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ASYMMETRIC SYNTHESIS OF *CIS*- AND *TRANS*-γ-LACTONES USEFUL IN HIV-1 PROTEASE INHIBITOR SYNTHESIS

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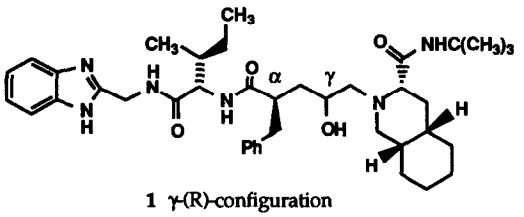
Abstract: Iodolactones **5** and **11** have been prepared in asymmetric form from a common precursor carboxylic acid **4**. These iodolactones were then transformed into lactones **7** and **12**, respectively. Lactones **7** and **12** were converted to potent HIV-1 protease inhibitors **1** and **2**, respectively, by a five-step sequence. Lactones **7** and **12** were also prepared in a 1:1 ratio from epoxide **14**.

Acquired Immune Deficiency Syndrome (AIDS), a disease of global significance, is believed to be caused by the Human Immunodeficiency Virus (HIV). Mutagenesis studies have shown that mutants which lack HIV-protease activity are non-infectious, lending credence to the hypothesis that inhibition of the protease will stop proliferation of the virus.[1] Numerous research groups around the world have embarked on the discovery and development of potential therapeutic agents to inhibit the HIV-protease function.[2] We have previously reported our results on the synthesis and biological evaluation of several series of HIV-1 protease inhibitors.[3] Herein, we report improved asymmetric syntheses of the two most potent inhibitors reported earlier.[3c]

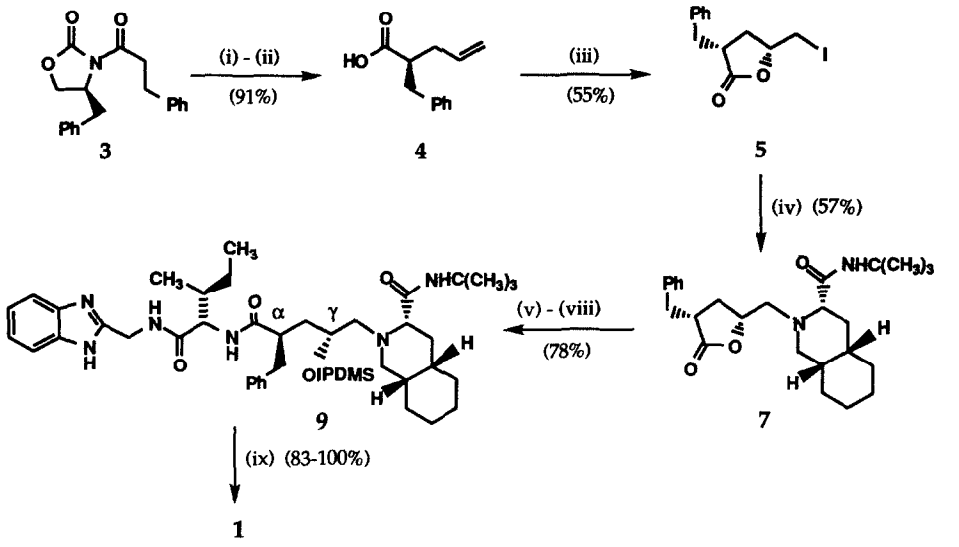


1 γ-(R)-configuration
2 γ-(S)-configuration

In a previous study[3c] we disclosed inhibitors **1** and **2**, and described their biological activities against the free enzyme, and against the virus in a cell assay. Compounds **1** and **2** are diastereomerically related, differing only in the configuration of the hydroxyl-bearing carbon atom. The alcohol was prepared by a non-stereospecific reduction of the corresponding ketone resulting in a mixture of diastereomers, the separation of which was tedious on small scale and very difficult on large scale. Additionally, the original synthesis contained a step which required stoichiometric osmium tetraoxide. Because we required gram quantities of each diastereoisomer **1** and **2** for additional biological evaluation, we developed an asymmetric synthesis amenable to the scale-up of either isomer.

In considering the syntheses of **1** and **2** in a retrosynthetic fashion, we envisioned these compounds deriving from lactones **7** and **12**, respectively.[4,5] The syntheses of lactones **7** and **12**, and their subsequent transformation to **1** and **2** are shown in **Schemes 1** and **2**.

Scheme 1.[a]



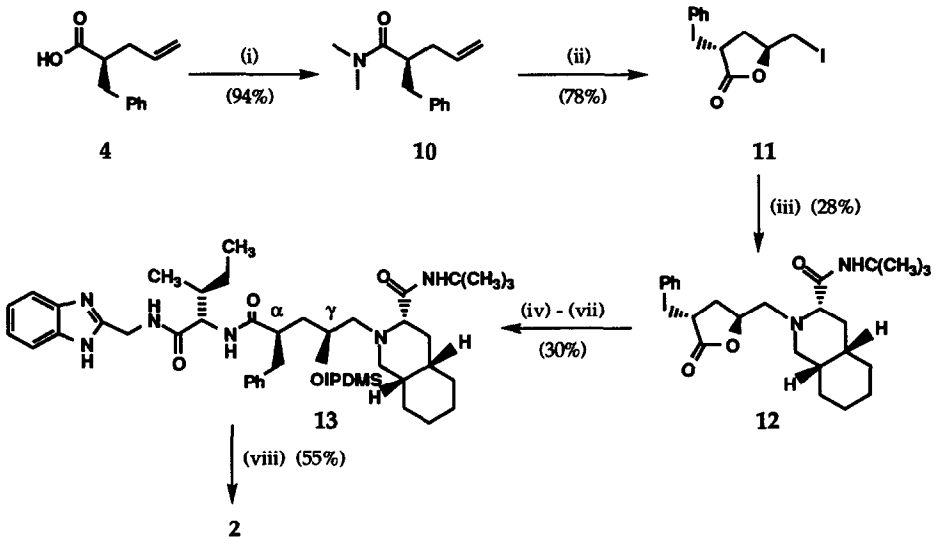
[a] (i) NaHMDS, THF; allyl iodide, (ii) LiOH, H_2O_2, THF, H_2O, (iii) KI, I_2, $KHCO_3$, THF, H_2O (iv) **6**, $(i\text{-Pr})_2EtN$, DMF, (v) NaOH, H_2O, (vi) IPDMSCl, NEt_3, DMAP, CH_2Cl_2, (vii) HOAc, THF, H_2O, acetone, (viii) **8**, BOP Reagent, $(i\text{-Pr})_2EtN$, CH_2Cl_2, (ix) TBAF, THF, H_2O (83%); or HOAc, H_2O (100%)

Oxazolidinone **3**[3c] was deprotonated with sodium bis(trimethylsilyl)amide (NaHMDS) in tetrahydrofuran (THF) and then allowed to react[6] with allyl iodide (**Scheme 1**).[7] The resulting alkylation product, obtained as a single diastereoisomer, was hydrolyzed with lithium hydroxide (LiOH) and hydrogen peroxide (H_2O_2) to give carboxylic acid **4** (91%). Carboxylic acid **4** was subjected to iodolactonization conditions[8] to give lactone **5** in 55% yield; the minor *trans*-isomer was removed by chromatography. That the major isomer bears a *cis*-relationship was readily verified by comparison of its ^1H NMR spectrum to literature examples.[8c] Iodolactone **5** was allowed to react with [3S-(3α,4aβ,8aβ)]-*N*-(1,1-dimethylethyl)decahydro-3-isoquinolinecarboxamide (**6**)[9] in hot dimethylformamide (DMF) in the presence of *N*,*N*-diisopropylethylamine (Hünig's base) to provide lactone **7** (57%) as a single diastereoisomer. Following procedures described earlier,[5] we hydrolyzed lactone **7** with sodium hydroxide (NaOH) and protected the resulting hydroxy-acid with chlorodimethylisopropylsilane (IPDMSCl). The resulting silylester-silylether was selectively hydrolyzed with dilute acetic acid (HOAc) to provide a carboxylic acid which was coupled with [S-(R*,R*)]-2-amino-*N*-(1*H*-benzimidazol-2-ylmethyl)-3-methylpentamide tris(trifluoroacetate) (**8**)[3c] by reaction with benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (BOP reagent)[10] in the presence of Hünig's base to give silylether **9** in 78%

overall yield from **7**. Deprotection of the silylether could be affected by reaction with tetrabutylammonium fluoride (TBAF) in wet THF (83%), or by extended hydrolysis with HOAc in water (100%) to give **1**.

The synthesis of **2** (**Scheme 2**) began with carboxylic acid **4** which was transformed into amide **10** in 94% yield using standard methodology. Amide **10** was then subjected to conditions described earlier,[11] namely iodine in wet 1,2-dimethoxyethane (DME), to provide iodolactone **11** in 78% yield; the minor *cis*-isomer was removed by chromatography. The *trans*-stereochemistry of **11** was confirmed by comparison of its ^{1}H NMR spectrum to literature values.[8c,11] Following the general synthetic scheme above, we reacted lactone **11** with amine **6**[9] to give lactone **12** (28%). Lactone **12** was then hydrolyzed (NaOH), protected (IPDMSCl), hydrolyzed (HOAc, THF, acetone, water), and coupled to amine **8**[3c] to provide silylether **13** in 30% overall yield from **12**. Final deprotection of the silylether **13** with TBAF in wet THF gave **2** (55%).

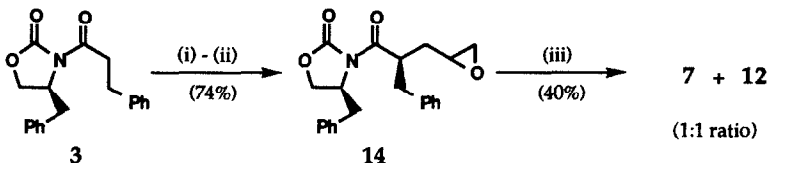
Scheme 2. [a]



[a] (i) $Me_2NH{\bullet}HCl$, BOP Reagent, (*i*-Pr)$_2$EtN , HOBT, CH_2Cl_2, (ii) I_2, H_2O, DME, (iii) **6**, (*i*-Pr)$_2$EtN , DMF (iv) NaOH, H_2O, (v) IPDMSCl, NEt_3, DMAP,CH_2Cl_2, (vi) HOAc, THF, H_2O, acetone, (vii) **8**, (*i*-Pr)$_2$EtN BOP Reagent,CH_2Cl_2, (viii) TBAF, THF, H_2O

Lastly, an alternative synthesis of lactones **7** and **12** was discovered and is shown in **Scheme 3**. The same alkylation product of **3** with allyl iodide was allowed to react with 3-chloroperoxybenzoic acid (*m*-CPBA) to give epoxides **14** (74%) as a 1:1 mixture of diastereoisomers. Attempts to improve this ratio in either direction were not investigated. The mixture of isomers **14** was allowed to react with amine **6**[9] in hot ethanol to give lactones **7** and **12** in 40% yield. Lactones **7** and **12** could be readily separated by flash chromatography and then transformed into **1** and **2**, respectively, as described above.

Scheme 3.[a]



[a] (i) NaHMDS, THF; allyl iodide, (ii) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, (iii) **6**, ethanol

Conclusions.

We have presented new asymmetric syntheses of two of our more potent HIV-1 protease inhibitors. The synthesis of each diastereoisomer **1** and **2** originates from a common carboxylic acid **4**, and establishes the alcohol stereochemistry by a stereospecific iodolactonization reaction. The synthesis permits the recovery of the oxazolidinone chiral auxillary, and does not require OsO_4 as was previously the case.[3c] Further, iodolactones **5** and **11**, and epoxide **14** may serve as useful synthons for future protease inhibitor synthesis.

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