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Synthesis of a Chiral Aziridine Derivative as a Versatile Intermediate for HIV Protease Inhibitors

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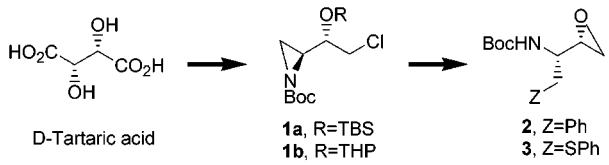
ABSTRACT



Chiral aziridine derivative 1 was prepared from D-tartaric acid. This compound could be utilized as a common intermediate for the synthesis of hydroxyethylamine class HIV protease inhibitors such as saquinavir, amprenavir, or nelfinavir.

Inhibitors of human immunodeficiency virus protease (HIV PR) have been developed as one of the most promising chemotherapeutic agents for the treatment of acquired immune deficiency syndrome (AIDS).[1,2] The HIV PR inhibitors often exhibit complex structures equipped with multiple stereogenic centers. Thus, development of an efficient and practical synthetic route for these inhibitors presents a challenge for synthetic organic chemists. HIV PR inhibitors such as saquinavir (**4**),[3] amprenavir (**5**),[4] and nelfinavir (**6**)[5] all belong to the hydroxyethylamine (HEA) class of inhibitors,[6] and there are many reports on the synthesis of this class of inhibitors.[7] However, general synthetic methodologies that provide access to a common intermediate for all three of the inhibitors are rare, since most of the HEA inhibitors are derived from phenylalanine derivatives, affording access to **4** and **5** only. The thiophenyl moiety in **6** has to be introduced from sources other than the phenylalanine derivative.[7g,j,k] We envisioned that if one had access

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to a 1,4-dielectrophilic chiron (**A**) as shown in Figure 1, a common synthetic intermediate could be obtained. The two terminal electrophilic sites of structure **A** should of course

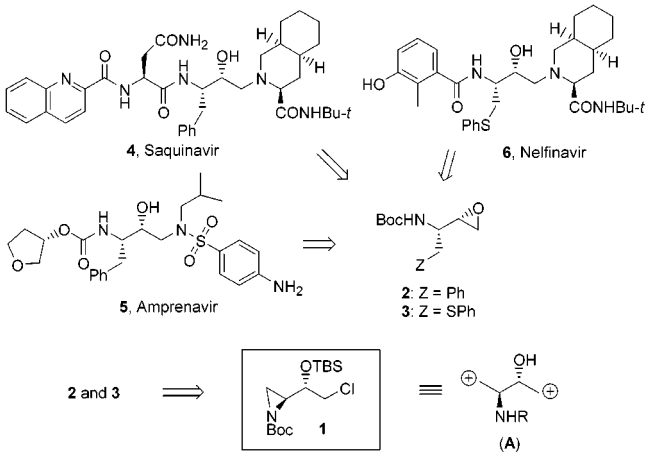
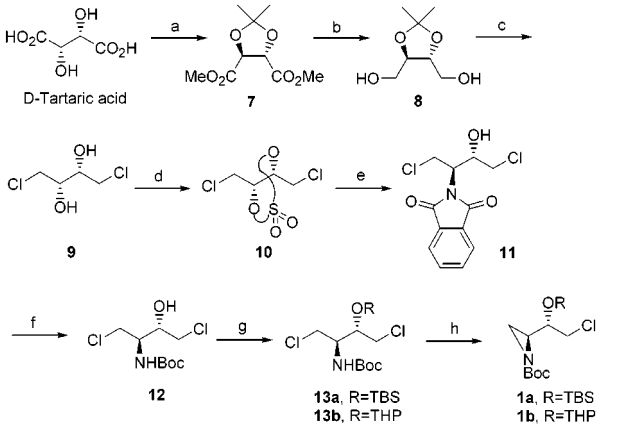


Figure 1.

be distinguishable, and we expected that this could be accomplished through introduction of an aziridine and an epoxide functionality sequentially from the corresponding 1,4-dielectrophile. Herein we report on the efficient synthesis of the new chiral aziridine derivative (**1**), which could be utilized as a versatile core intermediate for the preparation of diverse HEA class HIV protease inhibitors.

We previously reported the preparation of 3(*R*)-(*N*-(*tert*-butyloxycarbonyl)amino)-2(*S*)-hydroxy-1,4-dichlorobutane (**12**) through efficient desymmetrization of 1,4-dichloro-2(*S*),3-(*S*)-hydroxybutane cyclic sulfate (**10**).[8] This four-carbon chiron with a 2,3-*anti*-aminohydroxy and 1,4-dielectrophile arrangement could be utilized for the synthesis of the common intermediate **1** for HIV PR inhibitors. Although the cyclic sulfate **10** could be derived from diol **9**, which was prepared from asymmetric dihydroxylation of 1,4-dichloro-*trans*-2-butene,[9] we searched for more economical ways to generate the diol. Toward this goal, D-tartaric acid was a very convenient and economical solution. Scheme 1 outlines the preparation of chiral aziridine **1** from D-tartaric acid.[10] D-Tartaric acid was converted to acetonide diester **7** in an almost quantitative yield through either a two-step method involving conversion to dimethyl ester followed by acetonide formation or in one-step using 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid.[11] Reduction of **7** using $NaBH_4$ in methanol produced 2,3-*O*-isopropylidene-D-threitol **8** in 85% yield. A one-pot conversion of **8** to 1,4-dichloro-

Scheme 1[a]



[a] (a) (i) $SOCl_2$, MeOH; (ii) 2,2-dimethoxypropane, *p*-TsOH, dichloromethane or 2,2-dimethoxypropane, *p*-TsOH, benzene, MeOH, azeotropic removal of water; (b) $NaBH_4$, MeOH; (c) methanesulfonyl chloride, LiCl, Et_3N, CH_3CN, 55 °C; (d) $SOCl_2$, CCl_4 then $RuCl_3(3H_2O)$, $NaIO_4$, $CCl_4-CH_3CN-H_2O$ or SO_2Cl_2, imidazole, CH_2Cl_2; (e) potassium phthalimide, DMF; (f) (i) NH_2NH_2, EtOH; (ii) $(Boc)_2O$, aqueous NaOH; (g) for **13a**, TBSCl, imidazole, DMF; for **13b**, dihydropyran, catalytic *p*-TsOH·H_2O, CH_2Cl_2; (h) NaH, THF.

2(*S*),3(*S*)-butanediol **9** was accomplished through treatment with triethylamine, lithium chloride, and methanesulfonyl chloride in acetonitrile (50% yield).

With dichlorodiol **9** in hand, 1,4-dichlorobutane-2(*S*),3-(*S*)-diol sulfate was prepared either from a two-step sequence[12] involving thionyl chloride in chloroform followed by oxidation using ruthenium chloride and sodium periodate in ~95% yield or from sulfuryl chloride[5b] with imidazole as a base in carbon tetrachloride (~80−85% yield). As we had reported earlier,[8] the former two-step method gave higher yields (~93%) of the desired product. Though opening of this cyclic sulfate with LiN_3 proceeded smoothly,[8] a safer alternative was sought for a possibly large scale operation, and the use of potassium phthalimide was found to be quite efficient for this purpose. Thus, the cyclic sulfate of 4-dichloro-2(*S*),3(*S*)-butanediol was treated with potassium phthalimide in DMF to provide *N*-[1,4-dichloro-2(*S*)-hydroxy-3(*R*)-butyl]phthalimide (**11**) in quantitative yield. Deprotection of the phthalimide group was accomplished by treating **11** with 80% hydrazine monohydrate in 2-propanol followed by treatment with methanolic HCl, and the resulting free amine was converted to 2(*R*)-((*tert*-butyloxycarbonyl)-amino)-1,4-dichloro-3(*S*)-hydroxybutane (**12**) upon reaction with $(Boc)_2O$ in the presence of triethylamine in THF (75% from **11**). Reaction of **12** with either *tert*-butyldimethylchlorosilane or dihydropyran provided the protected amino alcohol **13a** or **13b**, respectively.[13] The desired aziridine functionality was installed from **13** upon reaction with sodium hydride in THF in an almost quantitative yield.

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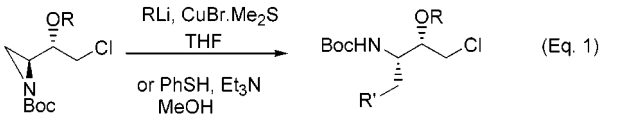
With the chiral aziridine **1** in hand, we investigated opening of the aziridine moiety with the proper alkyl or thioaryl group. Opening of an aziridine functionality with lithium dialkylcuprates has been documented,[14] and reaction of **1a** or **1b** with lithium diphenylcuprate proceeded smoothly to the corresponding ring-opened product **14a** or **14b**, respectively, in about 75% yield, which could be used as a precursor for the synthesis of amprenavir and saquinavir (eq 1). To obtain an intermediate for nelfinavir, opening of the



1a, R=TBS
1b, R=THP

14a, R=TBS, R'=Ph **15a**, R=TBS, R'=SPh
14b, R=THP, R'=Ph **15b**, R=THP, R'=SPh

aizirdine with thiophenoxide was also carried out to provide phenyl sulfide **15a** in 82% yield.

With proper installation of the necessary residues at the R′ position of compounds **14** and **15**, we carried out a synthesis of a complete HIV PR inhibitor taking Amprenavir as a target molecule as depicted in Scheme 2. Deprotection of the protecting group of **14a** or **14b** and concomitant epoxide ring formation was accomplished through the use of tetrabutylammonium fluoride (TBAF) or *p*-TsOH·H_2O followed by KOH/MeOH, respectively, and the epoxide **16** was obtained in good yield. Opening of the epoxide with isobutylamine (90% yield) followed by reaction with *p*-nitrobenznesulfonyl chloride provided **18** in 88% yield. Removal of the Boc protecting group followed by treatment with *N*-hydroxysuccinimidyl carbonate of 3(*S*)-hydroxytetrahydrofuran (**19**) furnished **20** in 85% yield. Reduction of the nitro group of **20** to the corresponding amino group using $SnCl_2$·$2H_2O$ (90% yield) completed the synthesis to furnish amprenavir.

(13) Protection of the alcohol of **12** as the tetrahydropyranyl (THP) ether **13b** provided a more economical reaction sequence. Using this protocol, up to 30 mol scale reactions have been carried out to provide epoxide **16** in ~30% overall yield from D-tartaric acid.

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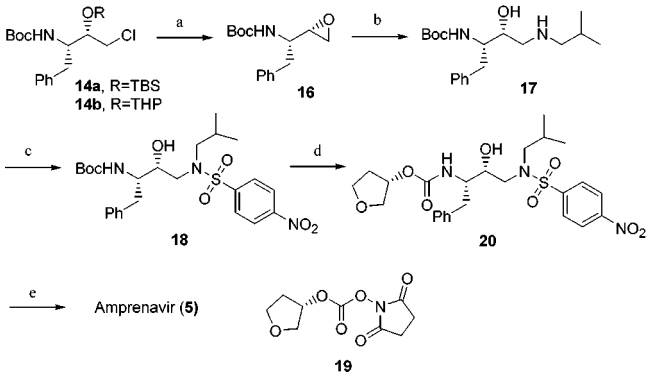
Scheme 2[a]



[a] (a) TBAF, THF; (b) *i*-$BuNH_2$, *i*-PrOH; (c) *p*-nitrobenzenesulfonyl chloride, Et_3N, CH_2Cl_2; (d) (i) HCl(g), CH_2Cl_2; (ii) **19**, Et_3N, CH_2Cl_2; (e) $SnCl_2$·$2H_2O$, EtOAc.

In summary, an efficient synthetic method was devised to prepare the chiral aziridine derivative **1**, a versatile synthetic intermediate for the synthesis of HEA class HIV PR inhibitors. Through opening of the aziridine ring with either carbon or sulfur nucleophiles, this intermediate could be used for the synthesis of intermediates for either saquinavir and amprenavir or nelfinavir. Investigation of the aziridine-opening reaction with a variety of other carbon and heteroatom nucleophiles for the preparation of important synthetic intermediates for other biologically active compounds is in progress.

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Supporting Information Available: Experimental procedure and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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