Approaches to tyrosine-linked peptidomimetic prodrugs of (S)-HPMP-based acyclic nucleoside phosphonates

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Abstract

Synthetic approaches to a new class of tyrosine-linked prodrugs of two 3-hydroxy-2-(phosphonomethoxypropyl) (HPMP) nucleotide analogues ((S)-HPMPC and (S)-HPMPA) are outlined.

Keywords
cidofovir; (S)-HPMPA; anti-viral agent; prodrug synthesis

Drugs containing polar or ionizable groups such as phosphonic acid moieties are poorly absorbed from the gastrointestinal (GI) tract due to their unfavorable permeability.1,2 To overcome the low oral bioavailability of the effective anti-viral 3-hydroxy-2-(phosphonomethoxypropyl) nucleoside phosphonates (S)-HPMPC (1) (cidofovir) and (S)-HPMPA, and related nucleotide analogues, we are currently elaborating a peptidomimetic prodrug approach, in which the phosphonate group is masked by esterification with the side chain hydroxyl of an appropriate amino acid or peptide derivative.3, 4

Here we report synthetic studies targeting the class of tyrosine-linked prodrugs derived from the cyclized form of the parent drug. Thus, (S)-HPMPC (1) was converted to its cyclic form (2) and monoesterified with (L)- or (D)-Boc-protected COX-substituted tyrosine (3) in a PyBOP-mediated, one-pot reaction (Scheme). A similar procedure was developed for (S)-HPMPA.

Cyclic (S)-HPMPC (2) (or alternatively (S)-HPMPA) contains a prochiral phosphorus atom, and so when coupled to the enantiomeric promoiety produces two diastereomers, each having a distinct 31P chemical shift (Δδ ~ 1.5 ppm). Available data for the ratio of the diastereomers obtained from the serine3 and tyrosine series indicate that the size and the nature (alkyl versus aryl) of the promoiety strongly influences the direction of the nucleophilic attack at the phosphorus atom. This results in a mixture enriched with the diastereomer having a downfield 31P NMR chemical shift in the tyrosine series or an upfield shift in the serine series.3

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The Boc-protected conjugates (4) were deprotected under acidic conditions (TFA in CH₂Cl₂) and the TFA was exchanged with HCl using 0.1N methanolic HCl (reversible using TFA-Dowex). Final compounds 5 were obtained as hydrochloride salts in fair to good yield (22-76%) and their structure and purity were confirmed using NMR spectroscopy, mass spectrometry and HPLC analysis.

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REFERENCES