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A Practical Synthesis of Nonpeptide Cyclic Ureas as Potent HIV Protease Inhibitors

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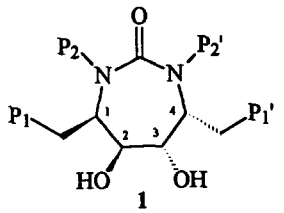
Abstract: The utilization of the oxydimethylene group to form a trioxepane ring for the protection of 1,2-diols was demonstrated. A process starting with natural L-tartaric acid as the chiral building block is utilized in the synthesis of optically active, nonpeptide cyclic ureas useful as HIV protease inhibitors.

Recently a series of rationally designed, bioavailable, nonpeptide cyclic ureas were identified as potent HIV protease inhibitors[1]. Their general structure is represented by **1**.



1

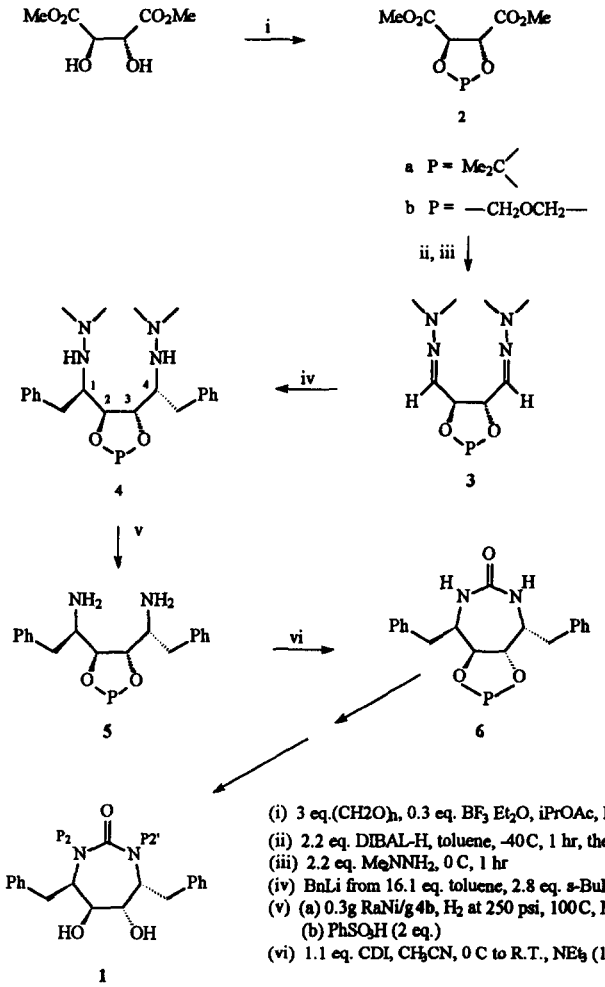
1a $P_1 = P_1' = Ph$; $P_2 = P_2' = H$

We report in this paper a practical and cost-effective synthesis of **1a** starting from natural L-tartaric acid. The C-2 symmetry of tartaric acid makes it a good starting material for the preparation of C-2 symmetric HIV protease inhibitors. Baker and Condon have reported a route to acyclic 1,4-diamino-2,3-isopropylidene-D-threitol as the chiral starting material.[2] Our approach modifies and improves this work and extends it to the preparation of cyclic ureas.

In the Baker and Condon route 2,3-isopropylidene-D-threitol was oxidized using Swern conditions and the resulting diadehyde was converted to a hydrazone using N,N-dimethyl hydrazine. The chiral centers at C1 and C4 were introduced by diastereoselective organometallic addition to the dihydrazone precursor. This chelation-controlled addition produced the S configuration at C1 and C4.

On the other hand, the absolute configurations for C1 to C4 of **1** are RSSR respectively and they can be derived from L-(+)-tartaric acid. Thus, starting with isopropylidene dimethyl tartrate **2a**, reduction of the ester function with DIBAL-H[3] and trapping the masked dialdehyde intermediate with 1,1-dimethylhydrazine will produce the dihydrazone **3a** (see Scheme 1). Chelation-controlled benzyllithium addition to the dihydrazone gives rise to the dihydrazine **4a**. The diamine **5a** can then be synthesized by hydrogenolysis of **4a** . The target cyclic urea **6a** can be prepared by treating the diamine **5a** with carbonyldiimidazole or similar reagents.

Scheme 1



However, cyclization of **5a** to **6a** has not been straightforward. The optimized yield for this step was 75% and the reaction was carried out in high dilution in boiling tetrachloroethane. We believe this difficulty in

cyclization is due to ring strain imposed by the trans-fused five-membered acetonide ring which makes it difficult for the two amino groups in **5a** to approach each other. The ring strain was reduced by protecting the diol as a trioxepane, thus increasing the ring size from five as in **5a** to seven as in **5b**. With this change, a high yield (85%) of the cyclic urea **6b** was obtained by this tetrachloroethane procedure.

The trioxepane dicarboxylate **2b**[4] was prepared in moderate yield using paraformaldehyde and was isolated by vacuum distillation. DIBAL-H reduction[3] of **2b** followed with 1,1-dimethylhydrazine trapping of the intermediate aluminate gave the dihydrazone **3b** in about 90% yield as an oil. This material was used in the next step satisfactorily without purification.

Chelation controlled addition of a benzyl carbanion to **3b** proved to be very dependent on the nature of the organometallic species. Benzyllithium gave both excellent yield and diastereoselectivity. The other two possible diastereomers were undetectetable by HPLC. In the Baker and Condon sequence benzyllithium was prepared from tetrabenzyl tin. With large scale synthesis in mind, we preferred a method that produced benzyllithium without generating an organotin waste stream. A report[5] on side chain lithiation of toluene with s-butyllithium in the presence of tetrahydrofuran was optimized to produce benzyllithium as a yellow slurry in toluene. The slurry was quenched with iodomethane and assayed to have ethylbenzene:xylenes >97:3. Addition of a solution of **3b** in toluene to the benzyllithium slurry produced **4b** in 90% yield.

Hydrogenoloysis of the N-N bond of hydrazines is not an easy reaction and the literature offers a variety of solutions.[6] In our hands, we found that the reaction was responsive to both temperature and hydrogen pressure. Using Raney nickel as catalyst, temperatures above 75° C and pressures above 150 psi gave complete conversion within 18 hours. At lower temperatures and pressures the reaction slowed down considerably or required such an excessive amount of catalyst to drive the reaction to completion[2] that the weight of wet catalyst used was greater than the weight of substrate.

Compound **5b** was isolated as its dibenzenesulfonate salt in 80% yield. This salt formation provided the first solid intermediate of the reaction sequence and helped to eliminate the low levels of impurities that accumulated in the previous steps. The dibenzenesulfonate salt also turned out to be an ideal starting material for the urea cyclization.

In the urea cyclization step, using carbonyldiimidazole (CDI) as reagent, the two amino groups of **5b** would compete for the CDI giving rise to bisimidazolides and oligomers would form. If the amino groups are somehow differentiated to allow only one amino group in the molecule to react with CDI and then the reactivity of the other amino group is restored, intramolecular cyclization will occur more readily than intermolecular oligomer formation. The dibenzenesulfonate salt of **5b** provides the means for differentiating the diamine groups.

When the dibenzenesulfonate salt of **5b** was treated in acetonitrile with one equivalent of triethylamine followed by one equivalent of CDI, HPLC assays shown more than 98A% of **6b**, which was isolated as a solid in 92% yield. The intramolecular cyclization occurred without further addition of triethylamine. This was due to the fact that the imidazole displaced in the first amino group attack on CDI served as base to deprotonate the second amino group. This strategy did not work well for the acetonide derivatives. When this procedure was applied to **5a**,

the cyclized product **6a** was obtained in 25% yield probably due to the ring strain imposed by the 5 member acetonide group.

Compound **6b** was alkylated to produce **1**. The oxydimethylene protecting group was removed by treatment with aqueous mineral acid in methanol at 30 to 50° C in 70 to 80 % yield.

Thus, a route for the large scale synthesis of HIV protease inhibitor **1** was identified with 45% yield from **2b**. This route demonstrates the oxydimethylene group as a useful protecting group for the 1,2-dihydroxyl system; the organotin waste stream is avoided in the preparation of benzyllithium; and the yield of the urea cyclization step is improved without using environmentally unfavorable solvents. Further progress on this work will be reported.

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