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Enantioselective synthesis of cyclopentyltetrahydrofuran (Cp-THF), an important high-affinity P2-ligand for HIV-1 protease inhibitors

Arun K. Ghosh *, Jun Takayama

Departments of Chemistry and Medicinal Chemistry, Purdue University, West Lafayette, IN 47907, USA

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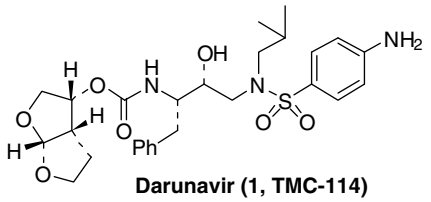
Abstract

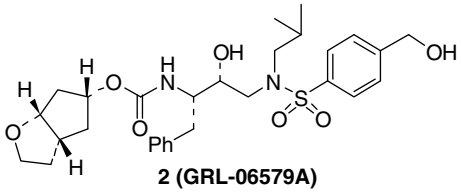
A convenient optically active synthesis of (3a*S*,5*R*,6a*R*)-5-hydroxy-hexahydrocyclopenta[*b*]furan, a high-affinity nonpeptidyl ligand for HIV-1 protease inhibitor **2**, is described. The synthesis utilizes commercially available (1*R*,5*S*)-(+)-2-oxabicyclo[3.3.0]oct-6-en-3-one as the starting material and oxymercuration or bromohydrin reaction as the key step. Enantiopure ligand was converted to protease inhibitor **2**.

Effective treatment of HIV/AIDS continues to be one of the most critical problems facing the medical community in the 21st century.[1] The advent of highly active antiretroviral therapy (HAART) with HIV protease inhibitors (PIs) in combination with reverse transcriptase (RT) inhibitors significantly improved HIV management and the quality of life for HIV/AIDS patients in developing countries. Despite these advances, there are major problems with HAART treatment regimens, particularly alarming is the adverse side effects including toxicity, complexity, and the occurrence of various cancers due to survival elongation.[2] Perhaps, most concerning is that a growing number of patients are developing drug-resistant HIV-1 variants and there are reports that these strains can be transmitted.[3,4] Therefore, the development of new classes of antiretroviral drugs with minimal adverse effects and potent activity against mutant strains resistant to currently approved PIs remains an important treatment objective.

Our recent structure-based design strategies specifically targeting the HIV-1 protease backbone led to a number of exceedingly potent PIs with impressive drug-resistance profiles.[5] One of these PIs is darunavir (**1**, TMC-114, Fig. 1) and it has been approved by the United States Food and Drug Administration for the treatment of HIV/AIDS patients harboring multidrug-resistant HIV-1 variants.[6,7] Darunavir contains a structure-based designed and privileged bis-THF ligand which makes extensive interactions with the HIV-1 protease backbone.[8] Subsequently, based upon darunavir-bound protein-ligand X-ray structures, we have designed a stereochemically defined cyclopentyltetrahydrofuran (Cp-THF)-derived urethane as the P2-ligand.[8,9] Inhibitor **2**, containing this ligand, has shown



Darunavir (1, TMC-114)



2 (GRL-06579A)

Fig. 1. Structure of inhibitor **1** and **2**.

* Corresponding author. Tel.: +1 765 494 5323; fax: +1 765 496 1612.
E-mail address: akghosh@purdue.edu (A. K. Ghosh).

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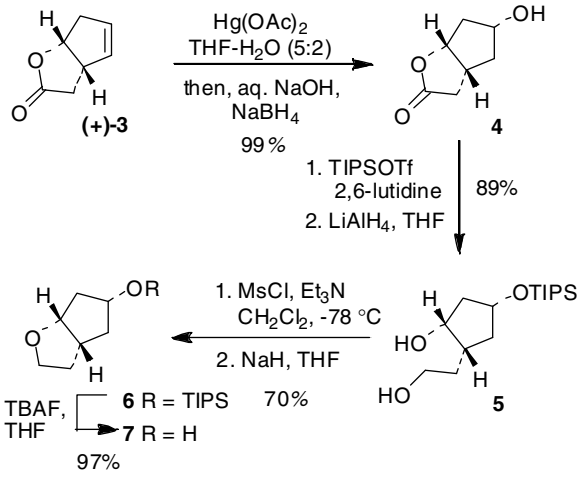
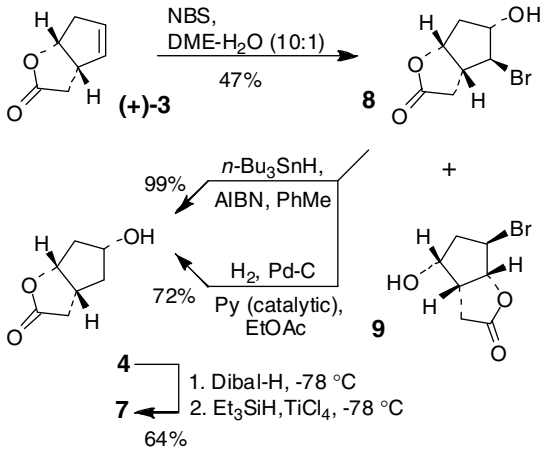


Scheme 1. Synthesis of hexahydrocyclopentafuran-5-ol.

remarkable potency against both wild-type and drug-resistant viruses (**2**, $K_i = 4.5$ pM and $ID_{50} = 1.8$ nM). Our initial synthesis of optically active Cp-THF ligand was based upon an enzymatic asymmetrization as the key step.[9] Recently, Shibasaki and co-workers have reported an optically active synthesis of Cp-THF ligand through Al-Li-bis(binaphthoxide) catalyst-controlled Michael addition of dimethyl malonate to racemic 4-O-protected cyclopentenone.[10] In our continuing studies aimed at broadening the scope and utility of the Cp-THF-derived PIs, we have carried out a convenient enantioselective synthesis of Cp-THF ligand utilizing commercially available (1*R*,5*S*)-(+)-2-oxabicyclo[3.3.0]oct-6-en-3-one (**3**). The route is amenable to quantities of Cp-THF ligand in high optical purity.

As shown in Scheme 1, commercially available (1*R*,5*S*)-(+)-2-oxabicyclo[3.3.0]oct-6-en-3-one **3** was utilized as a starting material. Stereoselective installation of the C5-hydroxyl group was accomplished by an oxymercuration–demercuration protocol in a one-pot operation as described by Olivo and co-workers.[11] As shown, exposure of **3** to 2 equiv of mercuric acetate in a mixture of THF and water at 0–23 °C for 2 h provided the corresponding organomercurial derivative. Aqueous sodium hydroxide followed by $NaBH_4$ was added to the mixture at 0 °C to afford the *endo*-alcohol **4** in near quantitative yield as a single diastereomer by ^1H NMR analysis. Protection of the hydroxyl group with TIPSOTf in the presence of 2,6-lutidine in CH_2Cl_2 at −50 °C for 3 h gave the corresponding silylether. Reduction of the resulting silyloxylactone with lithium aluminum hydride in THF at −20 °C furnished diol **5** (89% yield for two steps). The diol was converted to a tetrahydrofuranyl derivative by selective mesylation of the primary alcohol with mesyl chloride and triethylamine followed by a reaction of the resulting mono-mesylate with sodium hydride in THF at 23 °C for 2 h. This provided cyclopenta[*b*]furan **6** in a 70% yield for two steps. Removal of TIPS-group with TBAF in THF at 23 °C for 2 h afforded optically active hexahydrocyclopentafuran-5-ol **7** in 97% yield.[12]

As shown above, hydroxylation of alkene **3** by an oxymercuration–demercuration protocol provided excellent yield and diastereoselectivity. However, the overall procedure may be less suitable for scale up of Cp-THF ligand as it requires multi-gram quantities of mercuric acetate and a tedious work up with mercury byproducts. In this context, we have further investigated more practical halohydrin reactions using NBS and NIS. As shown in Scheme 2, reaction of **3** with 1.1 equiv of NBS in a mixture (10:1) of DME and water at 23 °C for 16 h provided bromohydrin **8** in 47% yield. This reaction was investigated under various reaction conditions as shown in Table 1. The choice of solvent and amount of water had a significant effect on the yield of the desired bromohydrin **8**. Alternative bromohydrin **9** is formed as a significant byproduct. Among various solvents examined (entries 1–5), aqueous DME showed the most reproducible results. The amount of water in DME was found to be critical (entries 5–9). A DME–water mixture ratio of 10:1 provided the best result (entry 9) with 47% yield of bromohydrin **8**. Reaction of NIS in DME also showed similar trends (entries 10 and 11). Reduction of bromohydrin **8** using *n*-Bu_3SnH in the presence of AlBN in refluxing toluene for 12 h afforded hydroxyl lactone **4**



Scheme 2. Synthesis of Cp-THF via bromohydrin reaction.

Table 1
Halohydrin reactions of lactone **3**

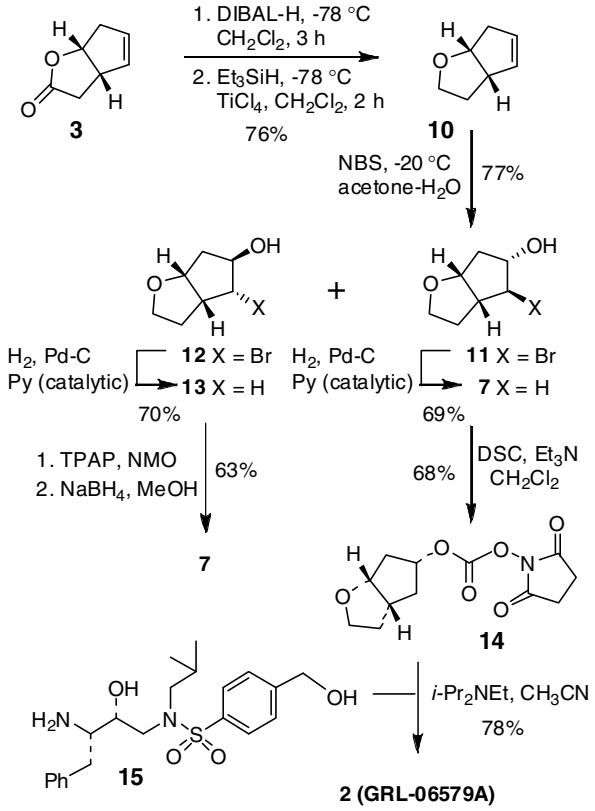
Entry	Reagent[a]	Solvent	(**8**:**9**)[b]	Yield[c] (%)
1	NBS	CH_3CN/H_2O (1:5)	27:73	29
2	NBS	THF/H_2O (1:5)	20:80	18
3	NBS	Acetone/H_2O (1:1)	50:50	34
4	NBS	CH_2Cl_2/H_2O (5:1)	—	NR
5	NBS	DME/H_2O (1:1)	36:64	31
6	NBS	DME/H_2O (2:1)	50:50	36
7	NBS	DME/H_2O (3:1)	52:48	42
8	NBS	DME/H_2O (4:1)	53:47	43
9	NBS	DME/H_2O (10:1)	57:43	47
10	NIS	DME/H_2O (1:1)	40:60	33
11	NIS	DME/H_2O (1:4)	40:60	42

[a] All reactions were carried out with 1 equiv of reagent.
[b] Ratios determined after separation by silica gel chromatography.
[c] Isolated yield of **8** after chromatography.

in near quantitative yield. We have also investigated catalytic hydrogenation conditions for reduction of bromohydrin **8**. This reduction proceeded in good yield (72%) in the presence of 10% Pd–C and a catalytic amount of pyridine in ethyl acetate providing lactone **4**.[13] When ethanol was used as the solvent, the reaction yield was reduced to 54%. The choice of solvent and the presence of a catalytic amount of pyridine are critical to this reduction process. Lactone **4** was converted to Cp-THF **7** by Dibal-H reduction in CH_2Cl_2 at −78 °C for 2 h to provide the corresponding lactol. Further reduction of this lactol with 2 equiv of Et_3SiH in the presence of 1 equiv of $TiCl_4$ in CH_2Cl_2 at −78 °C afforded optically active Cp-THF **7** in 64% yield over two steps.

To circumvent the formation of isomeric lactone **9**, we then investigated the bromohydrin reaction with the corresponding **3**-derived tetrahydro-2*H*-cyclopenta[*b*]furan derivative. As shown in Scheme 3, Dibal-H reduction followed by reduction of the resulting lactol with Et_3SiH in the presence of $TiCl_4$ provided **10** in 76% yield. Bromohydrin reaction of **10** with 1.1 equiv of NBS in a mixture (10:1) of acetone and water at −20 °C for 16 h provided a mixture (3.5:1) of diastereomeric bromohydrins **11** and **12** in 60% and 17% yields, respectively, after separation by silica gel chromatography (25% ethyl acetate in hexanes as the eluent).[14] Reduction of bromohydrin **11** by catalytic hydrogenation over 10% Pd–C in the presence of a catalytic amount of pyridine in ethyl acetate afforded optically active Cp-THF **7** in 69% yield. The minor isomer **12** was reduced to epimeric alcohol **13** in 70% yield as above. Alcohol **13** was converted to desired Cp-THF **7** by an oxidation/reduction sequence. Thus, TPAP oxidation[15] of **13** in CH_2Cl_2 at 23 °C for 2 h provided the corresponding ketone which was reduced with $NaBH_4$ in methanol at −20 °C to furnish optically active Cp-THF alcohol **7** in 63% yield for two steps. Alcohol **7** was converted to mixed carbonate **14** by treatment with *N*,*N*′-disuccinimidyl carbonate in the presence of Et_3N in CH_2Cl_2 at 23 °C for 12 h.[16] Mixed succinimidyl carbonate **14** was isolated in 68% yield. Reaction of this carbonate with previously described amine **15** in CH_2Cl_2 in the presence of diisopropylethylamine furnished inhibitor **2** in 78% yield.[9]

In summary, we carried out three different routes to the synthesis of optically active (3a*S*,5*R*,6a*R*)-5-hydroxyhexahydrocyclopenta-[*b*]furan ligand for HIV protease inhibitors using commercially available (1*R*,5*S*)-(+)-2-oxabicyclo[3.3.0]oct-6-en-3-one. The current synthetic routes would provide rapid access to this important nonpeptide high-affinity ligand for a variety of HIV-1 protease inhibitors.



Scheme 3. Synthesis of Cp-THF and inhibitor **2**.

Acknowledgment

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12. *Selected data for* **7**: $[\alpha]_D^{23}$ −13.2 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 4.37 (t, 1H, $J = 5.7$ Hz), 4.23–4.20 (m, 1H), 4.01 (dt, 1H, $J = 4.2$, 8.7 Hz), 3.59 (dd, 1H, $J = 8.6$, 15 Hz), 2.71–2.59 (m, 1H), 2.53 (br s, 1H), 2.25–2.14 (m, 1H), 2.06–1.96 (m, 2H), 1.87–1.76 (m, 2H), 1.67–1.59 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): 35.1, 41.3, 41.4, 42.5, 68.2, 74.8, 85.7. MS (CI): *m*/*z* 129.1 $[M+H]^+$.

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14. All new compounds gave satisfactory spectroscopic and analytical results. Compound **8**: $[\alpha]_D^{23}$ +14.7 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 2.20 (d, 1H, $J = 15.1$ Hz), 2.56 (ddd, 1H, $J = 4.8$, 6.7 and 11.6 Hz), 2.63 (dd, 1H, $J = 3.6$ and 18.6 Hz), 2.84 (dd, 1H, $J = 11.6$ and 18.6 Hz), 3.31–3.37 (m, 1H), 4.09 (dd, 1H, $J = 2.4$ and 4.1 Hz), 4.45–4.48 (m, 1H), 5.16 (t, 1H, $J = 7.0$ Hz). ^{13}C NMR ($CDCl_3$): δ 35.6, 38.4, 48.0, 58.1, 79.4, 84.0, 176.8. FT-IR (NaCl): 1075, 1198, 1750, 3444 cm^{-1}. MS (CI): *m*/*z* 220.98 $[M+H]^+$.
Compound **9**: $[\alpha]_D^{23}$ +15.2 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.01–2.12 (m, 1H), 2.34–2.45 (m, 1H), 2.74–2.86 (m, 2H), 3.27–3.37 (m, 1H), 4.14–4.22 (m, 1H), 4.40 (dd, 1H, $J = 5.1$ and 11.1 Hz), 5.04 (dt, 1H, $J = 3.0$ and 6.9 Hz). ^{13}C NMR ($CDCl_3$): δ 29.5, 33.5, 38.2, 40.8, 58.3, 82.3, 176.5. FT-IR (NaCl): 1180, 1768, 3429 cm^{-1}. MS (CI): *m*/*z* 220.98 $[M+H]^+$.
Compound **11**: $[\alpha]_D^{23}$ −15.5 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.86–1.95 (m, 2H), 2.19–2.27 (m, 1H), 2.44 (dt, 1H, $J = 6.1$ and 14.5 Hz), 2.82 (br s, 1H), 2.99–3.05 (m, 1H), 3.65 (dd, 1H, $J = 7.5$ and 16.0 Hz), 3.91–3.99 (m, 2H), 4.25–4.27 (br m, 1H), 4.45 (dt, 1H, $J = 2.4$ and 6.5 Hz). ^{13}C NMR ($CDCl_3$): δ 32.8, 37.5, 52.4, 60.2, 67.8, 80.4, 83.1. MS (CI): *m*/*z* 207.1 $[M+H]^+$.
Compound **12**: $[\alpha]_D^{23}$ −11.6 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.60–1.67 (m, 1H), 1.95–2.06 (m, 2H), 2.18 (dd, 1H, $J = 6.7$ and 14.0 Hz), 2.93–3.01 (m, 1H), 3.54 (dt, 1H, $J = 5.7$ and 8.9 Hz), 3.82–3.90 (m, 2H), 4.21–4.28 (m, 1H), 4.37 (t, 1H, $J = 6.7$ Hz). ^{13}C NMR ($CDCl_3$): δ 32.5, 38.0, 45.3, 59.9, 68.1, 76.4, 79.9. MS (CI): *m*/*z* 207.2 $[M+H]^+$.
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