.93 ml (47.22 mmol) of diethylzinc solution in toluene (1.1 M) within 5 min. at 25 – 35 °C
20 dropwise; the mixture was intermittently cooled and subsequently stirred for 40 min. at room temperature. After pouring onto 50 ml of ice-cold water and 50 ml of aqueous 25 % hydrochloric acid the mixture was extracted twice with each 50 ml of ethyl acetate. The organic phases were washed once with 50 ml of water, combined, dried over sodium sulfate and evaporated to dryness. 5.029 g of (2R,3S)-1-chloro-2-(2,4-difluoro-phenyl)-3-methyl-pent-4-yne-2-ol were obtained as a dark yellow oil (73 % pure) containing 76% of
25 the stated diastereomer, corresponding to a yield of 95.3 %.

The NMR spectrum was identified to that described in Example 3.

Example 5

18.29 g (259.5 mmol) of 1,2,4-triazole were dissolved in 120 ml of dimethylsulfoxide,
30 and 7.061 g (173.0 mmol) of sodium hydroxide were added. The mixture was stirred for 20 min. at 70 °C, cooled to room temperature, and a solution of 31.40 g (86.50 mmol) of (2R,3S)-1-chloro-2-(2,5-difluoro-phenyl)-3-methyl-pent-4-yne-2-ol (product of example

1) in 120 ml of dimethylsulfoxide was added. The mixture obtained was stirred for 3.5 hours at 70 °C.

The reaction mixture was poured onto 1 l of ice-water and 80 ml of aqueous 25 % hydrochloric acid, extracted twice with each 250 ml of toluene, the toluene phase extracted once with 50 ml of aqueous hydrochloric acid, the hydrochloric phases were combined, turned alkaline with about 150 ml of 6M potassium carbonate solution, extracted twice with each 250 ml of ethyl acetate, the organic phases washed twice with each 100 ml of water, combined, dried over sodium sulfate, the toluene phases extracted once with 100 ml and once with 40 ml of about 12 % aqueous hydrochloric acid. The hydrochloric acid phases were combined, turned alkaline with aqueous 6M potassium carbonate solution, extracted twice with each 200 ml of ethyl acetate, the organic phases washed twice with each 150 ml of water, combined with the ethyl acetate phases from the first extraction, dried over sodium sulfate, concentrated to about 200 g, insoluble material was filtered off, the filtrate concentrated to about 130 g, 25 ml of 30 % ethereal hydrochloric acid were added, and stirring was continued for 1 hour at room temperature and 1 hour at 0 °C. The mixture was filtered and washed twice with each 30 ml of ethyl acetate at 0 °C to yield 19.5 g of (2R,3S)-1-[2-(2,5 difluoro-phenyl)-2-hydroxy-3-methyl-pent-4-ynyl]-1H-[1,2,4]triazol-4-ium-chloride (purity 80.6 %) containing 87.4 % of the stated diastereomer, corresponding to a yield of 57.9 %.

NMR (DMSO): 0.93 (d,3H), 3.18-3.30 (m,2H), 4.6 (s,2H), 5.97 (s,1H), 6.9-7.2 (m,3H), 7.6 (s,1H), 8.3 (s,1H).

Example 6

15.12 g (214.5 mmol) of 1,2,4-triazole were dissolved in 120 ml of dimethylsulfoxide. 5.836 g (143.0 mmol) of sodium hydroxide were added, and stirring was continued for 20 min. at 70 °C. The mixture was cooled to room temperature, and a solution of 24.81 g (71.49 mmol) of (2R,3S)-1-chloro-2-(2,5-difluoro-phenyl)-3-methyl-pent-4-yne-2-ol (from example 2) in 100 ml of dimethylsulfoxide was added. The mixture was stirred 3 hours at 70 °C.

The reaction mixture was poured onto 1.5 l of water, extracted with 300 ml of toluene; separation was effected over glassfibre/filter paper. The aqueous phase was extracted with 300 ml of toluene and the organic phases twice with each 500 ml of water, subsequently with 200 ml of water and twice with each 50 ml of 2N aqueous hydrochloric acid. The aqueous phases were combined, made alkaline with 125 ml of 6M aqueous

- 10 -

potassium carbonate solution, extracted three times with each 150 ml of ethyl acetate, the ethyl acetate phases washed twice with each 250 ml of water, combined, dried over sodium sulfate and filtered. After the addition of 5.309 g (57.19 mmol) of oxalic acid the mixture was concentrated to about 60 g, stirred 1 hour at 0 °C, filtered and washed with 20 ml of ethyl acetate (0 °C) and with 20 ml ethyl acetate/n-hexane 1:1 gave 13.12 g of (2R,3S)-1-[2-(2,5-difluorophenyl)-2-hydroxy-3-methyl-penten-4-ynyl]-1H-[1,2,4]triazol-4-ium-oxalate (of purity 90 %) containing 98.5% of the stated diastereomer was obtained, corresponding to a yield of 45.0 %.

NMR (DMSO): identical with that of Example 5.

10

Example 7

3.174 g (45.03 mmol) of 1,2,4-triazole were dissolved in 22.0 ml of dimethylsulfoxide. 1.225 g (30.02 mmol) of sodium hydroxide were added and the mixture stirred for 20 min. at 70 °C. After cooling to room temperature a solution of 5.030 g (15.01 mmol) of (2R,3S)-1-chloro-2-(2,4-difluoro-phenyl)-3-methyl-pent-4-yne-2-ol (from example 4) in 20 ml of dimethylsulfoxide were added and the mixture was stirred for 3 hours at 70 °C.

The reaction mixture was poured onto 100 ml of water, extracted twice with each 100 ml of toluene, the organic phases were washed with each 100 ml of water and then extracted once with 100 ml and twice with each 80 ml of aqueous 2N hydrochloric acid; the hydrochloric acid phases were combined, made alkaline with aqueous 6M potassium carbonate solution, extracted twice with each 80 ml of ethyl acetate, the ethyl acetate phases were washed twice with each 50 ml of water, combined, dried over sodium sulfate, filtered, washed with each about 20 ml of ethyl acetate and evaporated to dryness. 3.074 g of (2R,3S)-2-(2,4-difluoro-phenyl)-3-methyl-2-[1,2,4]triazol-1-yl-pent-4-yn-2-ol were obtained (purity 82 %), corresponding to 46 % yield. This was boiled 1 hour in 25 ml of t-butyl-methyl ether, cooled to 0 °C, filtered and washed at 0 °C with t-butyl-methyl ether to yield 1.655 g of the product as white crystals which were 100% pure, corresponding to a yield of 39.8 %.

NMR (CDCl₃): 1.0 (d,3H), 2.3 (s,1H), 3.2 (q,1H), 4.47 (s,1H), 4.85 (qxd,2H), 6.7-6.8 (m,2H), 7.2-7.5 (m,1H), 7.5 (s,1H), 7.9 (s,1H).

30

Example 8

A solution of 27.51 g (128.6 mmol) of sodium (meta)periodate in 500 ml of deionized water was added to 71.30 mg (0.322 mmol) of ruthenium(IV)oxide hydrate

within 5 min. at 0 °C. The reaction mixture turned yellow. 101.3 µl (0.225 mmol) of ADOGEN[®] 464 were added, followed within 35 min. at 6 – 7 °C by a solution of 13.12 g (32.15 mmol) of (2R,3S)-1-[2-(2,5-difluorophenyl)-2-hydroxy-3-methyl-penten-4-ynyl]-1H-[1,2,4]triazol-4-ium-oxalate (from example 6) in 300 ml of acetic acid and 60 ml of deionized water, the last reactant added dropwise. After warming to room temperature the mixture was stirred for 2 1/2 hours at room temperature.

80 ml of isopropanol were added to the reaction mixture, and stirring was continued for 10 min. at room temperature (pH 1.4), whereafter the pH was adjusted to 4 at 22 – 26 °C with about 280 ml of aqueous 4N sodium hydroxide solution, diluted with 600 ml of water, extracted six times with each 500 ml of ethyl acetate, the organic phases were combined, dried over sodium sulfate and evaporated. 18.9 g of brown semi-crystalline (2R,3R)-3-(2,5-difluorophenyl)-3-hydroxy-2-methyl-4-[1,2,4]triazol-1-yl-butyric acid were obtained, which were dissolved in 100 ml of ethyl acetate, boiled under reflux conditions for 30 min., the solution cooled with ice to room temperature, 15 ml of about 30 % ethereal hydrochloric acid were added, the mixture stirred for 1 hour at room temperature and 30 min. at 0 °C, filtered, washed with ether and the obtained crystals dried for 2 hours under reduced pressure at 40 °C. 12.75 g of the product were obtained as a white powder (purity 80 %), containing 99.4 % of the stated diastereomer, corresponding to a yield of 95.1 %. The compound has an m.p. of 162 – 178 °C (dec.).

NMR (DMSO): 0.88 (d,3H), 2.50 (s,1H), 3.12 (q,1H), 4.75 (dxd,2H), 6.0 (vb,1H), 6.9-7.0 (m,1H), 7.1-7.25 (m,2H), 7.71 (s,1H), 8.5 (s,1H).

Example 9

2.499 g (11.68 mmol) of sodium (meta)periodate in 30 ml deionized water were added to 12.96 mg (0.0584 mmol) of ruthenium(IV)oxide hydrate within 10 min. at 0 °C. The reaction mixture turned yellow. 8.264 mg (0.0205 mmol) of ADOGEN[®] 464 were added and subsequently a solution of 810.0 mg (2.921 mmol) of (2R,3S)-2-(2,4-difluorophenyl)-3-methyl-1-[1,2,4]triazol-1-yl-pent-4-yn-2-ol (from example 7) in 20 ml acetic acid and 2 ml of deionized water were added dropwise within 15 min. at 5 – 8 °C. The mixture was stirred for 1 hour at room temperature.

2 ml of isopropanol were added to the reaction mixture, whereafter the pH was adjusted to 4 with about 40 ml of aqueous 2N sodium hydroxide, the mixture was diluted with 100 ml of water, extracted four times with each 40 ml of ethyl acetate, the organic phases combined, dried over sodium sulfate, filtered over 30 g of silicagel and evaporated

- 12 -

to dryness. 893 mg of (2R,3R)-3-(2,4-difluoro-phenyl)-3-hydroxy-2-methyl-4-[1,2,4]-
triazol-1-yl-butyric acid were obtained, which were heated under reflux condition in ethyl
acetate for 20 min., cooled to room temperature and evaporated. 760 mg of the product
were obtained containing 99 % of the stated diastereomer, corresponding to a yield of 88
5 %.

NMR (DMSO): 0.85 (d,3H), 3.1 (q,1H), 4.72 (dxd,2H), 5.8 (vb,1H), 6.8-6.90 (m,1H), 7.1-
7.35 (m,2H), 7.6 (s,1H), 8.30 (s,1H).

Example 10

In a glass pressure tube with magnet stirrer in an oil bath 250.0 mg (0.840 mmol) of
10 (2R,3R)-3-(2,5-difluorophenyl)-3-hydroxy-2-methyl-4-[1,2,4]triazol-1-yl-butyric acid
were dissolved in 10.00 ml of toluene.

219.0 µl (1.050 mmol) of hexamethyldisilazane and 534.8 µl (3.360 mmol) of O,O-
diethyldithiophosphate were added and the mixture stirred for 16 hours at 125 °C.

The reaction mixture was poured onto 12 ml of ice-cold aqueous 2N hydrochloric
15 acid. The pressure tube was rinsed with 10 ml of toluene and 3 ml acetic acid. After the
extraction the organic phases were reextracted with 5 ml of ice-cold aqueous 2N
hydrochloric acid, the aqueous phases combined, made alkaline with 10 ml of aqueous 4N
sodium hydroxide solution, extracted twice with each 25 ml of ethyl acetate, the organic
phases washed with 10 ml of water, combined, dried over sodium sulfate and evaporated
20 to dryness. 130 mg of (2R,3R)-3-(2,5-difluorophenyl)-3-hydroxy-2-methyl-4-[1,2,4]-
triazol-1-yl-thiobutyramide were obtained as yellow foam which was dissolved in about 3
ml of methylene chloride:n-hexane 1:1, filtered, washed with 1 ml of methylene chlorid:n-
hexane 1:1 and the resulting crystals dried under reduced pressure at room temperature to
yield 65 mg of the product as white crystals corresponding to a yield of 24.7 %.

25 NMR (DMSO): 0.94 (d,3H), 3.60 (q,1H), 4.52 (d,1H), 4.85 (d,1H), 6.6 (s,1H), 6.9-7.25
(3m,3H), 7.60 (s,1H), 8.3 (s,1H), 9.95 and 10.1 (2s,2x1H).

This product can be converted in known manner to (2R,3R)-3-[4-(4-cyanophenyl)-
thiazol-2-yl]-2-(2,5-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-butan-2-ol, e.g. as in South
African Patent 99/1763 (cf. Example 4h thereof).

30

Example 11

10 g (27 mmol) of (2R,3R)-3-(2,5-difluorophenyl)-3-hydroxy-2-methyl-4-[1,2,4]-
triazol-1-yl-butyric acid (oxalate salt) were dissolved in 200 ml of tetrahydrofuran and
after addition of 5.8 g (35 mmol) 1,1'-carbonyldiimidazole stirred at 60°C for 3 hours.
After evaporation of the solvent the reaction mixture was poured onto 300 ml of aqueous
5 0.5N-HCl and extracted 3 times with each 300 ml of ethyl acetate. The extract was dried
over Na₂SO₄ and evaporated. 7.1 g (94% yield) of (3R,4R)-4-(2,5-difluoro-phenyl)-3-
methyl-4-[1,2,4]triazol-1-ylmethyl-oxetan-2-one resulted.

NMR (CDCl₃): 1.12 (d,3H), 3.98 (q,1H), 4.90 (dxd,2H), 7.05-7.20 (m,3H), 7.88 (s,1H),
8.14 (s,1H).

10

Example 12

7.1 g (25.4 mmol) of (3R,4R)-4-(2,5-difluorophenyl)-3-methyl-4-[1,2,4]triazol-1-
ylmethyl-oxetan-2-one were dissolved in 250 ml aqueous ammonia (NH₄OH 25%) and,
after the addition of 64 mg (0.5 mmol) of dimethylaminopyridine, were stirred for 1 hour
at room temperature. Evaporation of the reaction mixture gave crude 7.55 g (100% yield)
15 of (2R,3R)-3-(2,5-difluoro-phenyl)-3-hydroxy-2-methyl-4-[1,2,4]triazol-1-yl-butyramide.

NMR (DMSO): 0.8 (d,3H), 3.20 (q,1H), 4.62 (d,1H), 4.74 (d,1H), 6.72 (s,1H), 6.89-6.95
(m,1H), 7.04-7.2 (m,2H), 7.6 (s,2H), 8.1 (s,1H), 8.3 (s,1H).

Example 13

5.8 g (20 mmol) of (2R,3R)-3-(2,5-difluoro-phenyl)-3-hydroxy-2-methyl-4-
20 [1,2,4]triazol-1-yl-butyramide were heated with 7.3 ml (78 mmol) of POCl₃ at 40°C for
3 hours. After cooling to room temperature the excess POCl₃ was evaporated at reduced
pressure to yield crude 10.3 g of (2R,3R)-3-(2,5-difluorophenyl)-3-hydroxy-2-methyl-4-
[1,2,4]triazol-1-yl-butyronitrile which was used directly in the next step (Example 14).

Example 14

25 6.16 g (20 mmol) of (2R,3R)-3-(2,5-difluorophenyl)-3-hydroxy-2-methyl-4-
[1,2,4]-triazol-1-yl-butyronitrile were dissolved in 150 ml of tetrahydrofuran and, after the
addition of 120 ml of a 20% aqueous solution of ammonium sulfide, the 2 phases of the
reaction mixture were shaken at 60°C for 4 hours. For work-up the reaction mixture was
poured onto 250 ml of water and extracted twice with each 300 ml of ethyl acetate. The
30 crude crystals were treated with 25 ml of t-butylmethylether at room temperature for
1 hour, filtered and dried. The first and second crop yielded 4.35 g (71%) of pure (2R,3R)-
3-(2,5-difluorophenyl)-3-hydroxy-2-methyl-4-[1,2,4]triazol-1-yl-thiobutyramide.

The NMR spectrum was identical to that described in Example 10.

Example 15

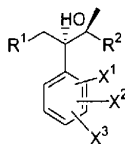
165 mg (0.55 mmol) of (2R,3R)-3-(2,4-difluorophenyl)-3-hydroxy-2-methyl-4-[1,2,4]triazol-1-yl-butyric acid were dissolved in 3.3 ml of tetrahydrofuran and, after the
5 addition of 120 mg (0.72 mmol) of 1,1'-carbonyldiimidazole, stirred for 2 hours at 60°C. The reaction mixture was poured onto 10 ml of aqueous 0.5N HCl, extracted twice with each 25 ml of ethyl acetate, dried and evaporated to dryness. The crude residue was dissolved in 6 ml of aqueous 25% ammonium hydroxide and, after the addition of 2 mg of dimethylaminopyridine, stirred at room temperature for 1 hour. After evaporation of the
10 reaction mixture the resulting residue was treated with 200 mg of POCl₃ at 40°C for 3 hours. After evaporation of the excess POCl₃ under reduced pressure the crude product was poured onto water and extracted twice with 15 ml of ethyl acetate. The organic phase was dried with Na₂SO₄ and evaporated. Column chromatography on silica gel (eluent ethyl acetate/n-hexane = 1:1) gave 95 mg (74%) of (2R,3R)-3-(2,4-difluorophenyl)-3-hydroxy-2-
15 methyl-4-[1,2,4]triazol-1-ylbutyronitrile.

NMR (DMSO): 1.05 (d,3H), 3.1 (q,1H), 4.70 (dxd,2H), 6.60 (s,1H), 6.95-7.05 (m,1H), 7.2-7.25 (m,1H), 7.30-7.40 (m,1H), 7.75 (s,1H), 8.40 (s,1H).

This compound can be converted to the thioamide in analogy to the above
Example 14. The thioamide can then be converted in known manner to (2R,3R)-3-[4-(4-
20 cyanophenyl)-thiazol-2-yl]-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-butan-2-ol, e.g. as in South African Patent 99/1763 (cf. Example 4h thereof) or in EP 0 667 346 A2 (cf. Example 88 thereof).

The claims defining the invention are as follows:

1. Halophenyl derivatives of the general formula



wherein R¹ is halogen, a leaving group or 1H-1,2,4-triazol-1-yl and R² is ethynyl, X¹ is halogen and X² and X³ are each independently hydrogen or halogen.

2. A process for the manufacture of (2R,3S)-1-chloro-2-(2,5-difluorophenyl)-3-methyl-pent-4-yne-2-ol according to formula (I) as claimed in claim 1, wherein it comprises reacting 2-chloro-1-(2,5-difluorophenyl)-ethanone with (R)-methanesulfonic acid 1-methyl-prop-2-ynyl ester in the presence of palladium (II)-dichloride-diacetonitrile as palladium catalyst and diethylzinc as organometallic reagent in tetrahydrofuran as apolar organic solvent.

3. A process for the manufacture of (2R,3S)-1-chloro-2-(2,4-difluorophenyl)-3-methyl-pent-4-yne-2-ol according to formula (I) as claimed in claim 1, wherein it comprises reacting 2-chloro-1-(2,4-difluorophenyl)-ethanone with (R)-methanesulfonic acid 1-methyl-prop-2-ynyl ester in the presence of palladium(II)-dichloride-diacetonitrile as palladium catalyst and diethylzinc as organometallic reagent in tetrahydrofuran as apolar organic solvent.

4. A process according to claim 2 or 3, which is carried out in the presence of the phosphine ligand triphenylphosphine.

5. A process according to claim 2 or 4 for the manufacture of

A) (2R,3S)-1-[2-(2,5-difluorophenyl)-2-hydroxy-3-methyl-pent-4-ynyl]-1H-[1,2,4]triazol-4-ium chloride or

B) (2R,3S)-1-[2-(2,5-difluorophenyl)-2-hydroxy-3-methyl-pent-4-ynyl]-1H-[1,2,4]triazol-4-ium oxalate

wherein 1,2,4-triazole is reacted with dimethylsulfoxide, sodium hydroxide and (2R,3S)-1-chloro-2-(2,5-difluorophenyl)-3-methyl-pent-4-yne-2-ol and the reaction product is further reacted with hydrochloric acid to give (2R,3S)-1-[2-(2,5-difluorophenyl)-2-hydroxy-3-methyl-pent-4-ynyl]-1H-[1,2,4]triazol-4-ium chloride or

with oxalic acid to give (2R,3S)-1-[2-(2,5-difluorophenyl)-2-hydroxy-3-methyl-pent-4-ynyl]-1H-[1,2,4]triazol-4-ium oxalate.

6. A process according to claim 3 or 4 for the manufacture of (2R,3S)-2-(2,4-difluorophenyl)-3-methyl-2-[1,2,4]triazol-1-yl-pent-4-yn-2-ol wherein 1,2,4-triazole is
s reacted with dimethylsulfoxide, sodium hydroxide and (2R,3S)-1-chloro-2-(2,4-difluorophenyl)-3-methyl-pent-4-yne-2-ol to give (2R,3S)-2-(2,4-difluorophenyl)-3-methyl-2-[1,2,4]triazol-1-yl-pent-4-yn-2-ol.

7. A halophenyl derivative as claimed in claim 1, substantially as hereinbefore described with reference to any one of the examples.

10 8. A process as claimed in claim 2 or 3, said process substantially as hereinbefore described with reference to any one of the examples.

9. A compound prepared by the process of any one of claims 2 to 6 or 8.

Dated 8 October, 2007

Basilea Pharmaceutica AG

15 **Patent Attorneys for the Applicant/Nominated Person**
SPRUSON & FERGUSON