A highly efficient synthesis of telaprevir by strategic use of biocatalysis and multicomponent reactions†

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A very short and efficient synthesis of the important drug candidate telaprevir, featuring a biocatalytic desymmetrization and two multicomponent reactions as the key steps, is presented. The classical issue of lack of stereoselectivity in Ugi- and Passerini-type reactions is circumvented. The atom economic and convergent nature of the synthetic strategy require only very limited use of protective groups.

Hepatitis C is a viral infectious disease affecting more than 200 million people worldwide[1] and is currently treated by a combination of PEGylated interferon and ribavirin. However, a significant number of patients do not respond to this therapy due to adverse effects or viral rebound due to resistant strains.[2] Recently, the hepatitis C virus (HCV) NS3 protease has emerged as a clinically validated target for the treatment of hepatitis C infection.[3] Two peptidic HCV NS3 protease inhibitors (telaprevir (**1**, Fig. 1)[4] and boceprevir[5]) are currently in Phase III clinical trials for the treatment of HCV infection.

The reported synthesis of **1** involves a lengthy, highly linear strategy relying on standard peptide chemistry.[6] For example, the central bicyclic proline derivative is synthesized in racemic form *via* a nine-step sequence. The desired enantiomer is only obtained after chiral HPLC separation.[6,7] Optimization of the synthesis of **1** could significantly lower the production costs, thereby making this promising drug candidate available to an increased proportion of the world population in the future.

Multicomponent reactions (MCRs)[8] have become essential tools in the efficient generation of molecular diversity and complexity. Although MCRs have been used in medicinal chemistry,[9] issues related to the infamously poor stereoselectivity seriously hamper wider application of this promising methodology. The broad repertoire of stereospecific conversions by biocatalysts[10] presents a unique opportunity to address the stereoselectivity issue of certain MCRs.

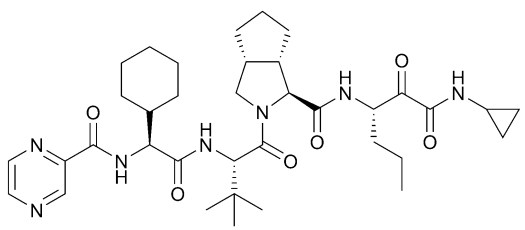
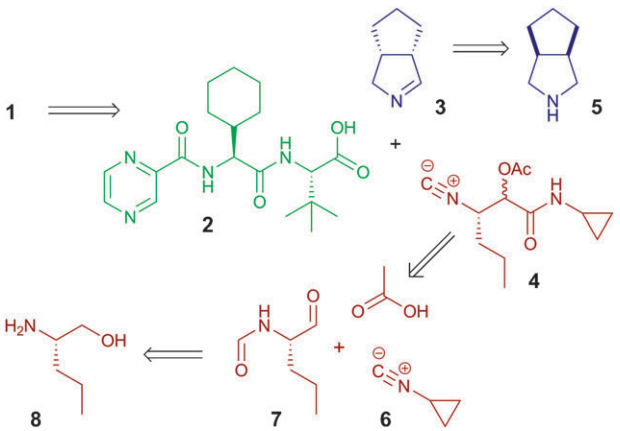


Fig. 1 HCV NS3 protease inhibitor telaprevir.



Scheme 1 Retrosynthetic analysis of telaprevir.

We recently reported the enzymatic desymmetrization of *meso*-pyrrolidines by means of a monoamine oxidase N (MAO-N) from *Aspergillus niger* optimized by directed evolution[11] and its combination with a highly diastereoselective Ugi-type three-component reaction (3CR).[12] We soon realized that this methodology could represent an efficient approach to the synthesis of telaprevir. A retrosynthetic analysis of **1** exploiting this biocatalysis/MCR sequence is presented in Scheme 1.

The required inputs for the key Ugi-type 3CR are carboxylic acid **2**, cyclic imine **3**, and isocyanide **4**. The known acid **2**[13] is readily available by standard peptide chemistry. Imine **3** can be generated *in situ* from commercially available **5** by MAO-N catalyzed oxidation. Isocyanide **4** is accessible *via* a Passerini three-component reaction (P-3CR)[14] of **6**, **7**, and acetic acid. Formamido aldehyde **7** can be derived from commercial (*S*)-2-amino-1-pentanol (**8**).

Thus, coupling of L-cyclohexylglycine methyl ester and pyrazinecarboxylic acid and subsequent saponification afforded **10** in excellent yield (Scheme 2). Subsequent coupling with L-*tert*-leucine methyl ester and saponification furnished the required optically pure acid **2**.

Compared to the reported synthesis of **2**,[13] we have significantly increased both the atom and step economy and the overall yield (74% *vs.* 11% over four steps). The use of

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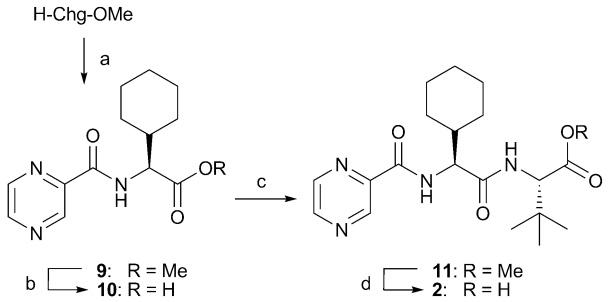
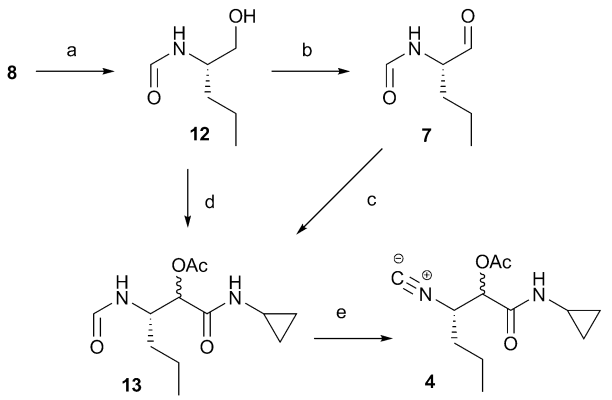
† Electronic supplementary information (ESI) available: Detailed experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/c0cc02823a



Scheme 2 Synthesis of carboxylic acid fragment **2**. *Reagents and conditions*: (a) pyrazinecarboxylic acid, BOP, Et_3N, DMF, 98%; (b) NaOH, THF/H_2O/MeOH, 95%; (c) H–Tle–OMe, EDC, HOAt, DMF, 84%; (d) NaOH, THF/H_2O/MeOH, 95%.

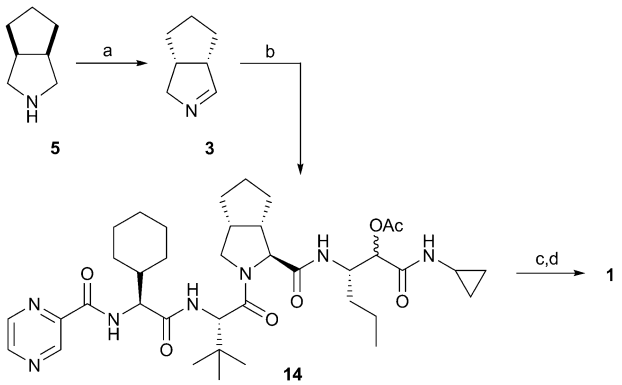


Scheme 3 Synthesis of isocyanide fragment **4**. *Reagents and conditions*: (a) EtOCHO, Δ, 99%; (b) DMP, CH_2Cl_2, 83%; (c) cyclopropyl isocyanide (**6**), AcOH, CH_2Cl_2, 56%; (d) DMP, **6**, CH_2Cl_2, 60%; (e) triphosgene, NMM, CH_2Cl_2, −30 °C, 87%.

carbamate protective groups is avoided by essentially using the N-terminal pyrazine carboxylate as an amine protective group.

We then turned our attention to the construction of the isocyanide fragment **4** (Scheme 3). Commercial (*S*)-2-amino-1-pentanol (**8**) was transformed to aldehyde **7** by N-formylation and subsequent Dess–Martin oxidation. A P-3CR between **6**, **7**, and acetic acid afforded **13** as a 78 : 22 mixture of diastereomers. However, aldehyde **7** proved difficult to isolate due to partial dimerization and the P-3CR proceeded in disappointing yield. We then realized that these two steps might be combined in a one-pot process. Ngouansavanh and Zhu have previously shown that the P-3CR is compatible with hypervalent iodine oxidants such as IBX.[15] In our case, both the Dess–Martin oxidation and the Passerini reaction are performed in CH_2Cl_2, and the acetic acid formed as a by-product in the Dess–Martin oxidation can be used as the carboxylic acid input in the P-3CR. Thus, one-pot Dess–Martin oxidation/Passerini reaction of **12** furnished **13** (60% compared to 46% in the two-step procedure). Dehydration then afforded the required isocyanide **4** in very good yield (87%). No racemization of the C3 stereocenter was observed.[16] This crucial fragment is thus accessible in only three steps from commercial starting materials.

Although the P-3CR has been used to construct telaprevir fragments similar to **13**,[17] our approach offers significant advantages compared to other approaches in terms of atom and step economy. We replaced the carbamate groups by a formamide that is actually incorporated in the final product.



Scheme 4 Multicomponent coupling of the fragments and completion of the synthesis. *Reagents and conditions*: (a) MAO-N, 100 mM KPO_4 buffer, pH = 8.0, 37 °C; (b) **2**, **4**, CH_2Cl_2, 76%; (c) K_2CO_3, MeOH; (d) DMP, CH_2Cl_2, 80% over 2 steps.

The next task at hand was the convergent three-component Ugi-type coupling (Scheme 4). Thus, commercial amine **5** was oxidized to imine **3** (94% ee) by MAO-N as described previously,[11] and then combined with **2** and **4** to give **14**. Finally, cleavage of the acetate followed by Dess–Martin oxidation[13] gave telaprevir (**1**) as a 83 : 13 : 4 mixture of diastereomers, with one minor diastereomer derived from the incomplete stereoinduction of the Ugi-type 3CR, and the other from the minor enantiomer of imine **3**. Flash chromatography allowed straightforward separation of the diastereomers to afford pure telaprevir (**1**) in 80% yield over the last two steps.

We have developed a very short and efficient synthesis of the important drug candidate telaprevir using a biotransformation and two multicomponent reactions as the key steps. The classical issue of lack of stereoselectivity in Ugi- and Passerini-type reactions is circumvented. The stereogenic carbon formed in the P-3CR is later oxidized to the corresponding ketone and the stereoselectivity of the Ugi-type 3CR is controlled by the absolute configuration of the cyclic imine, which is in turn derived from the highly stereoselective biotransformation. The use of protective groups is limited to two intermediate methyl esters and an acetate. The use of carbamate protective groups is avoided altogether. The synthesis comprises only eleven steps in total (seven steps in the longest linear sequence) compared to twenty-four in the originally reported procedure.[6,7] The total yield (over the longest linear sequence) is 45% starting from H–Chg–OMe. Our approach is general and will be applicable to many other HCV NS3 protease inhibitors that can be derived from *meso*-pyrrolidines, such as *e.g.* boceprevir[5] and narlaprevir.[17] The combination of synthetic efficiency and convergence in our approach allows both faster development of second generation inhibitors and a more economical production of telaprevir. We strongly believe that biocatalysis and MCRs will be increasingly important tools for the improvement of atom and step economy towards the sustainable production of fine chemicals and pharmaceuticals.

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