Bioorganic & Medicinal Chemistry Letters, Vol.1, No.4, pp. 219-222, 1991
Printed in Great Britain

0960-894X/91 $3.00 + .00

SYNTHESIS OF C_2-SYMMETRIC AND PSEUDOSYMMETRIC HIV-1 PROTEASE INHIBITORS FROM D-MANNITOL AND D-ARABITOL

Balan Chenera, Jeffrey C. Boehm, and Geoffrey B. Dreyer*

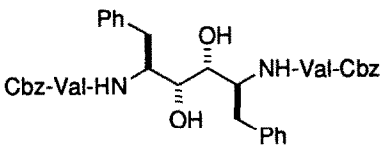
Department of Medicinal Chemistry, SmithKline Beecham Pharmaceuticals
709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406, USA

(*Received* 22 *April* 1991)

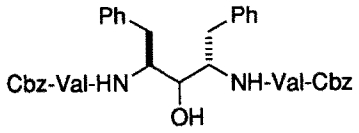
Abstract. Facile stereocontrolled syntheses of the potent HIV-1 protease inhibitors **1** and **2** are described, employing a unified synthetic route from carbohydrate precursors.

Since the recognition of its critical role in the human immunodeficiency virus life cycle, HIV-1 protease has become the focus of intensive investigation.[1] X-ray crystallographic[2] and biochemical[3] analyses have confirmed that HIV-1 protease is an aspartic protease with an unusual homodimeric, C_2-symmetric structure. Consistent with this mechanistic classification, established generic strategies for inhibition of aspartic proteases, employing nonhydrolyzable dipeptide isosteres, have been adapted to create potent inhibitors of HIV-1 protease.[4, 5] Furthermore, some of these peptide analogues are potent inhibitors of viral proteolytic processing and replication in cell cultures infected with HIV-1.[5] While these results are encouraging for the development of protease inhibitors as antiretroviral agents, the optimization of pharmacologic properties of these peptide-like molecules presents a significant challenge,[6] indicating the need for new inhibitory motifs. One approach to this problem is exemplified by the potent HIV-1 protease inhibitors **1** and **2**, reported recently by Erickson *et al.* and Kempf *et al.*,[7] which are designed to exploit the unique C_2 symmetry of the enzyme. In conjunction with our parallel studies in this area we have developed efficient syntheses of compounds **1** and **2** from readily available D(+)-mannitol and D(+)-arabitol, respectively. These syntheses, reported here, are advantageous in their brevity, absolute stereocontrol, and flexibility with regard to the synthesis of analogues.

Structures **1** and **2** can be considered as dimeric versions of the aminoterminal (P_n-P_1) portion of hydroxyethylene isostere inhibitors. As such, the choice of absolute stereochemistry within **1** and **2** derives from the known stereochemical requirements[4a] within hydroxyethylene isostere inhibitors.[8] D-Mannitol (**3**, Scheme 1) contains all of the requisite functionality, including the central (R, R)-diol, for a synthesis of structure **1** in which the 1- and 6-hydroxyl groups of **3** are replaced by phenyl groups and the 2- and 5-hydroxyl groups are converted



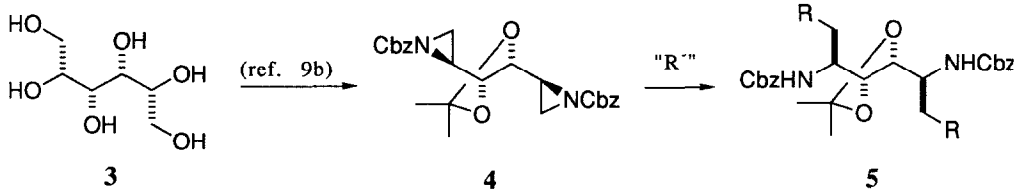
1



2

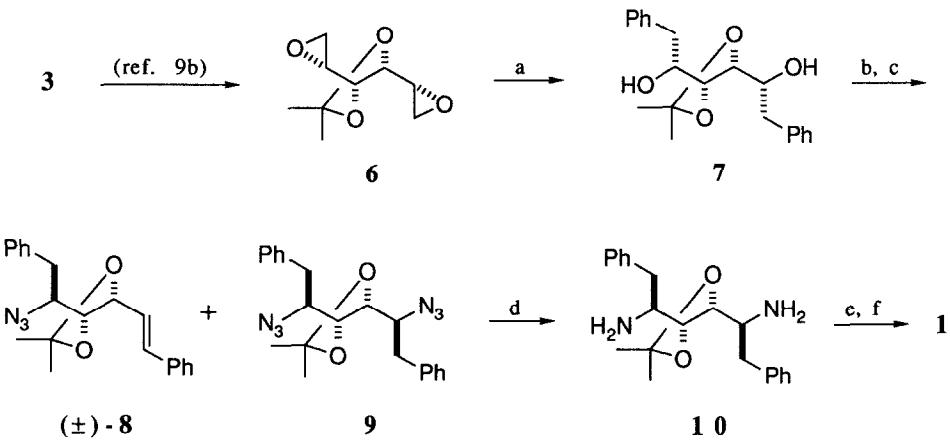
to amino groups with inversion of configuration. Indeed, the known diaziridine **4**, available in 5 steps from D-mannitol, provides access to a variety of analogues **5** of compound **1** by its reaction with nucleophiles R⁻.[9, 10] Unfortunately, we were unsuccessful in attempting to apply this procedure to the synthesis of **1** since diaziridine **4** was relatively inert to reaction with lithium diphenyl cuprate and only slow cleavage of the carbamate groups was observed. This led us to develop the modified route outlined in Scheme 2.

Scheme 1



3 **4** **5**

Scheme 2

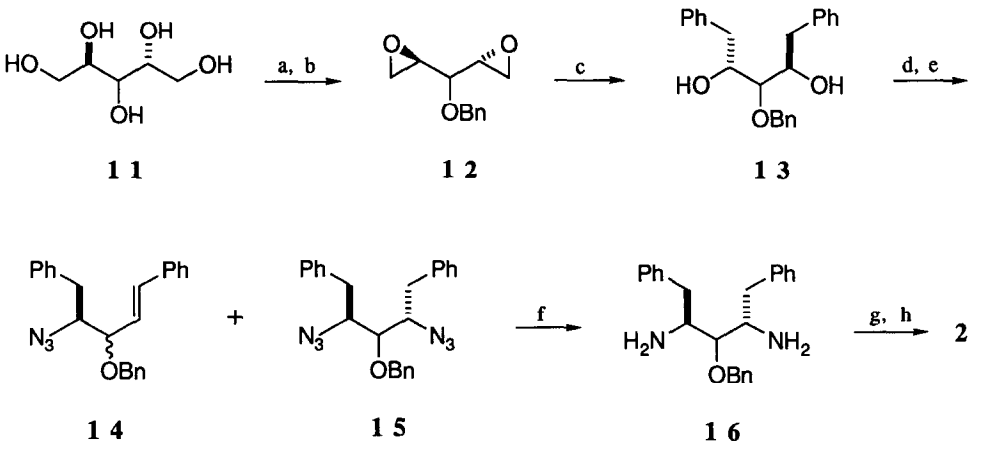


a. PhLi, CuI, ether, -78° → 25°; 87%. b. TsCl, pyridine; 92%. c. NaN_3, DMF, 90°; 84%; **8**:**9** = 1.0:4.6. d. H_2 (1 atm), $Pd(OH)_2/C$, ethyl acetate; **8**+**9** → **10**, 73%. e. Cbz-Val, iBuOCOCl, N-methyl morpholine, THF, -30°; 70%. f. 70% acetic acid, 85°; 88%.

As shown in Scheme 2, 1,2:5,6-dianhydro-3,4-O-isopropylidine-D-mannitol (**6**), easily prepared in 4 steps (40% overall yield) from D-mannitol by the procedure of Le Merrer *et al.*,[9b] reacted with lithium diphenyl cuprate to provide diol **7** in high yield. Heating the ditosylate derivative of **7** with sodium azide in dimethylformamide yielded diazide **9** along with the monoazide elimination product **8** in a ratio of 4.6 to 1 (based on NMR). Several attempts to circumvent the elimination side reaction by employing Mitsunobu-type conditions[11] were unsuccessful, leading to intractable mixtures. Nevertheless, while separation of the azides **8** and **9** was difficult, this was of little

consequence since catalytic reduction of the mixture provided the mono- and diamines from which diamine **10** was easily purified (57% overall yield from **7**) by column chromatography on Florisil®. Coupling of diamine **10** with carbobenzyloxy-L-valine by the mixed anhydride procedure[12] followed by removal of the acetonide protecting group with warm aqueous acetic acid furnished the inhibitor **1** in good yield.

Scheme 3



a. TsCl (2 eq.), pyridine; 74%. b. NaH, THF, 0°; BnBr, 0° → 25°; 42%. c. PhLi, CuI, ether, -78° → 25°; 82%. d. MsCl, pyridine, 0° → 25°. e. NaN_3, DMSO, 100°; 78%; **14**:**15** = 1.0:2.3. f. $LiAlH_4$, ether, 0° → 25°; **14**+**15** → **16**, 64%. g. H_2 (1 atm), Pd/C, methanol, HCl; 100%. h. Cbz-Val, iBuOCOCl, N-methyl morpholine, THF/DMF, -30° → 25°; 79%.

A synthesis directly analogous to that in Scheme 2 was then developed for the pseudosymmetric inhibitor **2** (Scheme 3). Treatment of D-arabitol (**11**) with two equivalents of p-toluenesulfonyl chloride in pyridine gave the corresponding primary ditosylate as an oil in 75% yield. A solution of the ditosylate in THF was treated successively with sodium hydride and benzyl bromide to provide the diepoxide, 3-benzyl-1,2:4,5-dianhydroarabitol, **12**.[13] As in the case of diepoxide **6**, reaction of **12** with lithium diphenyl cuprate led cleanly to diol **13**. As before, while a Mitsunobu reaction of **13** with TsNHBoc as the nucleophile[11b] led only to decomposition products, azide displacement of the dimesylate derivative of **13** provided diazide **15** contaminated with the elimination product **14**. Purification of the mixture from lithium aluminum hydride reduction of **14** and **15** was readily achieved by chromatography on Florisil® to provide diamine **16** in 50% overall yield from **13**. Hydrogenolytic deprotection of the hydroxyl group of **16** followed by mixed anhydride coupling[12] with carbobenzyloxy-L-valine provided the inhibitor **2**.

The overall yields of the inhibitors **1** and **2** from D-mannitol and D-arabitol are in the range of 10-15% (unoptimized) in two closely analogous, operationally straightforward synthetic pathways. The extension of these pathways to the preparation of analogues of **1** and **2** should help efforts to optimize inhibitory potency and pharmacologic properties of these novel compounds.

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[8]These design considerations are problematic in the case of structure **2** which possesses a nonstereogenic central carbon atom and is not properly C_2-symmetric. Hence, compounds containing the (2S, 3R, 4R, 5S)-1,6-dialkyl-2,5-diamino-3,4-hydroxyhexane structure (eg., **1**) were selected as our initial targets on the basis of their higher degree of symmetry. In agreement with our predictions, a recent crystallographic analysis (ref. 7a) indicates a dyssymmetric binding mode for compound **2** with HIV-1 protease that one would expect to entail 2-fold disorder. Molecular modeling studies leading to the structural types **1** and **2** will be described elsewhere (G.B.D., unpublished results).

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