Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 1577–1579

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Solid Phase Synthesis of Aminoboronic Acids: Potent Inhibitors of the Hepatitis C Virus NS3 Proteinase

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Received 27 March 2000; accepted 10 May 2000

Abstract—Use of a resin bound diol as a boronic acid protecting group has been developed to allow the parallel synthesis of potent inhibitors of the hepatitis C virus NS3 serine proteinase.

Hepatitis C Virus (HCV) is the cause of the majority of cases of transfusion-associated hepatitis and a significant proportion of cases of community-acquired hepatitis worldwide. Infection by HCV frequently leads to persistent infections that result in a range of clinical conditions including an asymptomatic carrier state, severe chronic active hepatitis, cirrhosis and, in some cases, hepatocellular carcinoma. One of the most intensively studied and hence best understood targets for antiviral therapy against HCV is the NS3 serine proteinase.[1]

Typically, serine proteinases may be inhibited by inhibitors derived from the cleaved sequence wherein the scissile amide bond is replaced by an electrophile.[2] Incorporation of a boronic acid electrophile has led to highly potent inhibitors of various serine proteinases with in vivo activity.[3] Having previously identified potent hexapeptide aldehyde inhibitors of the HCV proteinase,[4] we wished to synthesize a set of analogous boronic acid inhibitors.[5] Our initial route was based on a 5 + 1 fragment coupling strategy (Scheme 1) whereby a preformed protected pentapeptide was coupled to the aminoboronate. This had the advantage of minimising the number of steps through which the boronate unit had to be carried.

The above route served well to explore the P1 requirements in the boronic acid series, but significant further use of this route would obviously require the laborious synthesis of each peptide fragment. We therefore wished to identify a higher throughput method of synthesizing such compounds. A resin synthesis of peptide boronic acids has been reported[6] linking the resin to an amino-acid side chain. We wished to retain the option of complete aminoacid variance. The final step of our current synthesis being an aqueous TFA assisted removal of the pinacol protecting group suggested to us that a viable approach might be to link via a pinacol-like diol to resin.[7]

A suitable diol was straightforwardly synthesised from citronellic acid (**1**) (Scheme 2) giving a diol with a protected resin attachment point.

Introduction of the boronic acid moiety was achieved in an analogous fashion to our previous work, but due to the necessity for rapid acylation of the unstable boramine (**2**) we incorporated our preferred P2-residue directly (Scheme 3). Clearly there remains the option of incorporating a more diverse set of P2 amino acids at this point. Removal of the acid protecting group, coupling to MBHA resin and acetylation of remaining free sites thus furnished the key resin bound dipeptide aminoboronic acid intermediate, with a resin loading of 0.25 mmol/g.

Sequential acylation/deprotection steps with *F*moc protected amino acids incorporated residues P3-6, and a final acylation added the P7 blocking group. Treatment with TFA then globally deprotected sidechains and released the inhibitor from the resin (Scheme 4). Material prepared by this resin approach was checked by ^{1}H NMR and shown to be identical with material prepared by our solution phase 5 + 1 strategy described earlier.

For the purposes of rapid identification of novel P5, 6 and 7 residues, acylations with *t*-butyl glycine and 2-

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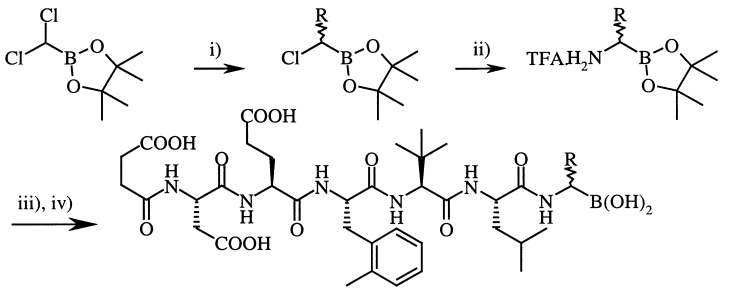
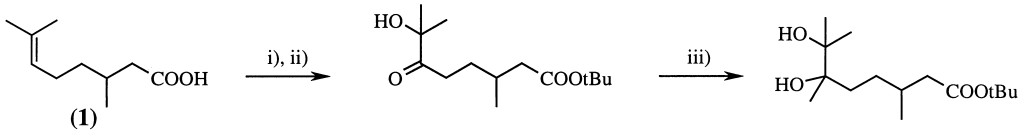
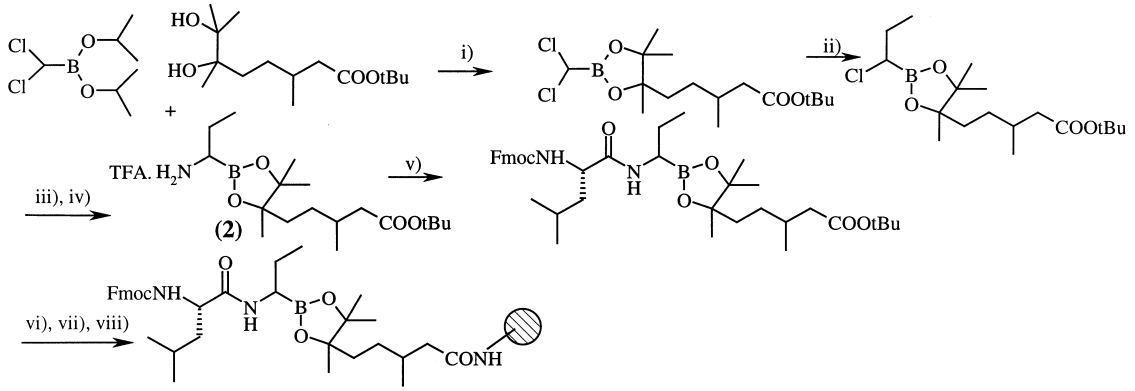


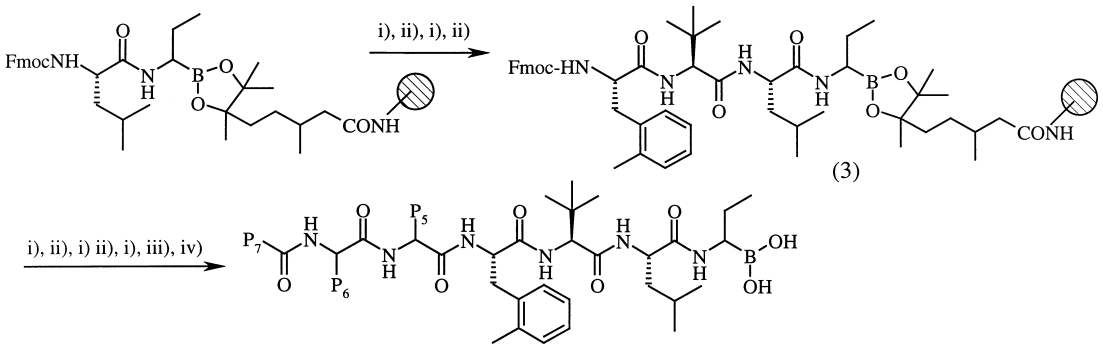
Scheme 1. (i) RMgBr, THF; (ii) $LiN(SiMe_3)_2$, THF then TFA, CH_2Cl_2; (iii) Protected pentapeptide fragment iso-NBuOCOCl, NMM, DMF, CH_2Cl_2; (iv) TFA, H_2O, CH_2Cl_2.



Scheme 2. (i) Isobutylene, c. H_2SO_4 (cat), DCM 81%; (ii) $KMnO_4$, AcOH, acetone H_2O, rt, 70%; (iii) 1.1 equiv MeMgBr, Et_2O, −78 °C, 20%.



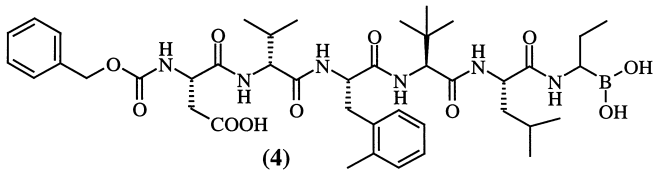
Scheme 3. (i) THF; quant; (ii) EtMgBr THF, −78 °C rt o/n; (iii) $LiN(SiMe_3)_2$, −78 °C rt; (iv) TFA, Et_2O; (v) *F*moc-Leu-OH, IBCF, NMM, DCM, 36% over 4 steps; (vi) 1:1 TFA, DCM, 15 min; (vii) MBHA resin, HBTU, DIEA, DMF; (viii) Ac_2O, NMM.



Scheme 4. (i) Piperidine, DMF; (ii) *F*moc-AA-OH, TBTU, DMF; (iii) RCOOH, TBTU; (iv) TFA, DCM, H_2O.

methyl phenylalanine, our preferred P3 and P4 residues, were carried out manually on bulk resin to give the intermediate (**3**), the start point for diversification. An Advanced Chemtech 496 synthesiser was then used to complete the synthesis, varying the N-terminal positions of the inhibitor.

Purity of compounds was judged by LC-MS, and in a typical run 41 out of 42 gave compounds of purity greater than 80%. This method allowed the rapid discovery of potent non-proteinogenic aminoacid-containing inhibitors such as (**4**), (80 nM)[8] and the discovery of novel P7 groups exemplified by (**5**) (80 nM).[9]



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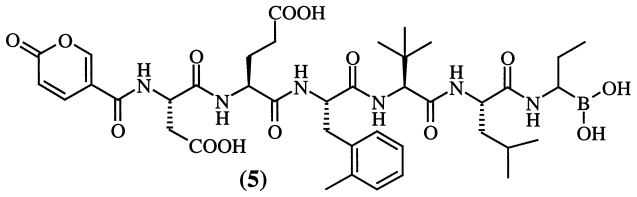

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Thus we have established a resin-based methodology for the synthesis of aminoboronic acids, which we have employed in the parallel synthesis of highly potent inhibitors of the HCV NS3 proteinase. Furthermore the selective removal of the linker protection to allow binding to the resin at any convenient point gives the linker wide application.

Acknowledgements

We thank James Bennett, Sara Cooper, Don Westmacott and Trevor Wilkinson for assaying these compounds.

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