Synthetic bicyclic iminosugar derivatives fused thiazolidin-4-one as new potential HIV-RT inhibitors

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**A B S T R A C T**

Novel bicyclic iminosugar derivatives fused thiazolidin-4-one were conveniently synthesized by double Pummerer rearrangements, and their HIV reverse transcriptase (RT) inhibitory activities were preliminary examined. The notable anti-HIV-RT activity demonstrated that such bicyclic azasugars hold potential as a new kind of HIV-RT inhibitors.

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Iminosugars or azasugars, which exhibit effective inhibition against carbohydrate-processing enzymes, have attracted great interest for their potential clinical applications as anti-HIV, antidiabetic, and anti-cancer agents and immunomodulators in past decade.1 The bicyclic azasugars, a special category of azasugars, such as the naturally occurring compounds A–D7 and the synthetic ones E–G8 (Fig. 1), have also been paid much attention due to their increased possibility leading to discovering new biologically active therapeutic agents. It has been suggested that the rigid bicyclic structures are responsible for their potent activities by mimicking the flattened-chair transition state of the enzymatic reaction.9 The promising activities and the potential applications in clinic trial of the bicyclic azasugars inspired us to explore its innovative analogs5 to develop novel iminosugar-based drugs.

Recently, by using one-pot tandem Staudinger/aza-Wittig condensation reaction, we have conveniently synthesized a series of novel bicyclic azasugars bearing a thiazolidin-4-one moiety (1, Fig. 1), who showed weak or none inhibitory activity against glycosidases.5 However, these 4-thiazolidinone-azasugar hybrids exhibited good HIV reverse transcriptase (HIV-RT) inhibitory activity in the preliminary HIV-RT inhibition test. This interesting result prompts us to continue our synthesis for exploring new HIV-RT inhibitory agent. Thus, the corresponding bicyclic azasugars fused thiazolidin-4,5-dione (7 and 9, Scheme 1) derived from 1a and 1bjc were prepared by double Pummerer rearrangements7 (Scheme 1). The novel bicyclic azasugars and some deprotected intermediates (10a, 10b and 11, Scheme 1) were preliminary evaluated for their HIV-RT inhibitory activity to further investigate the structure-activity relationship (SAR).

Our synthetic strategy towards the bicyclic azasugars fused thiazolidin-4,5-dione involved the key step of double Pummerer rearrangements in which an α-functionalized sulfide formed from the sulfoxide bearing α-hydrogen atom by an internal redox process described as the reduction of S=O group and the oxidation of the α carbon.9 The synthetic approaches were described in Scheme 1 beginning with the preparation of 1a, which was achieved starting from D-ribose followed by our previously reported procedure.6,6 The synthesis of 7 as example, the bicyclic azasugar 1a was firstly protected by acetylation and afforded 2. Then, 2 was oxidized with meta-chloroperbenzoic acid (m-CPBA) within one minute to provide the corresponding sulfoxides 3a (15-form) and 3b (1R-form) in very good yield of 82.6% with a stereoelectivity in ratio of 1.4:1. Subsequently, the mixture of 3a and 3b was directly used in next Pummerer rearrangement to generate 2-substituted 4a (less polar, 25-form) and 4b (more polar, 2R-form) with regiospecificity. The exploratory study of the Pummerer reaction was performed with the sulfoxides in AcOH which was employed as the nucleophilic reagent, catalyst, and solvent.9 The effects of temperature and reaction time on the Pummerer reaction were examined, and the results are listed in Table 1. As observed in Table 1, as the temperature went up from 60 °C to 100 °C, the reaction proceeded more efficiently and the total yields of 4a and 4b increased (entry 1, 2 and 3). However, under reflux condition (nearly 120 °C) (entry 4), when the starting sulfoxide mixture disappeared within 40 min, the total yields decreased to 58% due to
Pummerer rearrangement (Scheme 2a), the reaction could proceed effectively within 1 h and afford the diastereomeric mixtures of 4a and 4b in yields of 82.2% with a high stereoselectivity in ratio of 1: 9.5. However, when the pure 3b was used, the reaction completed within 8 h and gave 4a and 4b in yields of 79.6% with an opposite and low stereoselectivity in ratio of 1.5:1. In both cases, the dominant product was that the acetoxy group was introduced preferentially at the neighbouring stereocenter (C-9 in this case) other than sulfoxide bond. This result was consistent with the Glue’s report, and indicated that the stereoselectivity of the Pummerer rearrangement derived from the decomposition. Thus, the Pummerer reaction was performed effectively at 100 °C for 2.5 h to give 4a and 4b in yields of 80%.

Furthermore, it should be noted that, when the pure compound 3a (after flash silica column chromatography) was used in the Pummerer rearrangement (Scheme 2b), the reaction could proceed effectively within 1 h and afford the diastereomeric mixtures of 4a and 4b in yields of 82.2% with a high stereoselectivity in ratio of 1:9.5. However, when the pure 3b was used, the reaction completed within 8 h and gave 4a and 4b in yields of 79.6% with an opposite and low stereoselectivity in ratio of 1.5:1. In both cases, the dominant product was that the acetoxy group was introduced on the side of the ring formerly occupied by the sulfoxide bond. This result was consistent with the Glue’s report, and indicated that the stereoselectivity of the Pummerer rearrangement derived from the neighbouring stereocenter (C-9 in this case) other than sulfoxide was usually more effective.

To complete the second Pummerer rearrangement, the mixture of the diastereoisomers 4a and 4b was oxidized by the treatment with m-CPBA at rt for 10 min, which produced the corresponding inseparable sulfoxides 5 in 82%. The longer oxidation time was needed possibly due to the steric hindrance of 2-acetoxy which decelerated the reactivity. Finally, the second Pummerer rearrangement was performed at 100 °C for 3 h to result the protected bicyclic azasugar fused thiazolidin-4,5-dione 6 in 67% yield. A possible mechanism of the double Pummerer rearrangements are proposed in Scheme 3, the 2-carbonyl in 6 was converted from the corresponding unstable ketal precursor generated by the double Pummerer rearrangement. After the removal of the protecting group acetyl in 6, the final bicyclic azasugar fused thiazolidin-4,5-dione 7 was obtained only in 23% yield because 7 was unstable in basic condition.

The effects of temperature and time on the self-catalyzed Pummerer reaction are determined by their 1H, 13C NMR, and HRESIMS spectra (Table 1). The absolute configuration of the sulfoxide derived from the deacetyl reaction, which might be caused by the tautomerism between the amide carbonyl and its z-hydroxyl. The structures of all the synthesized new bicyclic azasugars were determined by their 1H, 13C NMR, and HRESIMS spectra (see Supplementary data). The absolute configuration of the sulfoxide 10a was determined to be of (1S) by its X-ray crystallographic data (Fig. 1). The observed long J coupling constant 1.8 Hz and the absence of NOE correlation between H-2 and H-9 indicated that H-2 and H-9 were in the anti orientation, while in the syn orientation in 4a due to the corresponding NOE signal.

HIV-1 reverse transcriptase (RT) inhibitory activity was preliminarily evaluated with the bicyclic azasugars 1a–b, 7, 9, 10a–b, and 11 by determining their percentage inhibition of HIV-RT activity in HIV-1 RT kit by comparison with AZT, and the results are shown in Table 1.
In vitro HIV-1-RT kit assay for the bicyclic azasugars

<table>
<thead>
<tr>
<th>Compds</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (µM) [HIV-RT kit assay]</th>
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<th>IC&lt;sub&gt;50&lt;/sub&gt; (µM) [HIV-RT kit assay]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>13.01 ± 1.48</td>
<td>1b</td>
<td>18.99 ± 1.62</td>
</tr>
<tr>
<td>7</td>
<td>4.22 ± 0.85</td>
<td>9</td>
<td>5.20 ± 0.91</td>
</tr>
<tr>
<td>10a</td>
<td>10.19 ± 1.41</td>
<td>10b</td>
<td>2.45 ± 0.52</td>
</tr>
<tr>
<td>11</td>
<td>1.74 ± 0.15</td>
<td>AZT</td>
<td>20.52 ± 1.63</td>
</tr>
</tbody>
</table>

Table 2. In vitro HIV-1-RT kit assay for the bicyclic azasugars.

It could be seen from the table that the tested bicyclic azasugars showed significant HIV-RT inhibitory activity, better than that of positive control AZT, implying that such bicyclic azasugar fused thiazolidine-4-one derivatives may be a new kind of HIV-RT inhibitor. It's also suggested that the additional carbonyl (7, 9, 10a–b) and hydroxyl (11) at thiazolidine-4-one ring would be favorable to the HIV-RT inhibitory activity. Especially, compound 11 with hydroxyl at 2-position showed a more significant HIV-RT inhibitory activity and the IC<sub>50</sub> value was 1.74 µM, which indicated that 11 may be better accommodated into the HIV-1 RT binding site. The inhibitory activity of sulfoxide 10a is less active than that of its isomer 10b, suggesting that the stereo configuration of the S=O group would be an important effect on their anti-HIV-RT activity.

In conclusion, two novel bicyclic azasugars fused thiazolidine-4,5-dione (7 and 9) were conveniently synthesized by double Pummerer reactions in total yields of 9% and 20%, respectively. The final compounds and its precursors (1a–b), the deprotected intermediates (10a–b and 11) had significant HIV-RT inhibitory activity, providing a new class of anti-HIV-RT inhibitors as the potent anti-HIV drugs.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.09.100.

References and notes


11. CCDC-894835 (for 10a) contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.