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Synthesis of the piperazine subunit of Indinavir

Rebeca Garcia Moura,[a] Marco Antonio Bueno Filho,[b] Liliana Marzorati,[a] and Claudio Di Vitta[a]*

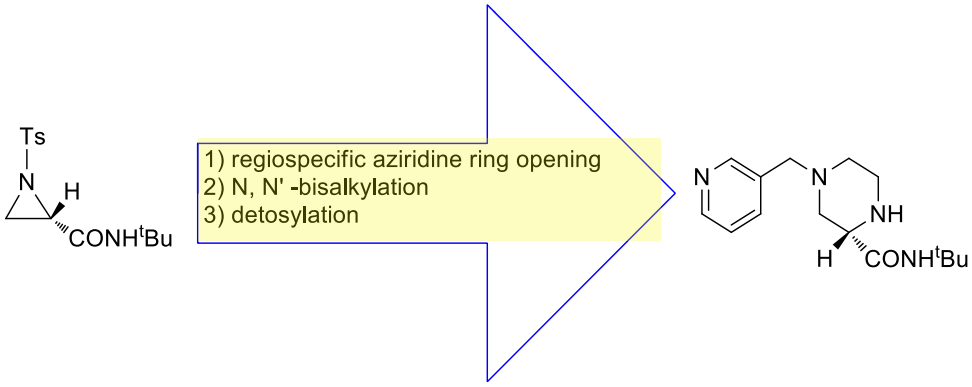
[a]Instituto de Química da Universidade de São Paulo, Av. Prof. Lineu Prestes 748, 05508-000, São Paulo, Brazil
[b]Universidade Federal do ABC, Centro de Ciências Naturais e Humanas, Av. dos Estados 5001, Santo André, SP, Brazil, 09210-580
Email: cldvitta@iq.usp.br

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Abstract

Aiming an alternative short synthesis of the piperazine fragment of Indinavir we developed the following strategy: i) regioselective C-3 ring opening of (*S*)-tert-butyl-*N*-*p*-tosylaziridine-carboxamide by 3-picolylamine; ii) *N*,*N*´-bisalkylation with diphenyl vinyl sulfonium triflate**;** iii) N-detosylation. By this sequence, after only three steps, the (*S*)-*N*-tert-butyl-4-(pyridin-3-ylmethyl)piperazine-2-carboxamide was obtained, in 20% overall yield.



Keywords: Indinavir, aziridine, piperazine, phase transfer catalysis

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Introduction

Indinavir (**1**, Figure 1), also known as Crixivan® (as the sulfate salt; L-735,524, MK-639), is an HIV protease inhibitor, acting in the last stage of replication of HIV. The Indinavir molecule presents the piperazine substructure **A** (red square, in Figure 1), and the synthesis of such fragment aroused our interest.

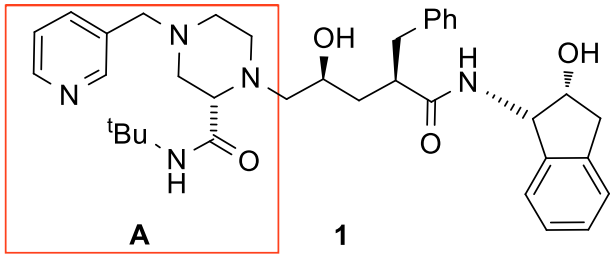
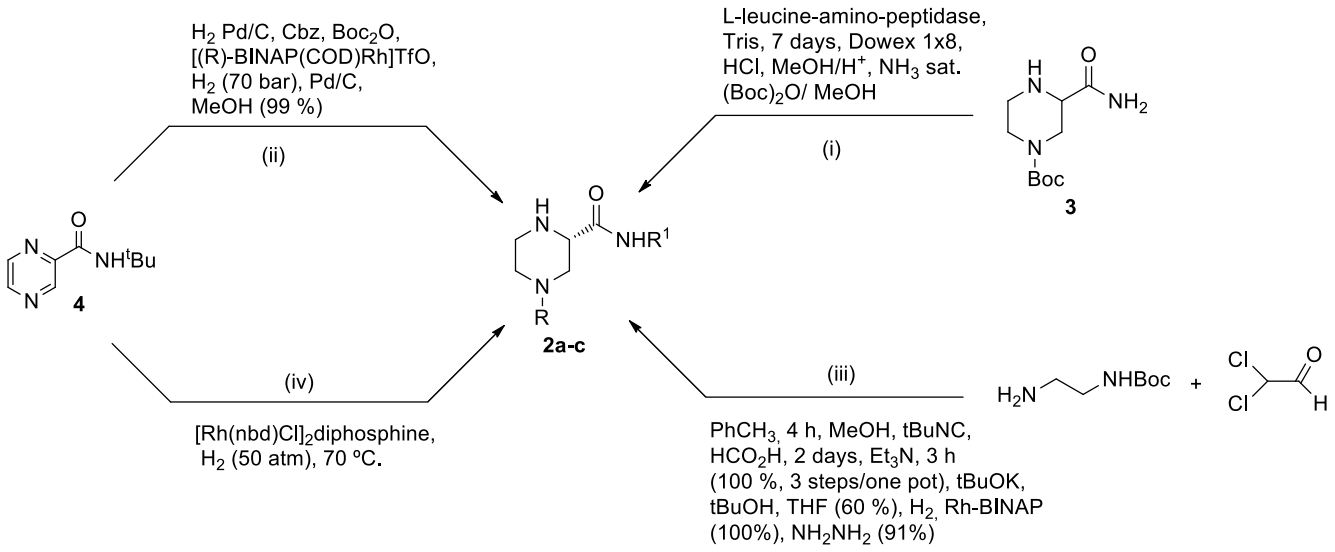


Figure 1. Indinavir (**1**) and the piperazine fragment **A**.

Most methods focusing the synthesis of Indinavir usually start from piperazines **2** (Scheme 1). For example, Bruce et al.[1] obtained compound **2a** (38%; R=Boc; R^1=H; route i, Scheme 1) by the catalyzed kinetic resolution of the racemic piperazine-2-carboxamide **3**, using L-leucine-amino-peptidase; Rossen et al.,[2] *via* hydrogenation of pyrazine-2-*tert*-butylamine **4**, in the presence of catalyst [(*R*)-BINAP(COD)Rh]TfO, obtained **2b** (96%; R=Boc; R^1=^{t}Bu; route ii, in Scheme 1). In 1999, Rossen[3] also established a new route to the same piperazine**,** by reacting the *N*-Boc-1,2-diaminoethane and dichloroacetaldeyde (58%; route iii, in Scheme 1); Fuchs,[4] in 1997, patented the synthesis of **2c** (67-88%; R=H; R^1=^{t}Bu) by asymmetric hydrogenation of compound **4**, using an optically active rhodium complex as catalyst (route iv, in Scheme 1).



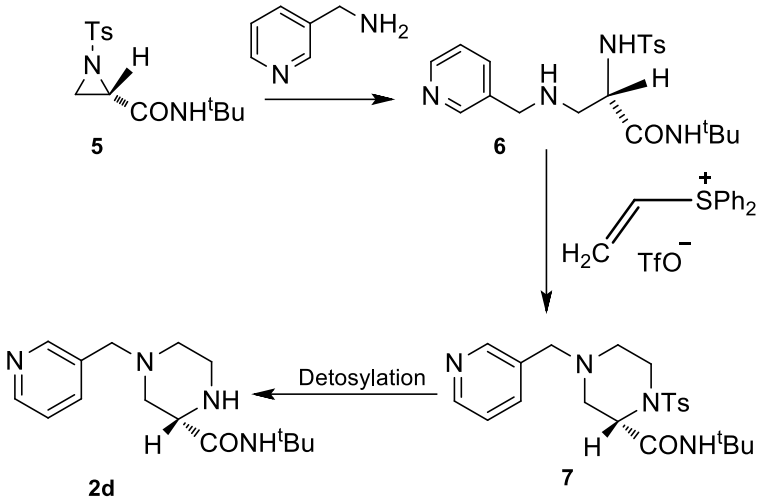
Scheme 1. Synthetic procedures for the synthesis of piperazines **2a-c.**[1-4]

In addition to the above described methods, and considering the usefulness of aziridines in organic synthesis,[5-7] we believe that a more concise synthesis of the piperazine fragment **A** can be developed by an aziridine ring opening process.

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Results and Discussion

In this work, we designed the synthesis of piperazine **2d** by our recently developed sequence comprising the aziridine C-3 ring opening by a primary amine, followed by alkylative cyclization of both nitrogen atoms of the resulting diamine with 1,2-dibromoethane.[8] After N-detosylation, the complete construction of subunit **A** can be completed in only three steps (Scheme 2). The starting *N*-tosylaziridine **5**, is prepared[9] from L-serine by the simple and inexpensive method previously described by us, as follows: N-tosylation of L-serine with TsCl/NaOH/H_2O; amidation using $^tBuNH_2$/DCC/HOBt/THF; cyclization employing K_2CO_3/TsCl/18-Crown-6/CH_2Cl_2.

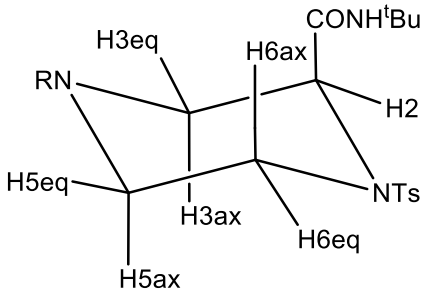


Scheme 2. Synthesis of piperazine **2d**, starting from *N*-tosylaziridine **5**.

In order to prepare aziridine **5**, the *p*-tosylated L-serine[10] was submitted to the amidation reaction employing *N,N'*-dicyclohexylcarbodiimide and *N*-hydroxisuccinimide *tert*-butylammonium salt,[11] *in lieu* of HOBt. By this modification of the previously described method,[9] the crude (*S*)-*N*-tert-butyl-3-hydroxy-2-(4-methylphenylsulfonamido)propanamide was obtained in almost pure state, without need of purification. Next, aziridination was carried out by PTC,[9] yielding pure aziridine **5**, in 84% yield. Ring opening of **5** by a stoichiometric amount of 3-picolylamine, in THF, in the presence of triethylamine, afforded **6**, in 55% yield. Initial attempts to prepare piperazine **7**, by *N,N´*-bisalkylation of **6** with 1,2-dibromoethane/K_2CO_3, under PTC conditions,[8] were unsuccessful. However, cyclization using diphenyl vinyl sulfonium triflate[12,13] yielded piperazine **7** in 98% yield. For this compound, the axial position of the carboxamide group can be advanced based on the close similarity of the piperazine ring protons chemical shifts and those of the *N*-benzylated compound (Table 1), prepared in 96% ee, by the analogous synthetic sequence.[8]

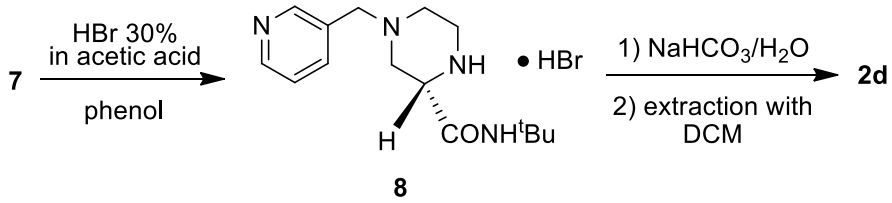
Table 1. Comparative chemical shifts (δ, in ppm) for some selected protons of **7** and those of the (*S*)-4-benzyl-*N*-tert-butyl-1-tosylpiperazine-2-carboxamide.

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	H2	H3ax	H3eq	H5ax	H5eq	H6ax	H6eq
R=3-picolyl	4.32	1.88	3.38	1.86	2.53	3.24	3.85
R=benzyl	4.30	1.97	3.34	1.86	2.58	3.21	3.78

Next, detosylation of **7** was successfully achieved using HBr 30% in acetic acid, in the presence of phenol.[14] After basification of the aqueous solution of salt **8** with sodium bicarbonate, and extraction with dichloromethane, **2d** was isolated, in 45% yield[15] (Scheme 3).



Scheme 3. Detosylation of piperazine **7**, and isolation of **2d**.

Conclusions

In summary, the chiral piperazine **2d** was successfully prepared from the readily available L-serine, in few synthetic steps. This new simple and greener synthetic route can be advantageously incorporated to the total synthesis of the HIV protease inhibitor Indinavir.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 300 MHz or on a Bruker AIII 500 MHz spectrometers in $CDCl_3$ or D_2O as solvents. A digital polarimeter JASCO model DIP-370 was used for the optic activity determination. Sigma-Aldrich silica gel 60 (2-25 µ) was used for *dry-flash* column chromatography, and TLC analyses were conducted using Merck F_{254} aluminum chromate sheets coated with silica gel 60. All the precursor chemicals were purchased from Merck, Sigma-Aldrich without any further purification. The solvents were acquired from Synth, purified and distilled according to the standard procedures prior to use.

(*S*)-*N*-*tert*-Butyl-2-(4-methylphenylsulfonamido)-3-(pyridin-3-ylmethylamino)propanamide (6). A mixture of **5** (0.562 mmol), prepared as previously described,[9] 3-picolylamine (0.563 mmol) and 14 µL of triethylamine, in 1.4 mL of THF, was stirred for 12 h, at rt. Removal of solvent under reduced pressure afforded a yellow oil, which was purified by *dry-flash* column chromatography (elution with a mixture chloroform/ methanol; 50:1), affording **6** (125 mg; as a yellow oil; 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.21 (9H, s), 2.39 (3H, s), 2.33-2,43

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(1H, m), 2.72 (1H, dd, *J* 12.0 and 5.1 Hz), 3.14 (1H, dd, *J* 12.5 and 5.8 Hz), 3.81-3.92 (2H, m), 6.99 (1H, s), 7.25-7.32 (3H, m), 7.70 (2H, d, *J* 8.2 Hz), 7.76-7.83 (1H, m), 8.53-8.60 (2H, m).

Preparation of (*S*)-*N*-tert-butyl-4-(pyridin-3-ylmethyl)-1-tosylpiperazine-2-carboxamide (7). A mixture of **6** (90.1 mg, 0.223 mmol) and DBU (68.8 mg, 0.452 mmol), in dichloromethane (10 mL), was stirred for 10 min., at 0 °C. Diphenyl vinyl sulfonium triflate (86.0 mg, 0.237 mmol), dissolved in dichloromethane (5 mL), was then added, dropwise. The mixture was stirred for 2 h, at 0 °C, and at rt for 24 h. After this time, the mixture was washed with a saturated ammonium chloride aqueous solution, and the organic phase was extracted with three portions of dichloromethane (10 mL). The organic phase was dried with anhydrous sodium sulfate and the solvent evaporated under reduced pressure, resulting in an oil, that was purified by *dry flash* column chromatography (elution with hexane/ethyl acetate; 1:1), affording **7** (92.8 mg; as a yellow oil; 98 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.34 (9H, s), 1.80-1.96 (2H, m), 2.46 (3H, s), 2.48-2.56 (2H, m), 3.22-3.48 (2H, m), 3.84-3.89 (2H, m), 4.31 (1H, bs), 6.41 (1H, s), 7.34 (2H, d, *J* 8.5 Hz), 7.48-7.52 (1H, m), 7.71 (2H, d), 7.80 (1H, d, *J* 8.3 Hz), 8.49 (1H, bs), 8.53-8.55 (1H, m).

N-detosylation of piperazine 7. A mixture of piperazine **7** (114 mg, 0.265 mmol), phenol (50 mg), and HBr 30% (0.41 mL, in acetic acid solution), was stirred for 16 h at rt. After this period, diethyl ether was added, the resulting white solid (**8**) was filtered. ^{1}H NMR (500 MHz; D_2O): δ_H 1.30 (9H, s), 2.70-2.83 (2H, m), 3.08 (1H, t, *J* 12.0 Hz), 3.27-3.35 (2H, m), 3.53-3.57 (1H, m), 4.00 (2H, s), 4.07 (1H, dd, *J* 10.3 and 3.5 Hz), 8.09-8.13 (1H, m), 8.67 (1H, d, *J* 8.1 Hz), 8.78 (1H, d, *J* 5.5 Hz), 8.86 (1H, s). The salt **8** was dissolved in saturated sodium bicarbonate solution, and the solution was extracted with three portions of dichloromethane (20 mL). The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure, affording the (*S*)-*N*-tert-butyl-4-(pyridin-3-ylmethyl)piperazine-2-carboxamide (**2d**) (33 mg; colorless oil; 45%); $[\alpha]^{25}_D$ -3.9 (*c* 3.3, $CDCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.30 (9H, s), 2.14-2.25 (2H, m), 2.57 (1H, d, *J* 11.3 Hz), 2.84-3.00 (3H, m), 3.37 (1H, dd, *J* 8.7 Hz, 3.3 Hz), 3.48 (2H, s), 6.85 (1H, s), 7.22-7.26 (1H, m), 7.64 (1H, d, *J* 7.7 Hz), 8.47-8.49 (2H, m). ^{13}C NMR (75 MHz; $CDCl_3$): δ_C 170.7, 150.4, 148.7, 136.9, 133.3, 123.5, 60.4, 59.0, 55.9, 53.0, 51.0, 44.2, 28.8.

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Supplementary Material

Copies of NMR spectra of compounds **6** and **7** are given in the Supplementary Material file associated with this paper.

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