Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2012, 4(1):310-314

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

A facile synthesis of carbamic acid [(1S, 2R)-2-hydroxy-3-[(2-methylpropyl) [4-nitrophenyl) sulphonyl] amino]-1-(phenylmethyl) propyl]-1, 1-dimethylethyl ester; a useful component block of HIV protease inhibitor

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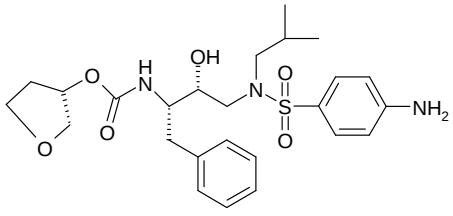
ABSTRACT

(S)-3-tert-Butoxycarbonylamino-1-nitro-2-oxo-4-phenylbutane was converted to tert-butyl (2S,3R)-4-amino-3-hydroxy-1-phenylbutane-2-yl carbamate by NaBH4 reduction followed by hydrogenation, which was converted to Carbamic acid[(1S,2R)-2-hydroxy-3-[(2-methylpropyl)[4-nitrophenyl)sulphonyl]amino]-1-(phenylmethyl)propyl]-1,1 dimethylethyl ester by treatment with nocyl chloride followed by n-butyl bromide in favorable diastereselectivity,a component of the HIV protease inhibitor Amprenavir

Keywords: N-Boc-L-Phenyl Alanine, carbonyl diimidazole, nitroketone,racemization,stereoselective reduction, nitroalcohol, reductive alkylation.

INTRODUCTION

Amprenavir **1** is an oral medication that is used for treating infections with the human immuno deficiency virus (HIV).It is in a class of drugs called protease inhibitors [1-4]. Protease is the enzyme that forms the new structural proteins and enzymes.Amprenavir blocks the activity of protease and results in the formation of defective viruses that are unable to infect the body cells. Amprenavir bear a carbamic acid [(1S, 2R)-2-hydroxy-3-[(2-methylpropyl) [4-nitrophenyl)sulphonyl]amino]-1-(phenylmethyl)propyl]-1,1 dimethylethyl ester **2** as a subunit. Several synthetic methods of **2** analog via intermediates of unstable phenylalanine [5] have been reported. The method for synthesizing these HIV protease inhibitor compounds are often complicated and expensive.



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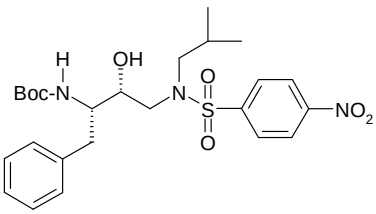

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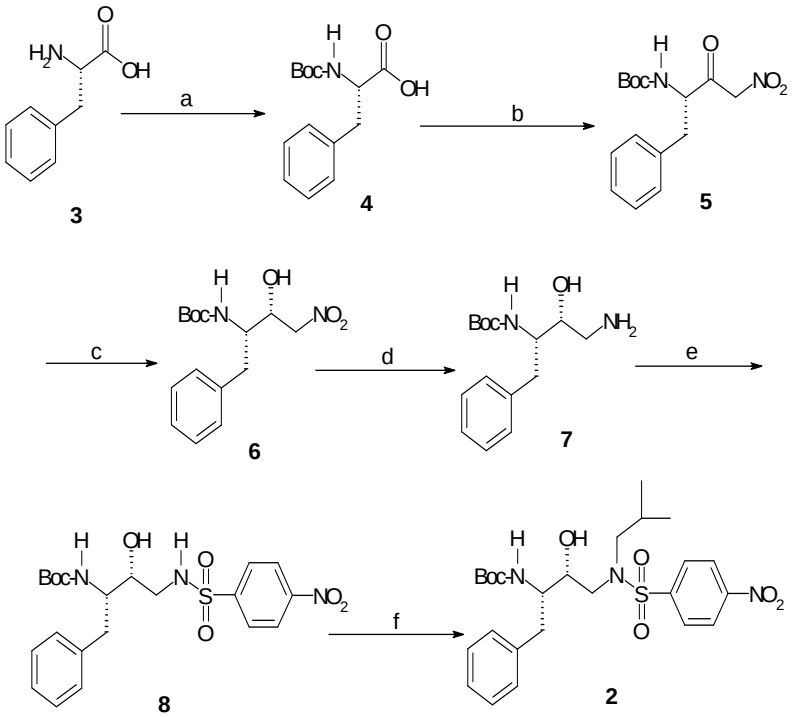
We have been interested in developing a straightforward synthetic methodology towards these block **2.**We wish to report here a facile synthesis of **2** from L-phenylalanine as a starting material. The synthetic pathway is shown in scheme I.



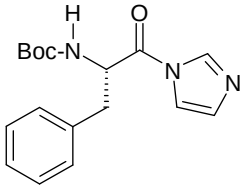
Scheme-I

Reagents and conditions a) *Boc-anhydride, NaOH, TBAB, 20-25^{o}C, 12h* b) *CH3NO2, CDI, t-BuOK, MDC, THF, 35-40$_o$C, 1h.* c) *NaBH4, MeOH, MDC, -5 to -10^{o}C* d) *Raney Ni, H_2, MeOH, 40^{o}C, 6h.* e) *Nocyl chloride, 15-20^{o}C, 1h.* f) *n-BuBr, K_2CO_3, DMSO, 20-25^{o}C, 24h.*

The process for the preparation of enantiomerically pure nitroketone **5** is discussed in various reports. Generally the process involves reaction of N-(tertbutoxycarbonyl)-L-phenylalanine **4** with nitromethane in the presence of an activating agent and an anhydrous base to obtain the enantiomerically pure nitroketone.However; all these processes for the preparation of nitroketone **5** are disadvantageous.

The literature [6, 7, 8] describes a general process for the preparation of α-nitroketone. **5** form N-(tert-butoxycarbonyl)-L-phenylalanine **4**.

A typical example of said process was carried out by in our laboratory to check chiral purity of the nitroketone **5**.The process for the preparation of nitroketone **5** described all above reports mostly yields the product, N-(tert-butoxycarbonyl)-L-phenylalanylimidazole **A** with almost 50 % racemization.



(**A)**

In view of this, it is highly unlikely to obtain the nitroketone **5** having the desired chiral purity from compound **A** with almost 50 % racemization,

There are several methods known in the literature for the preparation of stereochemically pure nitroalcohol (6).The process reported [9] by involves use of optically active rare earth Li-BINOL catalyst. The process is disadvantageous, as: (i) it involves use of a large excess of nitromethane i.e.20 equivalent, (ii) the process also involves use of La-Li-(R)-BINOL complex [10, 11, 12], which is an expensive catalyst, thereby rendering the process costly and hence, is not a commercially viable process. Also the process reported [13], provides good

diastereomeric purity, the yield of desired isomer is very low. As the process uses titanium tetrachloride the resulting nitroalcohol may contain traces of titanium.Moreover, titanium tetrachloride being very expensive reagent, its use renders the process costly.

In addition to the aforementioned processes, another process using mixture of solvent has been reported [1], involves preparation of nitroalcohol (6) of through reduction of the carbonyl group in nitroketone (5) using sodium borohydride,as reducing agent in the presence of a solvent mixture of methanol and tetrahydrofuran at a temperature 0^oC to yield merely 12.3% of pure (1S, 2R) diastereomer of nitroalcohol (6).

Based on literature survey, reduction of nitroketone (5) leads to the formation of diastereomer in almost as high as in 83:17 ratio. The method of purification adopted in all the reaction is column purification followed by solvent purification with poor yield that makes the process non-commercial.

EXPERIMENTAL SECTION

Preparation of L-phenylal Boc-anhydride

To a stirred solution of sodium hydroxide (1.5 mol) in water (7.0 vol) was added L-phenylalanine (1.2 mol), tetra butyl ammonium bromide (2.0mol %) at 20 to 25^oC and reaction mixture cooled 0 to 5^oC.

A solution of Boc-anhydride(1.6 mol) was added drop wise to above solution at 0 to 5^oC.After the addition reaction mixture was stirring for 12 hr at 20 to 25^oC.The solution was washed with hexane (2x 1.0 vol) and acidified with 15% potassium hydrogen sulphate solution, extracted with ethyl acetate(8.0vol). The organic layer was concentrated to 20% and diluted with hexane (1.0 vol). The white slurry was stirring for 1hr at 20 to 25^oC and filtered, residue washed with hexane (0.5 vol) and dried to get compound **4** with 98%yield.

Melting Point:-86^oC
IR: - (In KBr)
3314 cm^{-1},2978cm^{-1}, 1712cm^{-1},1649cm^{-1}, 1156cm^{-1}.
^1H NMR (Solvent-$CDCl_3$)
1.4 (9H,s),2.9(1H,m),3.2(1H,m),4.9(1H,m),7.1(2H,m),7.2(2H,m), 7.3(1H,m)7.4 (1H,s),12.3 (1H,s)
^{13}C NMR (Solvent-$CDCl_3$)
28.4,36.5,57.0,79.5,126,127.7,127.7,128.7,128.7,139.4,155.9,174.8
MS (m/z) = 265.31

Preparation of (3S)-3-tert-Butoxycarbonylamino-1-nitro-2-2oxo-4-phenylbutane (5).

To a stirred solution of 1, 1'-carbodiimidazole (1.45 mol) in dichloromethane (1.0vol) was added N-t-butoxycarbonyl-L-phenylalanine **4** (1.21 mol) at 0 to -5^oC for 2 hr.to form a carbonyldiimidazole Boc-phenylalanine solution.

A solution of nitromethane (1.7 mol) in dichloromethane (0.5 vol) was added in drop wise potassium t-butoxide (1.45 mol) in dry THF at 5 to 10^oC, with stirring for 30 mins.Then increased temperature to 25 ± 2^oC and the carbonyldiimidazole Boc-phenylalanine solution was added .After the addition, the reaction mixture was stirring for 1 hr.at 35-40^oC.Reaction mixture was washed with 20%$KHSO_4$ solution and extracted with dichloromethane (2x1vol). The solvent was evaporated and then solid filtered from hexane to give compound **5** with 92% yield.

Melting Point:-111^oC
IR: - (In KBr)
3368 cm^{-1},2986cm^{-1},2934 cm^{-1}, 1740cm^{-1},1690cm^{-1},1559cm^{-1}, 1519cm^{-}1167cm^{-1}.
^1H NMR (Solvent-$CDCl_3$)
1.4(9H,s),2.9(1H,m),3.2(1H,m),4.9(1H,m),5.5(1H,d),5.4 (1H,d),7.1-7.3(5H,m), 7.4 (1H,s)
^{13}C NMR (Solvent-$CDCl_3$)
28.4,34.0,64.0,79.5,81.3,126,127.7,127.7,128.7,128.7,139.4,155.9,207.1
MS (m/z) = 308.34

Preparation of nitro alcohol (6).

To a solution of **5** (1.03 mol) in methanol (2.5 vol) and dichloromethane (3.5 vol), $NaBH_4$ (0.63 mol) was added lot wise at -5 to -10^oC over 1 hr.The reaction mixture was stirred for 15-30 minutes at -5 to -10^oC and then quenched in 5%$KHSO_4$ solution at 10-15^oC.Filtered the product and washed with mixture of dichloromethane: Hexane (1:4, 0.7vol).

Residue was washed with dichloromethane at 25^{o}C to get pure desired isomer of **6** with 78% yield
Melting Point:-167^{o}C
IR: - (In KBr)
3362 cm^{-1},2968cm^{-1},2867 cm^{-1}, 1682cm^{-1},1530cm^{-1}, 1161cm^{-1}.
^{1}H NMR (Solvent-$CDCl_3$)
1.4 (9H, s), 2.6(1H, m), 3.0(1H, m), 3.8(1H, m), 4.0(1H, m),
4.4(1H, m), 4.6(1H, m), 4.8(1H, s), 7.2-7.3(5H, m), 7.6(3H, m),
^{13}C NMR (Solvent-$CDCl_3$)
28.4,35.6,55.0,71.1,79.5,84.0,126.0,128.1,128.1,128.6,128.6,138.6,155.6
MS (m/z) 310.35

Preparation of Amino alcohol (7).
A stainless steel autoclave was charged with (0.64 mol) of nitro alcohol **6,** methanol (10 vol) and Raney Ni (10% w/w) under N_2.Hydrogen gas was then charged at 5 Kg /cm^2 and stirred at 40^{o}C for 6 hr.The catalyst was then filtered through celite and the solvent was evaporated to give a solid of **7** with 95% yield.
Melting Point:-174^{o}C
IR :- (In KBr)
3360 cm^{-1},2978cm^{-1},2869 cm^{-1}, 1682cm^{-1},1524cm^{-1}, 1167cm^{-1}.
^{1}H NMR (Solvent-$CDCl_3$)
1.4(9H,s),2.0(2H,s),2.6(2H,m),2.9(2H,m),4.0(2H,m), 4.8(1H,s),
7.2-7.3 (5H,m), 7.6 (1H,s)
^{13}C NMR (Solvent-$CDCl_3$)
28.4,36.6,44.9,54.5,79.3,79.5,126.0,128.1,128.1,128.6,128.6,138.6,155.6
MS (m/z) 280.37

Preparation of sulphonamid (8).
To a solution of **7** (0.054mol) in ethyl acetate (5.0vol) and triethylamine (0.11 mol) was added drop wise a solution of nosyl chloride (0.056 mol) at 15 to 20^{o}C over 30 minutes. The reaction mixture was stirred for 1 hr. at 15 to 20^{o}C and then diluted with water.Aqeuous solution was extracted with ethyl acetate (3x1.0 vol). Organic layer dried over Na_2SO_4 and evaporated to dryness. Residue was filtered from Hexane and dried to obtain compound **8** with 93% yield**.**
IR (In KBr)
3548 cm^{-1}, 3250 cm^{-1}, 3120 cm^{-1}, 2840 cm^{-1}, 1755 cm^{-1}, 1575 cm^{-1}, 1240 cm^{-1}
^{1}H NMR (Solvent-$CDCl_3$)
1.4 (9H,s),2.6(1H,m),3.0(1H,m),3.2(1H,m),3.4(1H,m),
4.1(2H,m),4.9(1H, s), 7.2 -7.3 (5H, m), 7.7 (2H, d),
8.1-8.3 (4H, m)

^{13}C NMR (Solvent-$CDCl_3$)
28.4,36.6,43.2,54.5,75.7,79.5,126.0,124.2,124.2,128.0,128.0,128.3,128.3,128.6,128.6,138.6,145.8,151.1,155.6
MS (m/z) = 463.51

Preparation of carbamic acid [(1S, 2R)-2-hydroxy-3-[(2-methylpropyl)[4-nitrophenyl)sulphonyl]amino]-1-(phenylmethyl)propyl]-1,1 dimethylethyl ester 2
To a solution of **8** (0.004 mol), potassium carbonate (0.004 mol) in DMSO (10 vol) was added drop wise a solution of n-Butyl bromide (0.005 mol) at 20 to 25^{o}C over 30 minutes, followed by tetra butyl ammonium bromide (2.5 % w/w) as phase transfer catalyst . The reaction mixture was stirred for 24 hr. at 20 to 25^{o}C and then diluted with water.Aqeuous solution was extracted with ethyl acetate (3x2.0 vol). Organic layer dried over Na_2SO_4 and evaporated to dryness to give title compound **2** with 86% yield
Melting Point:-167^{o}C
IR (In KBr)
3540 cm^{-1}, 3100 cm^{-1}, 2850 cm^{-1}, 1750 cm^{-1}, 1585 cm^{-1}, 1250 cm^{-1}
^{1}H NMR (Solvent-$CDCl_3$).
1.0 (6H,m),1.4 (9H,s),2.0 (1H,m),2.6(1H,m),3.0(1H,m), 3.2(2H,d),4.1(2H,m),4.8(1H,s),7.2-7.3 (5H,m),7.6 (1H,s), 8.0 (2H,d), 8.3 (2H,d)
^{13}C NMR (Solvent-$CDCl_3$)
20.6,20.6,25.5,28.4,36.6,48.2,54.8,54.8,73.5,79.5,124.2,124.2,126.0,128.0,128.0,128.3,128.3,128.6,128.6,138.6,145.8,151.1,155.6
MS (m/z) = 519.62

RESULTS AND DISCUSSION

Our main objective in this route is to achieve high diastereoselectivity in the reduction .We simplify the process to obtain high yield and purity employing simple method of isolation without column purification by providing simple purification method for improving chiral purity.

In conclusion, we have described an efficient and practical route for the direct synthesis of key intermediate **2** as a component of the HIV protease inhibitor.

Acknowledgments
Authors are thankful to PHL NMR facility

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