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Nonpeptidal P_2 Ligands for HIV Protease Inhibitors: Structure-Based Design, Synthesis, and Biological Evaluation

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Design and synthesis of nonpeptidal bis-tetrahydrofuran ligands based upon the X-ray crystal structure of the HIV-1 protease−inhibitor complex **1** led to replacement of two amide bonds and a 10π-aromatic system of Ro 31-8959 class of HIV protease inhibitors. Detailed structure−activity studies have now established that the position of ring oxygens, ring size, and stereochemistry are all crucial to potency. Of particular interest, compound **49** with (3*S*,3a*S*,-6a*S*)-bis-Thf is the most potent inhibitor (IC_{50} value 1.8 ± 0.2 nM; CIC_{95} value 46 ± 4 nM) in this series. The X-ray structure of protein−inhibitor complex **49** has provided insight into the ligand-binding site interactions. As it turned out, both oxygens in the bis-Thf ligands are involved in hydrogen-bonding interactions with Asp 29 and Asp 30 NH present in the S_2 subsite of HIV-1 protease. Stereoselective routes have been developed to obtain these novel ligands in optically pure form.

The understanding of protein−ligand interactions has been greatly advanced by the unprecedented advances in molecular biology and modern spectroscopic and X-ray crystallographic techniques. Concurrent to these remarkable achievements, structure-based design and synthesis of molecular probes for biologically important peptides and proteins has become a subject of great interest in contemporary bioorganic and medicinal chemistry.[1] Because of the therapeutic potential for the treatment of AIDS, the structure-based design and synthesis of HIV protease inhibitors perhaps has attracted the most attention.[2] An impressive number of X-ray crystal sturctures of the protein−ligand complexes of HIV protease have been resolved to obtain molecular insight into the ligand-binding site interaction.[3] A number of therapeutically promising HIV protease inhibitors have already resulted from structure-based design strategies.[4,5]

We recently reported a number of nonpeptidal high-affinity ligands for the HIV protease substrate-binding site.[6−10] These ligands are designed based upon various available three-dimensional structures of the protein−ligand complexes. The key feature in our ligand design is the incorporation of a conformationally constrained functionality that replaces a peptide bond and mimics the biological mode of action. As exemplified, a stereochemically defined tetrahydrofuran ring can serve as a surrogate (inhibitor **2**) for the asparagine side chain of Ro 31-8959-based HIV protease inhibitors.[7] An examination of the X-ray crystal structure of inhibitor Ro 31-8959 bound to HIV protease led us to further speculate that a fused bicyclic ligand with oxygens positioned properly could effectively hydrogen bond to the NH of the Asp 29 and 30 residues corresponding to the quinaldic amide−asparagine amide fragment of the Ro 31-8959 inhibitor.[5a] Furthermore, we presumed that due to considerable rotational freedom about the four bonds connecting the two carbonyls involved, such constrained ligands may provide additional gains in binding energy and thereby offset the loss of the P_3 hydrophobic binding of the quinoline ring. Indeed, as described[8] in a recent communication, the structure-based design of a stereochemically defined fused bicyclic tetrahydrofuran effectively replaced two amide bonds and a 10π-aromatic system of **1** (Ro 31-8959).[5a] Subsequently, structure−activity studies established that the position of ring oxygens, ring size, and stereochemistry are all important to effective binding. In this article, we report the structure-based design, synthesis, and structure−activity studies of a new class of protease inhibitors incorporating novel nonpeptidal ligands which interact specifically at the HIV protease substrate-binding site.

Chemistry

The enantioselective synthesis of bis-tetrahydrofuran (bis-Thf) **7** is illustrated in Scheme 1. Allylation of 3(*R*)-diethyl malate (**3**) according to Seebach's procedure[11] afforded the desired diasteoreomer **4** as the major (selectivity 12:1) product after distillation (85% yield). The above mixture was reduced by LAH in diethyl ether, and the resulting triol was treated with a catalytic amount of *p*-TsOH in acetone to provide the isopropylidene derivative **5** (74% yield). Swern oxidation of **5** provided the aldehyde which upon treatment with camphorsulfonic acid (CSA) in methanol furnished the methyl acetal **6** as a mixture (ratio 4:1) in 50% yield. The acetal mixture **6** was converted to bis-Thf ligand **7** by the following reaction sequence: (1) ozonolytic cleavage of the terminal olefin, (2) $NaBH_4$ reduction of the resulting aldehyde in ethanol at 0 °C, and (3) exposure of the corresponding alcohol with CSA in methylene chloride at 23 °C for 12 h (74% from **6**). The mixed acetal **6** was also converted to the bicyclic ligand **8** by

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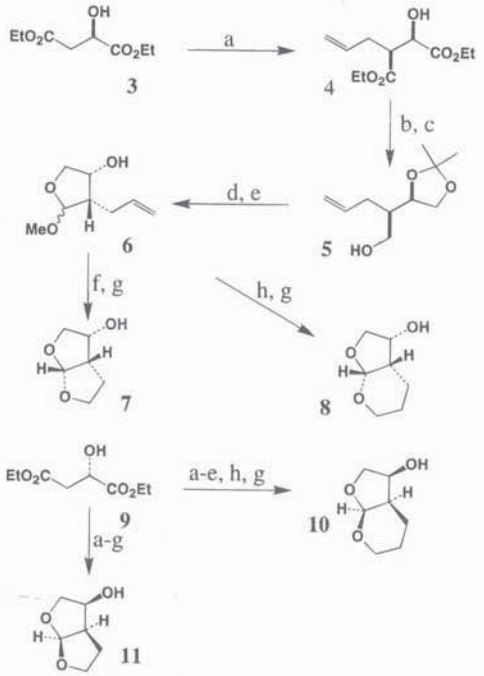
Scheme 1. Enantioselective Synthesis of the Bicyclic Ligands[a]

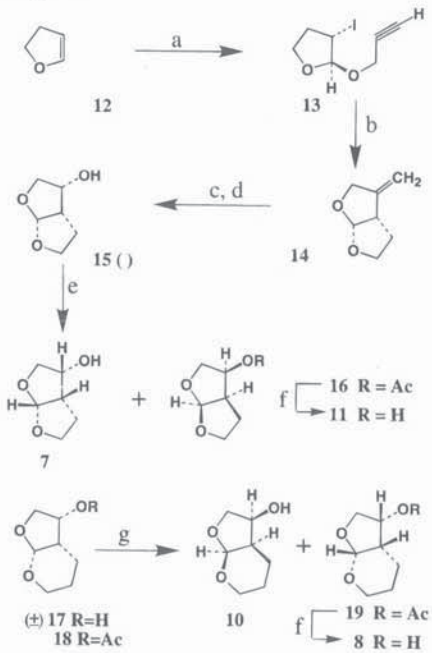


[a] Key: (a) LDA, CH=CHCH$_2$Br; (b) LAH, Et$_2$O; (c) acetone, pTsOH; (d) Swern oxidation; (e) CSA, MeOH; (f) ozonolysis then NaBH$_4$; (g) CSA, CH$_2$Cl$_2$; (h) 9-BBN, THF, aqueous NaOH, H$_2$O$_2$.

hydroboration with 9-BBN followed by reaction of the resulting alcohol with CSA in methylene chloride. Similarly, enantiomeric bicyclic ligands **10** and **11** were synthesized, starting from optically pure 3(*S*)-diethyl malate (**9**) following the sequence of reactions described above.

Alternatively, racemic synthesis of these ligands followed by their enzymatic resolution provided an easy access to these ligands in optically active form.[12] As shown in Scheme 2, reaction of commercial 2,3-dihydrofuran (**12**) with *N*-iodosuccinimide and propargyl alcohol in methylene chloride at 0−23 °C for 3 h resulted in the iodo ether **13** in excellent yields (91−95%). Radical cyclization of the iodo ether **13** with tributyltin hydride[13] in refluxing toluene in the presence of a catalytic amount of AIBN afforded the bicyclic acetal **14** in good yield (70−80%) after silica gel chromatography. This radical cyclization was more conveniently effected with sodium borohydride reduction in the presence of a catalytic amount (10 mol %) of cobaloxime (Scheme 2)[14] in 95% ethanol at 65 °C for 3 h affording the bicyclic acetal **14** in comparable yield (70−75%). Ozonolytic cleavage followed by the reduction of the resulting ketone with sodium borohydride in ethanol at −15 °C furnished the racemic endo alcohol **15** (74−78%) after chromatography.[16] The optical resolution of the racemic alcohol **15** was carried out efficiently by exposure to Amano lipase[17]-mediated acylation as well as the hydrolysis of the corresponding acetate. Thus, acylation of **15** with immobilized[18] lipase PS-30 (25% by weight with respect to lipase PS30) in the presence of acetic anhydride in dimethoxyethane at 23 °C for 3 h afforded the unacylated alcohol **7** (42% yield) and the acylated alcohol **16** (45% yield) which were separated by silica gel chromatography. The optical purity of the

Scheme 2. Synthesis and Optical Resolution of the Bicyclic Ligands[a]



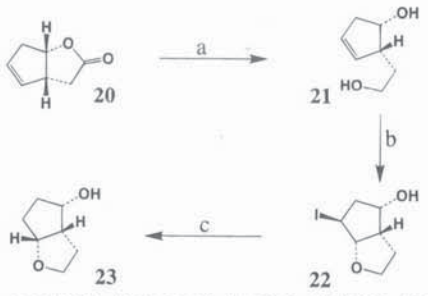
[a] Key: (a) *N*-iodosuccinimide, propargyl alcohol, CH$_2$Cl$_2$, 0−23 °C; (b) cobaloxime (cat), NaBH$_4$, EtOH; (c) O$_3$, CH$_2$Cl$_2$−MeOH, Me$_2$S, −78−23 °C; (d) NaBH$_4$, EtOH, −15 °C; (e) immobilized lipase 30, Ac$_2$O, DME, 23 °C; (f) aqueous LiOH, THF−H$_2$O; (g) immobilized lipase 30, pH 7 buffer, 23 °C.

alcohol **7** (95% ee, $[\alpha]^{23}_D$ −11.9°, MeOH) was determined by formation of Mosher ester and ^{19}F-NMR analysis.[19] The acylated alcohol **16** was hydrolyzed by treatment with aqueous lithium hydroxide to provide optically active **11** (87% ee, $[\alpha]^{23}_D$ +11.7°, MeOH). Similarly, racemic **17** was synthesized utilizing dihydropyran as the starting material. The resolution of **17** was effected by formation of the corresponding acetate **18** followed by the enzymatic hydrolysis with immobilized lipase PS-30 in phosphate buffer (pH = 7.0) at 23 °C for 24 h. The hydrolyzed alcohol **10** (yield 34%, 90% ee) and the acetate **19** (40%) were separated by silica gel chromatography. Ester hydrolysis of **19** furnished the alcohol **8** in optically active form (94% ee). The represented absolute configurations of the resolved alcohols were assigned based on comparison of their optical rotation with the ligands synthesized utilizing 3(*S*)- and 3(*R*)-diethyl malates as described above.

Enantiomerically pure fused tetrahydrofuran **23** was synthesized from commercial *cis*-(−)-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one (**20**) according to Scheme 3. As shown, reduction of **20** with LAH in tetrahydrofuran at 23 °C afforded the diol **21** (isolated yield 96%). Treatment of the diol **21** with iodine and potassium iodide in methylene chloride at 23 °C furnished the iodo ether **22**.[20] Radical dehalogenation of the iodine with tributyltin hydride in refluxing dioxane in the presence of a catalytic amount of AIBN provided the bicyclic ligand **23** with defined absolute configuration.

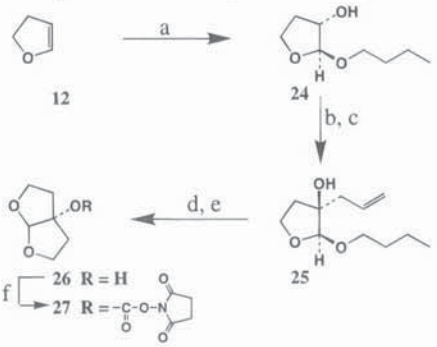
Synthesis of symmetric bicyclic ligand **26** is outlined in Scheme 4. Reaction of 2,3-dihydrofuran (**12**) with mCPBA in 1-butanol at −15−0 °C for 2 h afforded the alcohol **24** after distillation (65%). Oxidation of **24** with

Scheme 3. Enantioselective Synthesis of the Bicyclic Ligands[a]



[a] Key: (a) $LiAlH_4$, THF, 23 °C; (b) KI, I_2, $NaHCO_3$, CH_2Cl_2, 23 °C; (c) nBu_3SnH, AIBN, dioxane, reflux.

Scheme 4. Synthesis of the Symmetric Bicyclic Ligand[a]



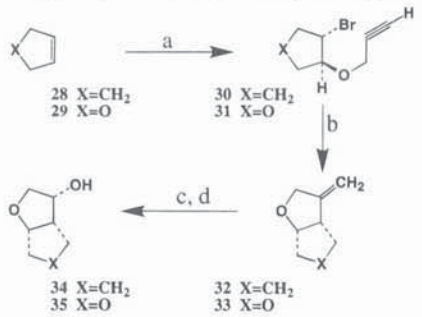
[a] Key: (a) mCPBA, *n*-butanol, 0 °C; (b) Pyr·SO_3, DMSO, Et_3N; (c) allylmagnesium bromide, Et_2O, 0–23 °C; (d) O_3, CH_2Cl_2–MeOH, −78–0 °C, then $NaBH_4$, EtOH, 0 °C; (e) pTsOH, CH_2Cl_2, 23 °C; (f) $COCl_2$, pyridine, $PhCH_3$, then *N*-hydroxysuccinimide, CH_3CN, Et_3N, 23 °C.

pyridine·SO_3 complex in methylene chloride gave the corresponding ketone which was reacted with allylmagnesium bromide in diethyl ether at 0–23 °C for 4 h to furnish the alcohol **25**.[21] Ozonolysis of the terminal olefin followed by reduction of the ozonide with sodium borohydride in ethanol at 0 °C provided the corresponding alcohol which was treated with *p*-TsOH in methylene chloride to afford the symmetric ligand **26**. Reaction of **26** with phosgene and pyridine in toluene followed by reaction with *N*-hydroxysuccinimide in acetonitrile furnished the mixed active carbonate **27** after silica gel chromatography.[22]

Racemic bicyclic ligands **34** and **35** were prepared (Scheme 5) utilizing a similar synthetic route as described for racemic **15**. Reaction of cyclopentene with *N*-bromosuccinimide and propargyl alcohol provided good yield of the corresponding bromo ether **30** (yield 72%). However, the reaction with 2,5-dihydrofuran proceeded with modest yield (35%) of the corresponding bromo ether **31**. Tributyltin hydride-mediated radical cyclization of **30** and **31** provided the bicyclic olefins **32** and **33** which were converted to racemic bicyclic ligands **34** and **35** for structure–activity studies.

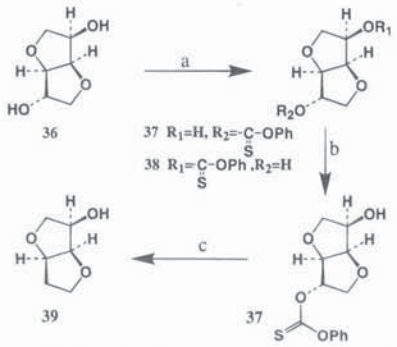
Bicyclic ligand **39** with oxygens in a vicinal relationship was synthesized in enantiomerically pure form starting from commercially available 1,4:3,6-dianhydro-D-sorbitol (**36**) (Scheme 6). Treatment of **36** with commercial chlorothionoformate and triethylamine in methylene chloride at 23 °C for 4 h afforded a mixture (2:1) of thionocarbonates **37** and **38**. The isomers were separated on silica gel by column chromatography, and

Scheme 5. Synthesis of Racemic Bicyclic Ligands[a]



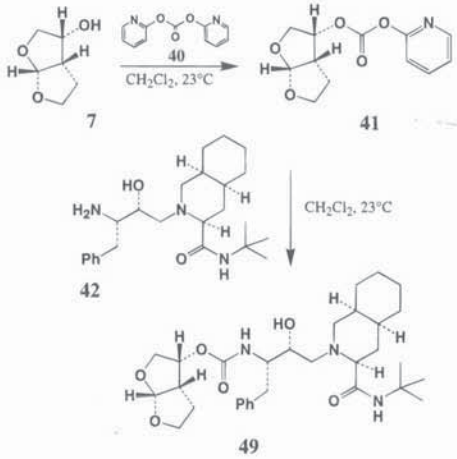
[a] Key: (a) *N*-bromosuccinimide, propargyl alcohol, CH_2Cl_2, 0–2? °C; (b) nBu_3SnH, AIBN, PhH, reflux; (c) O_3, CH_2Cl_2–MeOH, Me_2S, −78–23 °C; (d) $NaBH_4$, EtOH, −15 °C.

Scheme 6. Synthesis of the Bicyclic Ligand[a]



[a] Key: (a) PhOC(S)Cl, Et_3N, CH_2Cl_2; (b) separated by silica gel chromatography; (c) nBu_3SnH, AIBN, PhMe, reflux.

Scheme 7



the major isomer **37** was exposed to the radical deoxygenation[23] conditions to provide the ligand **39**.

Synthesis of various inhibitors with bicyclic ethers as the P_2 ligands and decahydroisoquinolinecarboxamide as the P_1' ligand was carried out according to Scheme 7. The previously described[6,7] hydroxyethylamine isostere **42** was transformed into the various target inhibitors listed in Tables 1 and 2 by an alkoxycarbonylation of the respective alcohol.[24] For example, reaction of bis-Thf ligand **7** with dipyridyl carbonate (**40**) and triethylamine in methylene chloride afforded the active carbonate **41** after chromatography. Reaction of the mixed carbonate **41** with amine **42** in methylene chloride

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