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SYNTHESIS AND OPTICAL RESOLUTION OF HIGH AFFINITY P_2-LIGANDS FOR HIV-1 PROTEASE INHIBITORS

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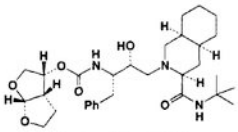
Abstract

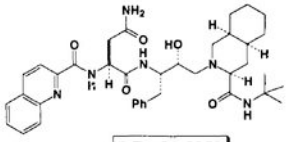
Racemic bis-tetrahydrofuran ligand **6** was efficiently synthesized utilizing catalytic cobaloxime **10** mediated radical cyclization as the key step. Optical resolution of the racemic alcohol with immobilized-Amano lipase, afforded optically pure ligands.

Significant advances have been made in the design and synthesis of non peptidal ligands for the HIV protease substrate binding site. We recently reported the structure-based design of bistetrahydrofuran ligands that can effectively replace two amide bonds and a 10π-aromatic system of the present clinical candidate **2** (Ro 31–8959). These ligands were synthesized in optically pure form utilizing 3(S)- or 3(R)-malic acid as the starting material. Since we required both enantiomers for further structure-activity studies, we became interested in devising a more efficient route to these ligands. In this report, we describe an efficient synthetic route to these ligands in racemic form and their enzymatic resolution, providing optically active ligands with high enantiomeric excess.



1 L-739,594

IC_{50} [HIV-1] = 1.8±0.2 nM (n=6)
CIC_{95} = 46±4 nM (n=4)



2 Ro 31-8959

IC_{50} [HIV-1] = 0.23±0.1 nM (n=3)
CIC_{95} = 22±7 nM (n=10)

The synthesis of the racemic ligands is illustrated in Scheme I. As shown, treatment of 2,3-dihydrofuran **3** with 1.2 equiv, of N-iodosuccinimide and 2 equiv, of propargyl alcohol in methylene chloride at 0° to 23°C for 3 h, furnished the iodo-ether **4** in high yields (91–95%). Reaction of the iodo-ether **4** with tri-n-butyl tin hydride in refluxing toluene in the presence of a catalytic amount of AIBN provided the corresponding radical cyclization product 5 in 77% yield after silica gel chromatography. Alternatively, radical cyclization utilizing a catalytic amount (10 mole %) cobaloxime **10** in 95% ethanol at 65°C for 3 h in the presence of 1.2 equiv, sodium borohydride afforded **5** in 72% yield (8 g scale) after silica gel chromatography. This is an operationally simple and potentially useful procedure for large scale synthesis. Interestingly, cobaloxime mediated reduction of the corresponding bromo-ether of **4** however, provided only 40% yield of **5**. The ozonolytic cleavage of the olefin **5** afforded the corresponding ketone which was reduced with sodium borohydride in ethanol at −15°C to furnish the endo alcohol **6** (74–78%) after purification by silica gel

chromatography. The racemic alcohol **6** was then exposed to Amano lipase mediated acylation as well as the hydrolysis of the corresponding acetate **11**. Thus, acylation of 6 was accomplished with immobilized lipase PS30 (25% by weight with respect to lipase PS30) in the presence of 3 equiv, of acetic anhydride in dimethoxyethane (DME) at 23°C. The reaction was monitored by TLC (50% ethyl acetate/hexane) and ^{1}H NMR (by withdrawal of a small aliquot and workup) until a 50% conversion was reached (about 3 h). After this period, the reaction mixture was simply filtered and the filtrate was evaporated. The resulting residue was chromatographed over silica gel to furnish the unacylated alcohol **7** (42% yield) and the acylated alcohol **8** (45% yield) after further workup with 5% aqueous sodium carbonate to remove acetic anhydride. The control experiment without the enzyme verified that the non-enzymatic acylation reaction is extremely slow (only trace amount of acylation after 48 h). Also, acylation with acetic anhydride and 25% by weight of lipase PS30 at 23°C after 24 h provided only trace amount of acylated product. The optical purity of the alcohol **7** (95% ee, α_D23° −11.9°, MeOH) was obtained by formation of Mosher ester and ^{19}FNMR analysis. To determine the optical purity of the acylated alcohol **8**, the ester was hydrolyzed by treatment with aqueous lithium hydroxide and the resulting alcohol was analyzed as described above (87% ee, α_D23° +11.7 °, MeOH).

Alternatively, the enzymatic hydrolysis of the racemic acetate **11**, obtained by acetylation with 1.5 equiv, of acetic anhydride and 3 equiv, of triethylamine in methylene chloride (80%), has also resulted in optically active ligands with high enantiomeric excess. Thus, hydrolysis of **11** with immobilized lipase PS30 (25% by weight with respect to lipase PS30) in phosphate buffer (pH=7.0) at 23°C for 24 h furnished the hydrolyzed alcohol **9** (yield 34%, 90% ee) and the acetate **12** (40%). Reaction of **12** with 2 equiv, of methyllithium in THF at 0°to 23°C for 3 h resulted in alcohol **7** (82% yield, 94% ee). The represented absolute configuration of the resolved alcohols **7** and **9** were assigned based on comparison of their optical rotation with the ligands synthesized previously with defined absolute configuration utilizing 3(S)- and 3(R)-diethyl malates. Also, the alcohol 7 has been converted to HIV protease inhibitor I as described previously.

Thus, efficient synthesis of the racemic alcohol **6** and its resolution by immobilized Amano lipase PS 30, provided an easy access to optically active high affinity ligands **7** and **9** in high enantiomeric purity. The resolution process is convenient, economical and simple to carry out. Further application of this protocol is currently underway in our laboratory. The following procedures are illustrative.

Preparation of Immobilized Amano Lipase 30 (modified procedure):

Commercially available 4 g of celite 521 (Aldrich) was loaded on a buchner funnel and washed successively with 50 mL of deionized water and 50 mL of 0.05 N phosphate buffer (pH = 7.0; Fisher Scientific). The washed celite was then added to a suspension of I g of Amano lipase 30 in 20 mL of 0.05 N phosphate buffer. The resulting slurry was spread on a glass dish and allowed to dry in the air at 23°C for 48 h (weight 5.4 g; water content about 2% by Fisher method).

Immobilized lipase catalyzed acylation:

To a stirred solution of racemic alcohol **6** (2 g, 15.4 mmol) and acetic anhydride (4 g, 42.4 mmol) in 100 mL of DME, was added 2.7 g (about 25% by weight of lipase PS30) of immobilized Amano lipase and the resulting suspension was stirred at 23°C. The reaction was monitored by TLC and ^{1}H NMR analysis until 50% conversion was reached. The reaction mixture was filtered and the filter cake was washed repeatedly with ethyl acetate. The combined filtrate was carefully concentrated in a rotary evaporator, keeping the bath temperature below 15°C. The residue was chromatographed over silica gel to provide 843 mg (42%) of 7 (95% ee ; α_D23° −11.9°, MeOH); ^{1}H-NMR (CDC1$_3$) δ 1.85 (m, 2H), 2.3 (m, 1H), 2.9 (m, 1H), 3.65 (dd, J=7.0, 9.1, 1H), 3.85–4.0 (m, 3H), 4.45 (dd, J=6.8, 14.6, 1H), 5.7 (d, J=5.1, 1H) ; also, 1.21 g of 8 after washing with 5% aqueous sodium carbonate (45%, α_D23° +31.8°, MeOH); ^{1}H-NMR (CDC1$_3$) δ 1.85–2.1 (m, 2H), 2.1 (s, 3H), 3.1 (m, 1H), 3.75 (dd, I=6.6, 9.2,1H), 3.8–4.1 (m, 3H), 5.2 (dd, J=6.4, 14.5,1H), 5.7 (d, J=5.2, 1H).

Acknowledgment:

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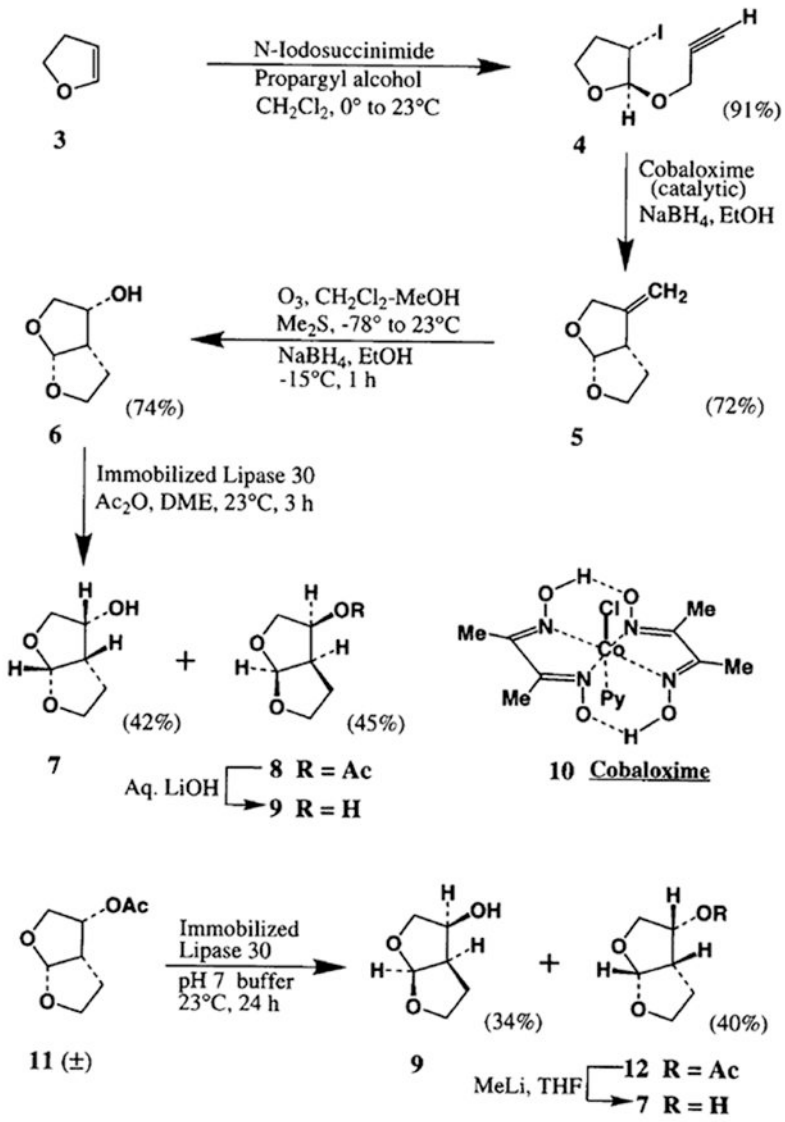

Scheme I.