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Synthesis of novel amino acids, L-bis-tetrahydrofuranylglycines

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Abstract—Novel amino acids, enantiomerically pure L-bis-tetrahydrofuranylglycines, were efficiently synthesized from dihydrofuran utilizing radical cyclization and chiral azidation as the key steps. The absolute stereochemistry of both diastereomers has been ascertained by their crystal structures. © 2002 Elsevier Science Ltd. All rights reserved.

Human immunodeficiency virus type 1 (HIV-1) protease, a virally encoded aspartic protease essential for the production of infectious virions, remains an important target of anti-AIDS (acquired immunodeficiency syndrome) chemotherapeutic agents. Much effort has been made to find potent, orally bioavailable and peptidomimic inhibitors of this enzyme.[1] In connection with our work on HIV-1 protease inhibitors,[2] we required a novel amino acid surrogate for aspargine at the P2 site. Previously, the S2 sub-site of the protease has been shown to favorably receive various types of ligands such as tetrahydrofuranylcarbamates,[3] bis-(tetrahydrofuranyl)carbamate,[4] cyclosulfolanes,[5] cyclic sulfone-3-carboxamides,[5] and tetrahydrofuranylglycine.[6] Particularly, tetrahydrofuranylglycine **1** and bis-(tetrahydrofuranyl)carbamate **2** ligands (Fig. 1) led to significant improvement in the inhibitory potency by acting as hydrogen acceptors from Asp-29 and Asp-30 residues of the HIV-1 protease active site.

Our experience in this area[7] suggested that L-bis-tetrahydrofuranylglycine should fit in the S2 sub-site equal to **1** and **2**. In this report, we describe synthesis of novel unnatural amino acids, *N*-Boc-protected L-bis-tetrahydrofuranylglycines (**3a** and **3b**) illustrated in Fig. 2.

The retrosynthetic analysis of the target amino acid suggested the bis-(tetrahydrofuranyl) acetic acid as its

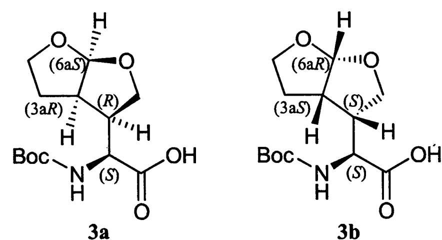

Figure 2. Structure of *N*-Boc-protected L-bis-tetrahydrofuranylglycine.

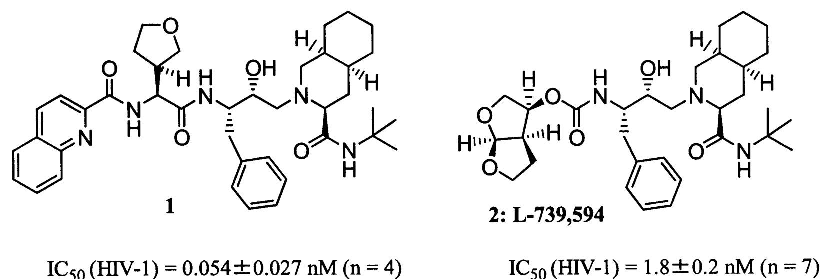

Figure 1. Structure of HIV-1 protease inhibitors containing THF ligands.

Keywords: HIV-1 protease; HIV-1 protease inhibitor; radical cyclization; novel amino acid.

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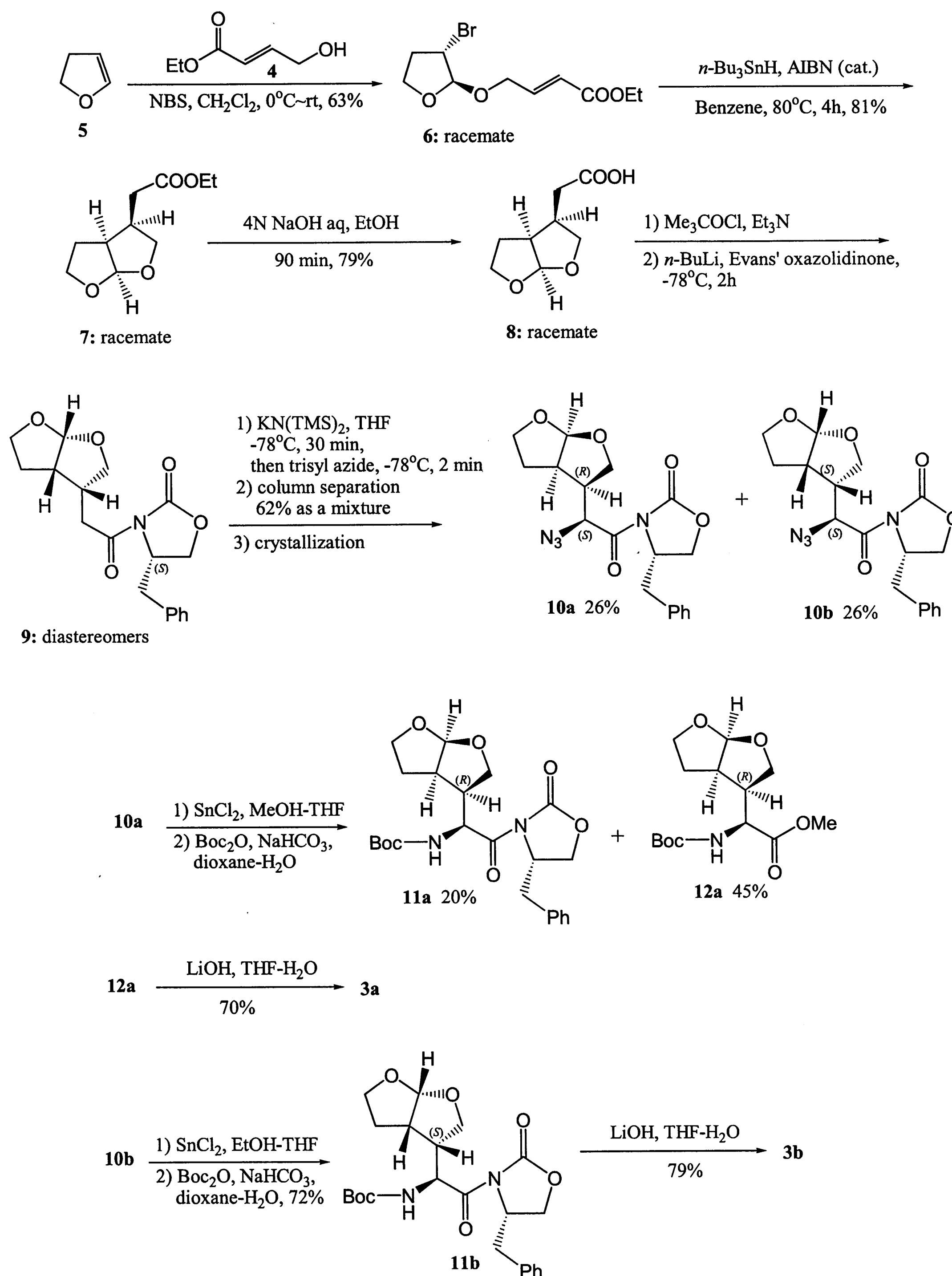
precursor, which in turn was proposed to be synthesized from (*E*)-bromoether **6** or (*Z*)-bromoether **13**. (*E*)-Allyl alcohol **4** was obtained from the fumaric acid monoethyl ester by the selective reduction of carboxylic acid.[8]

The synthesis of **3a** and **3b** is shown in Scheme 1. Treatment of commercially available 2,3-dihydrofuran **5** with 1 equiv. of *N*-bromosuccinimide (NBS) and ethyl (*E*)-4-hydroxy-2-butenoate **4** in CH_2Cl_2 at 0°C to room temperature for 1 h, furnished the bromoether **6** in 63% yield after silica gel chromatography. Reaction of **6** with tri-*n*-butyl tin hydride in refluxing benzene in the presence of a catalytic amount of α,α′-azobisisobutyronitrile (AIBN) gave the corresponding 5-*exo* radical cyclization product **7** in 81% yield after column chromatographic purification. In this step, three continuous asymmetric centers of the carbon atoms were spontaneously configured in the desired alignment. Hydrolysis of bicyclic ester **7** in a mixture of aqueous 4N NaOH and EtOH provided the corresponding *endo*-carboxylic acid **8** in 79% yield.



Scheme 1. Synthetic route to L-bis-tetrahydrofuranylglycines **3a** and **3b**.

Alternatively, (*Z*)-alkene **13**, prepared from 2,3-dihydrofuran **5** and monoacetate **12** by the same procedure as that for bromo-ether **6**, was subjected to the radical cyclization reaction to yield bicyclic acetate **14** in 85% after column separation. Compound **14** was hydrolyzed by the treatment of aqueous 4N NaOH, and the resulting alcohol was subjected to Jones oxidation to give the corresponding carboxylic acid **8** in 78% for two steps (Scheme 2).

We planned to separate both *endo*-enantiomers through coupling to Evans' oxazolidinone[9] and to perform chiral azidation of these two isomers separately. The carboxylic acid **8** was coupled to (*S*)-4-benzyl-2-oxazolidinone using a mixed anhydride method.[9] Unexpectedly, the oxazolidinones **9** could not be separated through silica gel column chromatography. Hence, we submitted the mixture to enantioselective introduction of the azide group. Azidation using the standard Evans protocol afforded a mixture of diastereomers (**10a** and **10b**) in 62% yield after column chromatography. Fortunately, one of the diastereomers could be crystallized out of an ethyl acetate solution through slow diffusion of *n*-hexane. The mother liquor was subjected to chromatographic purification again to separate the two diastereomers. The diastereomeric azides also showed a characteristic difference in their melting points. The stereochemistry of the crystallized diastereomer **10a**[10] was determined to be (*R*)-configuration at C-3 by single-crystal X-ray diffraction analysis (Fig. 3). However, efforts to crystallize the other diastereomer **10b**[11] failed.

Both azides **10a** and **10b** were reduced using $SnCl_2$ in MeOH–THF and EtOH–THF, respectively, and subsequently were protected as *N*-Boc derivatives (**11a** and **11b**). Interestingly, there was concomitant transesterification in the case of the (*R*)-isomer as this was largely insoluble in MeOH–THF and hence necessitated the use of an excess of MeOH and a small amount of $CHCl_3$. After 3 h reduction, and subsequent overnight reaction with Boc_2O, a 45% yield of transesterified product **12a** and 20% of the *N*-Boc protected oxazolidinone **11a** were obtained. The use of large amounts of $CHCl_3$ to dissolve the azide retarded the reduction and led to the recovery of 18% of the starting material. This transesterification was also observed in the other diastereomer **11b** with increased reaction time of $SnCl_2$ reduction. However, the reaction could be avoided in **10b** with the use EtOH–THF. The absolute stereochemistry of isomer **11b** was determined to be (*S*)-configuration at C-3 by X-ray analysis (data not shown). The C-terminal of these amino acids was then deprotected through hydrolysis of the corresponding methyl ester **12a** and oxazolidinone **11b** using LiOH. Thus, we were able to obtain both the *threo*-**3a**[12] and *erythro*-**3b**[13] forms of L-bis-tetrahydrofuranylglycines in an optically pure form.

In conclusion, the novel amino acids were synthesized efficiently and the enantiomers were easily purified by crystallization. The importance and usefulness of these amino acids in medicinal chemistry will be shown by incorporation to the KNI series of HIV-1 protease inhibitors.[7c] Further studies on the structural modification as well as their SAR are actively under way.

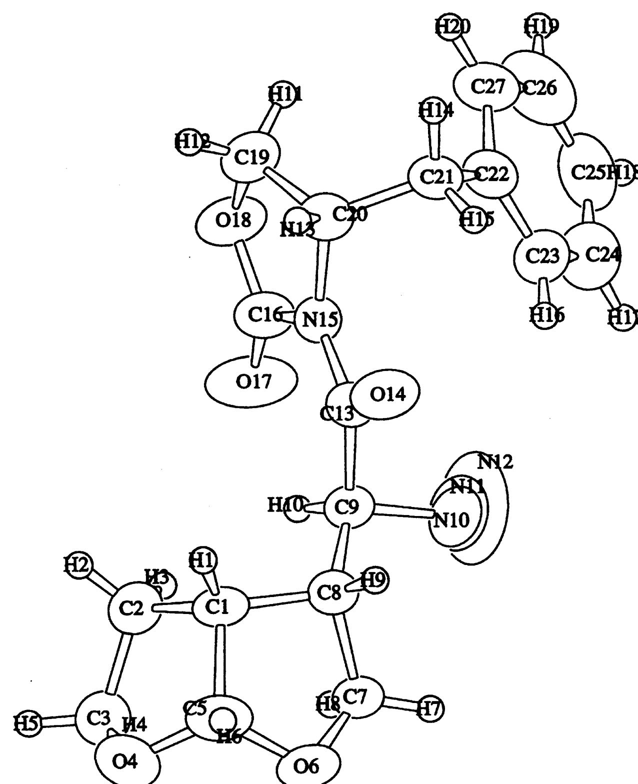
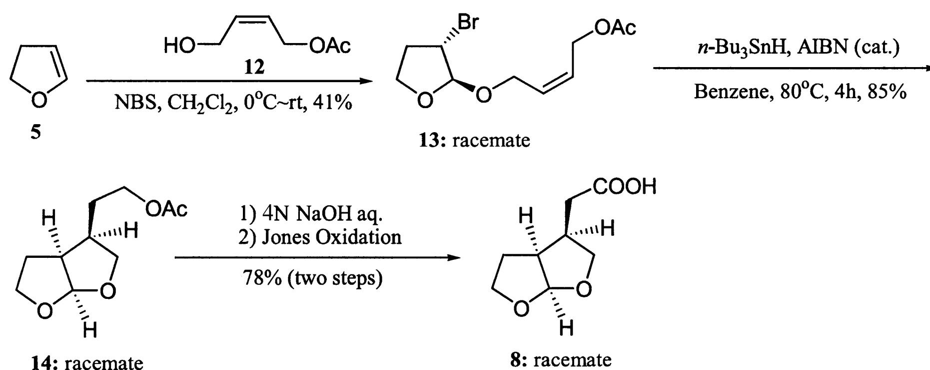


Figure 3. X-Ray crystal structure of **10a**.



Scheme 2. Alternative route to **8**.

Acknowledgements

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11. Selected data for *tert*-butyl-*N*-{(1*S*)-1-[(3*S*,3a*S*,6a*R*) perhydrofuro [2,3-*b*] furan-3-yl]-2-[(4*S*)-4-benzyl-2-oxo-1, 3-oxazolan-3-yl]-2-oxoethyl} carbamate (**10b**): mp 91°C. ^{1}H NMR (400 MHz/CDCl$_3$) δ 7.38–7.21 (m, 5H, aromatic protons), 5.79 (d, 1H, $J=4.8$ Hz), 5.19 (d, 1H, $J=11.0$ Hz), 4.75–4.69 (m, 1H), 4.31–4.24 (m, 2H), 4.02–3.89 (m, 2H), 3.84 (dd, 1H, $J=7.7$, 7.5 Hz), 3.59 (dd, 1H, $J=8.2$ Hz), 3.30 (dd, 1H, $J=3.3$, 13.6 Hz), 3.10–3.04 (m, 1H), 3.03–2.96 (m, 1H), 2.87 (dd, 1H, $J=9.0$, 13.6 Hz), 2.11–2.00 (m, 2H). HR-MS (EI$^+$) calcd for $C_{18}H_{20}N_4O_5$ (M$^+$) 372.1434, found m/z 372.1437. $[\alpha]_D=+37.73$ ($c=0.8$ in THF).
12. Selected data for (2*S*)-2-[(3*R*,3a*R*,6a*S*) perhydrofuro [2,3-*b*] furan-3-yl]-2-[(*tert*-butoxycarbonyl) amino] ethanoic acid (**3a**): syrup, ^{1}H NMR (300 MHz/CDCl$_3$) δ 6.67 (broad s, 1H), 5.74 (d, 1H, $J=5.0$ Hz), 5.38 (d, 1H, $J=9.0$ Hz), 4.40–4.36 (m, 1H), 4.10–3.80 (m, 4H), 2.94–2.82 (m, 1H), 2.12–2.07 (m, 2H), 1.44 (s, 9H). HR-MS (FAB$^+$) calcd for $C_{13}H_{21}NO_6$ (M$^+$) 287.1369, found m/z 310.1263 (M$^+$+Na). $[\alpha]_D=-3.06$ ($c=0.6$ in CHCl$_3$).
13. Selected data for (2*S*)-2-[(3*S*,3a*S*,6a*R*) perhydrofuro [2,3-*b*] furan-3-yl]-2-[(*tert*-butoxycarbonyl) amino] ethanoic acid (**3b**): syrup, ^{1}H NMR (300 MHz/CDCl$_3$) δ 6.44 (broad s, 1H), 5.72 (d, 1H, $J=4.8$ Hz), 5.21 (d, 1H, $J=8.1$ Hz), 4.30–4.15 (m, 1H), 4.03–3.85 (m, 3H), 3.76 (dd, 1H, $J=9.5$ Hz) 2.991–2.87 (broad s, 1H), 2.59–2.52 (m, 1H), 1.97 (broad s, 2H), 1.45 (s, 9H). HR-MS (FAB$^+$) calcd for $C_{13}H_{21}NO_6$ (M$^+$) 287.1369, found m/z 310.1261 (M$^+$+Na). $[\alpha]_D=-5.29$ ($c=0.9$ in CHCl$_3$).