Stereoselective Synthesis of the Key Intermediates of the HIV Protease Inhibitor Fosamprenavir and Its Diastereomer

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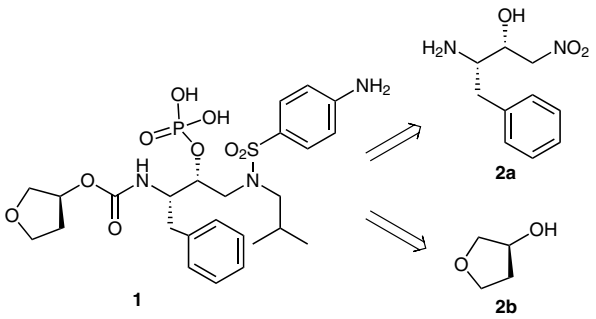
In memory of Professor RNDr. Antonín Holý, DrSc., dr.h.c.

Abstract: Highly stereoselective Henry reaction has been used in the synthesis of the fosamprenavir precursor (2*S*,3*R*)-*N*-*tert*-butyloxycarbonyl-2-amino-3-hydroxy-1-phenyl-4-nitrobutane and its 2*S*,3*S* diasteromer from *N*-*tert*-butyloxycarbonyl-(*S*)-phenylalaninal and nitromethane. The complex of (2*S*,5*R*)- or (2*R*,5*S*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-one with copper(II) acetate has been used as the catalyst which provided the product with 2*S*,3*R* absolute configuration (dr = 90:10, overall yield 89%) or 2*S*,3*S* (dr = 99:1, overall yield 94%), respectively.

Key words: aldol reaction, diastereoselectivity, HIV, homogenous catalysis, ligands

The reverse transcriptase inhibitors developed by the team of Professor Antonín Holý belong among clinically applied chemotherapeutic agents which prevent the development of human acquired immunodeficiency syndrome (AIDS) in the patients infected with HIV.[1] Besides these inhibitors, successful suppression of HIV was also achieved by application of peptidomimetic inhibitors of HIV-proteases including other chemotherapeutic agents such as amprenavir,[2] fosamprenavir,[3] nelfinavir,[4] or saquinavir.[5] The fosamprenavir (**1**, Scheme 1) contains three stereocenters and is often prepared[6,7] by exploiting (2*S*,3*R*)-2-amino-3-hydroxy-1-phenyl-4-nitrobutane (**2a**) and (*S*)-3-hydroxytetrahydrofuran (**2b**) as chiral building blocks (Scheme 1).



Scheme 1 Structure of fosamprenavir (**1**) and its precursors (2*S*,3*R*)-2-amino-3-hydroxy-1-phenyl-4-nitrobutane (**2a**) and (*S*)-3-hydroxytetrahydrofuran (**2b**)

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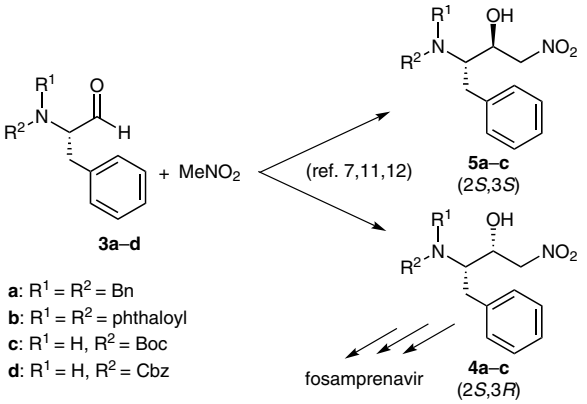
Alternative synthesis of fosamprenavir (**1**) from (2*R*,3*R*)-3-azido-4-phenylbutane-1,2-diol and (*S*)-3-hydroxytetrahydrofuran (**2b**) has also been recently published,[8] which comprises a (*S*,*S*)-salenCo(OAc) complex catalyzed hydrolytic kinetic resolution of racemic 2-(1-azido-2-phenylethyl)oxirane and **2b** as the chirality-inducing step. Other published synthetic methods for the preparation of fosamprenavir key intermediates involve natural optically pure compounds, for example, D-tartaric acid,[9] L-malic acid,[6] and L-phenylalanine derivatives.[6,7,10] In earlier papers,[7,11,12] the synthesis of the most common key intermediate, that is, the protected alaninals **3a**–**d**, was based on the enantioselective Cu(II)-catalyzed Henry reaction[13–15] of *N*,*N*-dibenzyl-(*S*)-phenylalaninal (**3a**), *N*-phthalyl-(*S*)-phenylalaninal (**3b**), *N*-*tert*-butyloxycarbonyl-(*S*)-phenylalaninal (**3c**), or *N*-benzyloxycarbonyl-(*S*)-phenylalaninal (**3d**) with nitromethane (Scheme 2). The reaction was catalyzed by rigid chiral quaternary ammonium salts derived from cinchonidine[7] **Q1** and **Q2**, by the Cu(II) complex of **C1**[11] (Figure 1), or by the La-Li–(*R*)-BINOL complex (**D1**)[12].



Scheme 2 Synthesis of key intermediates of fosamprenavir or its diastereomer by diastereoselective Henry reaction

In our previous papers we have dealt with the preparation and characterization of optically pure functionalized 4,5-dihydro-1*H*-imidazole-5-ones,[16] imidazolidine-4-ones,[17,18] and their complexes with Cu(II) ions. We also tested their enantiocatalytic properties in the Henry reaction starting from simple aldehydes. For example, the re-

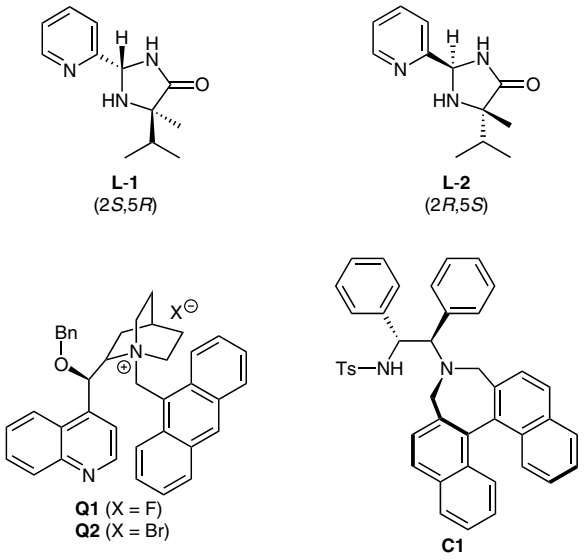
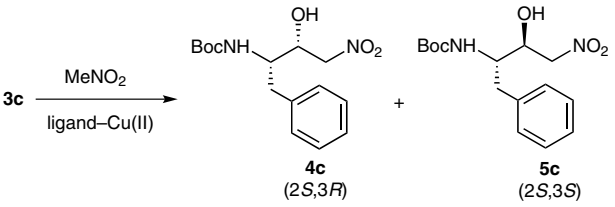


Figure 1 Structure of (2*S*,5*R*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-one (**L1**) and (2*R*,5*S*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-one (**L2**)

action of 2,2-dimethylpropanal with nitromethane catalyzed by the complex of (2*R*,5*S*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-one (**L2**) with $Cu(OAc)_2$ showed up to 96% of enantiomeric excess.[17] Hence, we aimed to apply our ligands **L1** and **L2** (Figure 1) in the copper-catalyzed Henry reaction with N-protected (*S*)-phenylalaninal in order to obtain both precursor of fosamprenavir and its diastereomer (Scheme 2).

First, we tested the Henry reaction of *N*,*N*-dibenzyl-(*S*)-phenylalaninal (**3a**) with nitromethane catalyzed by the ligand **L1** or **L2** in the presence of copper(II) acetate.[19] However, this reaction was slow even at room temperature, and the dehydration product, that is, functionalized nitrobutene, was detected in the reaction mixture in considerable amounts. Similarly, the Henry reaction with *N*-phthaloyl and *N*-benzyloxycarbonyl (*S*)-phenylalaninals **3b** and **3d** was unsuccessful. The failure of these compounds is quite surprising because they provided good yields and stereoselectivities in reactions[11,12] catalyzed by the ligands **Q1** and **D1**. Finally, we applied the same protocol[19] for the reaction of *N*-*tert*-butyloxycarbonyl-(*S*)-phenylalaninal (**3c**) catalyzed by the **L1***$Cu(OAc)_2$ complex, and we obtained the desired *N*-*tert*-butyloxycarbonyl-2-amino-3-hydroxy-1-phenyl-4-nitrobutanes **4c** and **5c** in the overall yield of 94% (Table 1, entry 1). The ratio of both diastereomers in the product was determined by liquid chromatography,[20] and their configurations were determined from 1D NOESY experiments. The diastereomeric ratio of 99:1 was in favor of derivative **5c**[21] (2*S*,3*S*), that is, derivative identical with the intermediate of the diastereomeric fosamprenavir.[7] Our catalytic system is more successful than the reported catalysis with complex **C1**,[11] where the attained overall yield was only 73%, and the diastereomeric ratio of derivative **5c** vs. **4c** was 97:3 (cf. Table 1, entry 4). The same reaction was carried out with the complex **L2***$Cu(OAc)_2$. In this case the overall yield of both diastereomers was 89%, and the diastereomeric ratio of **4c**[22] vs. **5c** was 90:10 (Table 1, entry 2). Both the diastereoselectivity and chemical yield of the reaction are comparable with other reported catalysts **Q2**[7] and **D1** (cf. Table 1, entries 3 and 5), where the Henry reaction of **3c** gave slightly less overall yields (86% and 81%) of **4c** and **5c** with the diastereomeric ratio of 94:6 and 96:4, respectively. However, these slightly better diastereoselectivities were attained at substantially lower temperature. From comparison of results obtained for **L1** and **L2** it is clear that the diastereoselectivity of the reaction is dictated almost exclusively by the chirality of the copper complex, rather than by the configuration of the substrate stereocenter. In other words, the chirality of (*S*)-alaninal better matches the chirality of **L1**.

Table 1 Henry Reaction of *N*-*tert*-Butyloxycarbonyl-(*S*)-phenylalaninal (**3c**) with Nitromethane Catalyzed by **L1** and **L2** in the Presence of $Cu(OAc)_2$



Entry	Temp (°C)	Ligand	Yield (%)[a]	dr **4c**/**5c**
1	18	**L1**	94	1:99
2	18	**L2**	89	90:10
3	–10	**Q2**[7]	86	94:6
4	r.t.	**C1**[11]	73	3:97
5	–40	**D1**[12]	81	96:4

[a] Isolated yield.

In summary, the results show that our original[17] ligands **L1** and **L2** possess a high application potential. It was proved that they are applicable as further alternative and highly selective catalysts of the Henry reaction in the synthesis of key intermediates of the peptidomimetic inhibitor fosamprenavir and its diastereomer.

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(19) One of the ligands **L1** or **L2** (0.055 mmol) and $Cu(OAc)_2$ (9.1 mg, 0.05 mmol) were stirred for 1 h in a mixture of EtOH (1.5 mL) and $MeNO_2$ (0.54 mL, 10 mmol) at r.t. to generate the catalyst. The solution was cooled to 18 °C, and then the aldehyde (1 mmol) was added. The mixture was stirred for the 96 h, the solvents were removed under reduced pressure, and the product was purified by short flash chromatography using EtOAc as an eluent.
(20) The diastereomeric ratio of **4c**/**5c** was determined by HPLC with a Chiralcel AD-H column [hexane–isopropyl alcohol (90:10), 0.8 mL/min, 254 nm]: t_R (**5c**) = 12.1 min; t_R (**4c**) = 23.1 min.
(21) Compound **5c**: yield 291 mg (94%); mp 168–170 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 75 °C): δ = 7.28–7.15 (m, 5 H, ArH), 6.47 (br s, 1 H, NH), 5.51 (d, *J* = 6.9 Hz, 1 H, OH), 4.67 (dd, *J* = 12.5, 3.0 Hz, 1 H, CH_2), 4.39 (dd, *J* = 12.5, 9.2 Hz, 1 H, CH_2), 4.19–4.10 (m, 1 H, CH_{OH}), 3.69–3.61 (m, 1 H, CH_{NH}), 3.02 (dd, *J* = 13.5, 3.8 Hz, 1 H, CH_2), 2.62 (dd, *J* = 13.5, 10.1 Hz, 1 H, CH_2), 1.28 (s, 9 H, *t*-Bu). ^{13}C NMR (100 Mz, DMSO-d_6): δ = 155.4, 139.0, 129.2, 128.1, 125.9, 80.0, 77.9, 71.2, 54.7, 36.0, 28.2.
(22) Compound **4c**: yield 280 mg (89%); mp 133–134 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 75 °C): δ = 7.28–7.17 (m, 5 H, ArH), 6.31 (br s, 1 H, NH), 5.42 (d, *J* = 6.6 Hz, 1 H, OH), 4.67 (dd, *J* = 12.5, 2.0 Hz, 1 H, CH_2), 4.37–4.32 (m, 1 H, CH_2), 4.23–4.19 (m, 1 H, CH_{OH}), 3.79–3.77 (m, 1 H, CH_{NH}), 2.88 (dd, *J* = 13.7, 5.1 Hz, 1 H, CH_2), 2.66 (dd, *J* = 13.6, 9.4 Hz, 1 H, CH_2), 1.31 (s, 9 H, *t*-Bu). ^{13}C NMR (100 Mz, DMSO-d_6): δ = 155.4, 139.0, 129.2, 128.2, 126.1, 79.5, 78.0, 69.8, 54.4, 35.7, 28.2.

