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Synthesis of a first thiophene containing analog of the HIV protease inhibitor nelfinavir

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Abstract—A stereoselective and efficient preparation of a thiophene containing intermediate **2** from ethyl 3-thienyl propenoate **4** as the core of new possible HIV protease inhibitors is described. The chiral intermediate has been successfully used for the preparation of the analog **1** of the potent HIV inhibitor nelfinavir.

The effort for an efficient therapy against AIDS was recently considerably aided by the discovery of a new class of drugs, which were designed in order to block the action of the so-called HIV protease (HIV-Pr), an essential enzyme for maturation of the infectious virus.[1] HIV-Pr inhibitors were transformed into drugs as peptidomimetic compounds,[2] while others arose by the application of computer-assisted design.[3] The transition state structure analogs, which were found most effective in the actual drugs in therapeutic use, are dipeptido isosteres.[4] Many of these inhibitors belong to the class of the hydroxyethylamine (HEA) inhibitors, such as nelfinavir and saquinavir (see Fig. 1). There are already many synthetic approaches to these compounds,[5] which mainly focused the efforts on the synthesis of the core HEA segment with the correct relative and absolute stereochemistry.

We focused our attention on nelfinavir, since it is the only developed HIV-Pr inhibitor in therapeutic use, with sulfur containing core segment. Furthermore, to our knowledge, no thienyl containing HIV-Pr inhibitor has so far been prepared and tested. This could probably be due to some difficulties in the introduction of the thienyl moiety in the core of the compound, although it is well known that the thienyl group well mimics the phenyl group[6] of phenylalanine in many peptidomimetics and, therefore, was successfully introduced in many drugs.[6b,c,d]

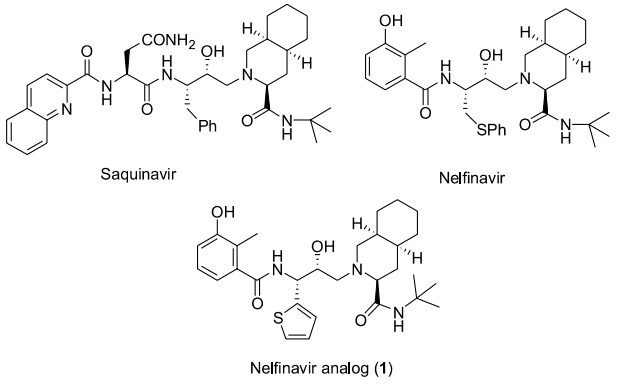

Figure 1.

Therefore we were induced to design and synthesise a first thiophene containing HIV-Pr inhibitor analogue such as the compound **1**, illustrated in Figure 1.

The development of a practical synthetic route to a core intermediate such as **2** (see Scheme 1) was found to be crucial to the final preparation of **1**. Furthermore, chiral compound **2** could in turn be introduced in different cores of potential HIV-Pr inhibitors. This intermediate, already containing the thienyl group, could be derived from the chiral α,β-dihydroxy ester **3**, eventually obtained by Sharpless AD procedure, from the thiophene acrylate **4**.

According to this retrosynthetic scheme, the regio- and stereoselective introduction of the nitrogen group on the

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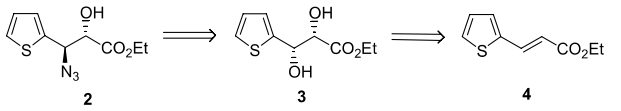


Scheme 1. Retrosynthetic analysis for compound **2**.

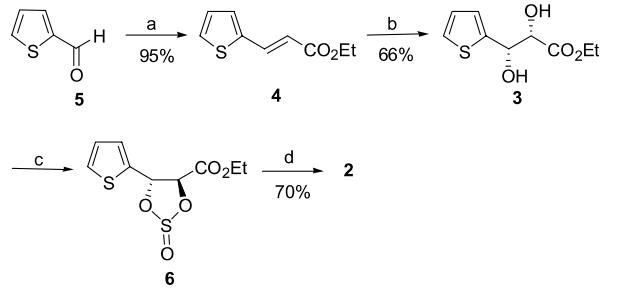
diol **3** was recognised as the key step of the overall sequence.

As outlined in Scheme 2, the synthesis of compound **2** started from commercial thienyl aldehyde **5**, which was transformed into the ethyl 3-thienylpropenoate ester **4**, almost quantitatively (95% yield) by Horner–Emmons olefination. The Sharpless AD[7] was successfully performed on **4**, as developed by our procedure on thiophene acrylates,[8] with indeed improved yields (66%) and excellent ee (>98%) of the final diol **3**.[9]

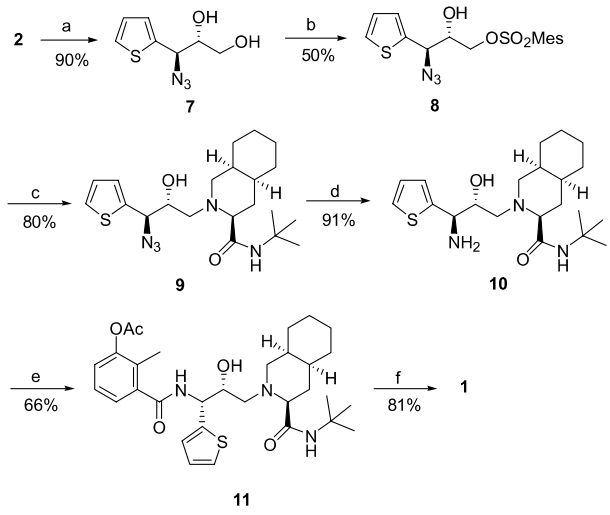
In order to properly introduce the nitrogen functionality, the diol **3** was first transformed into the sulfite **6**.[10] Then, to avoid possible thiophene ring oxidation, the azido group was directly introduced by sodium azide on compound **6**,[11] without the previous oxidation to the usually used cyclic sulfate, as usually performed on analog substrates.[10a] The reaction proceeded smoothly regio- and stereoselectively, without the isolation of the intermediate acyclic sulfite, affording the target azido alcohol **2**,[12] in good overall yield (70% in two steps). It is noteworthy that, in similar nucleophilic substitution of azido group for the HIV-Pr inhibitor synthesis,[5] the reaction was always performed on the corresponding cyclic sulfate, with one more step required for the synthesis.

We decided to use this chiral precursor in order to perform the total synthesis of an analog of already used HIV-Pr inhibitors and we focused our efforts on the compound **1**, which is a structural analog of the thienyl containing nelfinavir.

In Scheme 3, the synthesis of **1**, starting from azido alcohol **2**, was reported. After several attempts on the preliminary reduction of the azido group,[13] we decided to proceed with the synthesis in the presence of the unprotected azido alcohol, which actually resulted in a more straightforward synthetic sequence avoiding protection and deprotection manipulation, as described in



Scheme 2. Reaction conditions: (a) NaH 60%, $(EtO)_2POCH_2CO_2Et$, toluene, rt; (b) AD mix-β, $[DHQD]_2PHAL$, $MeSO_2NH_2$, H_2O/*t*-BuOH, 0–15 °C, 15 h; (c) $SOCl_2$, Pyr, CH_2Cl_2, 0 °C, 15 h; (d) NaN_3, DMF/CH_3CN, 15 °C, 15 h.



Scheme 3. Synthesis of nelfinavir analog **1**. Reaction conditions: (a) $BH_3{\cdot}SMe_2$, $NaBH_4$, THF, MeOH, 3 h, rt; (b) $MesSO_2Cl$, Pyr, CH_2Cl, 0 °C, 22 h; (c) K_2CO_3, PHIQ, *i*-PrOH, 50 °C, 21 h; (d) H_2, Pd/C, MeOH, 3 h, rt; (e) 3-Acetoxy-2-methyl bezoic acid, DCC, DMAP, CH_2Cl_2, 2 h, rt; (f) Na, MeOH, 1 h rt.

other approaches.[14] The direct reduction of ester **2**, to obtain azido diol **7**, was achieved with satisfactory result (90% yield) using $BH_3{\cdot}SMe_2$ and catalytic $NaBH_4$, a system known to perform chemoselective reductions on α-hydroxy esters.[15] Then, the regioselective activation of the primary hydroxyl group to compound **8** was smoothly performed with the more hindered mesitylenesulfonyl chloride (70% yield), instead of the tosyl derivative (50% yield).

Then, the first amino side chain, was easily introduced by treating **8** with the commercially available[16] [3*S*-(3α,4aβ,8aβ)]-*N*-(*tert*-butyl)decahydro-3-isoquinoline carboxamide (PHIQ), so that we obtained azido alcohol **9** (80% yield) without isolation of possible intermediate epoxide. The azido group in compound **9** was finally reduced via catalytic hydrogenation, affording amino alcohol **10** in high yield (91%).

The synthesis was completed with the amide bond formation, by a condensation between **10** and 3-acetoxy-2-methyl benzoic acid, which gave the protected compound **11** (66% yield).

The deprotection of the phenol group with Na/MeOH, afforded the target compound **1**[†] in 81% yield.

[†] (−)(3*S*,4a*S*,8a*S*,2′*R*,3′*R*)-2-[2′-hydroxy-3′-(3-hydroxy-2-methyl-benzoylamino)-3′-(thiophen-2-yl)-propyl]-decahydro-isoquinoline-3-carboxylic acid *tert*-butylamide (**1**) $[\alpha]_D^{20}$ −27 (*c* 0.6, EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.26–7.24 (m, 1H), 7.13–7.12 (m, 1H), 7.05–7.02 (m, 1H), 6.99–6.98 (m, 2H), 6.90–6.85 (m, 2H), 6.05 (br s, 1H), 5.47–5.43 (m, 1H), 4.22–4.19 (m, 1H), 2.68–1.20 (m, 19H), 2.14 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 169.8, 155.1, 140.2, 137.9, 127.3, 126.8, 126.7, 125.8, 122.6, 119.0, 116.9, 71.2, 70.1, 60.0, 59.4, 53.1, 51.5, 35.9, 33.4, 30.9, 30.7, 28.8, 26.2, 25.9, 21.1, 12.6. Anal. Calcd for $C_{29}H_{41}N_3O_4S$: C, 66.00; H, 7.83. Found: C, 66.03; H, 7.82.

In conclusion, the main features and novelties of this work are: (i) the original synthesis of a novel chiral intermediate as HEA core, via Sharpless AD and highly regioselective introduction of the azido group; (ii) the manipulation of the chiral azido alcohol **2** without protection–deprotection sequence; (iii) the complete preparation of the first thiophene containing analog of an HIV-Pr inhibitor. The application of this sequence for the preparation of similar and novel analogs is currently under intensive investigation.

Acknowledgements

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