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Synthesis of Cyclic Valine Analogs

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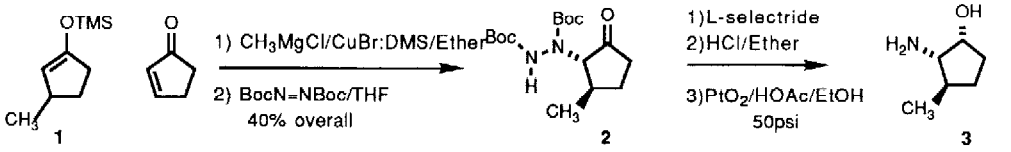
Abstract: Versatile and concise routes to both racemic and chiral cyclopentane analogs of valinol are described. These compounds are constrained analogs of a key amino acid found in the aspartyl protease inhibitors of HIV-1.

A principal objective in our investigation of orally active inhibitors of the vital aspartyl protease from HIV-1 is to improve the pharmacological profile of the inhibitor candidates previously prepared in these laboratories.[1] One approach is to incorporate non-peptide fragments into strategic locations of these peptide inhibitors.[2] In this regard we reasoned that the aminohydroxycyclopentane derivative **3** would serve as the cyclic analog for the amino acid derivative valinol. Herein we describe concise routes which provide this amino acid surrogate in both racemic and enantiomerically pure forms. Moreover, this methodology can be readily extended to provide homologous members of this class of compounds.

Scheme 1



1 **2** **3**

During the incipient structure-activity phase of our study we focused on the synthesis of racemic **3** beginning with cyclopent-2-en-1-one (Scheme 1). A standard cuprate addition was employed to introduce the methyl appendage. The abundance of available alkyl cuprate reagents provide the flexibility to examine a variety of other alkyl substituents as well. In the present case, conversion of the methylcuprate addition product to the corresponding TMS enol ether[3] was followed by Lewis acid catalyzed addition of di-tert-butylazodicarboxylate[4] to afford **2** containing the desired skeletal

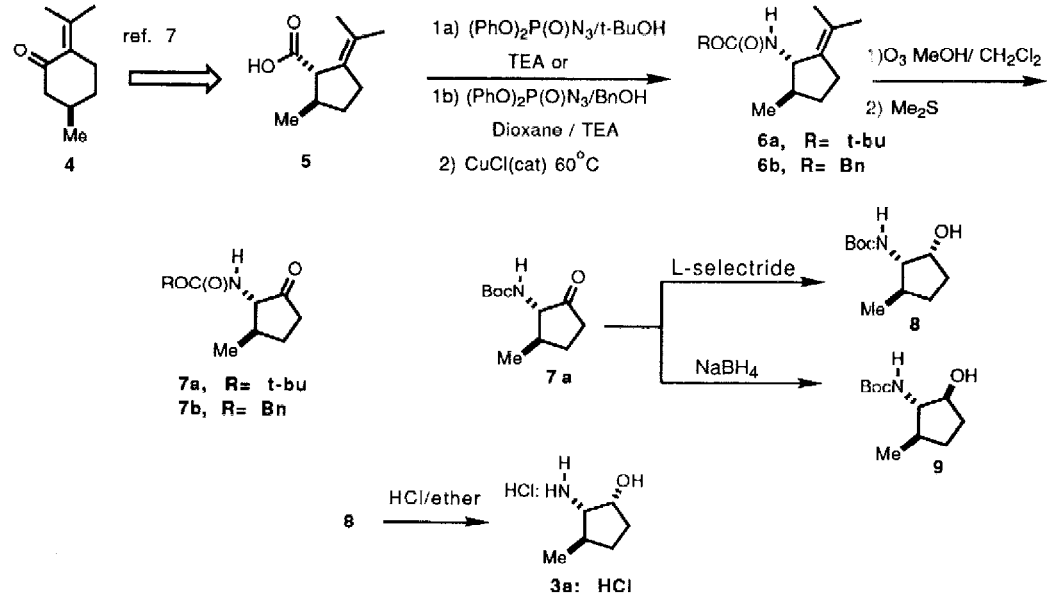
framework. However, the disappointing low yields in the latter reaction necessitated the development of an alternative approach. Accordingly, the cuprate addition to cyclopent-2-en-1-one was conducted under catalytic conditions (25mol% CuBr•DMS, ethyl ether) followed by the addition of the azodicarboxylate in THF at -78°C. This one pot method produced material in 40-60% overall yield. The use of catalytic quantities of copper salts was found to be beneficial in minimizing the decomposition of the azodicarboxylate under the reaction conditions employed. The ketone **2** was then converted to the aminohydroxycyclopentane **3** without purification of intermediates. Initial stereoselective reduction using L-selectride[5] was followed by cleavage of the Boc protecting group (HCl, ethyl ether, 0°C-23°C). The crude hydrazide was then hydrogenated directly at 50psi using Adams catalyst. While this approach to aminohydroxycyclopentanes is workable, an efficient enantioselective synthesis of **3** was dictated by the practical limitations in the resolution of the trisubstituted cyclopentanes and by the demand for quantities of chiral material required for in depth *in vivo* studies.

A survey of the literature revealed a lack of suitable homochiral cyclopentanes with this type of substitution pattern exhibited by **3.** Nevertheless, the connectivity of **3**, particularly the configuration at the center bearing the methyl group can be correlated with several naturally occuring terpenes, such as (R)-(+)-pulegone **4**.[6] This suggested that Favorskii rearrangement of inexpensive pulegone would provide pulegenic acid as an ideal progenitor for **3**[7]. Thus, pulegenic acid **5** ($[\alpha]_D^{25}$+57 neat, lit. $[\alpha]_D^{20}$+48.2 neat)[7] was submitted to Curtius rearrangement (diphenylphosphorylazide, triethylamine, t-butanol, 60°C)[8]. After one hour the evolution of N_2 was complete and without isolation, the crude isocyanate was treated with 10 mol% copper (I) chloride[9]. The reaction mixture was then heated for an additional 3-5 hours and following workup and recrystallization ($EtOH/H_2O$) gave the Boc-protected derivative **6a** in 70% isolated yield; mp.56-57°C; $[\alpha]_D^{25}$-8.1 (c=17.95, $CHCl_3$). By slight modification of the reaction conditions (1.2 equiv benzyl alcohol, dioxane), the Cbz-protected derivative **6b** could be obtained in a similar fashion; 80% mp. 77-78°C; $[\alpha]_D^{25}$-1.3 (c=24.52, $CHCl_3$). The latent ketone in **6a** was exposed by ozonolysis of the exocyclic olefin using a dimethylsulfide workup in 92% yield; mp.73-74°C $[\alpha]_D^{25}$+26.3 (c=1.0 $CHCl_3$).

We briefly examined reductions of the cyclopentanone **7a**. The *trans* amino alcohol isomer **8** could be obtained in homogeneous fashion and in excellent yield by performing the reduction with sodium borohydride in methanol at -78°C. One recrystallization of the crude product gave analytically pure material **9**; mp.120-121°C; $[\alpha]_D^{25}$-6.4 (c=10.9, $CHCl_3$). In analogy with the racemic series, the use of L-selectride produced predominantly the *cis* amino alcohol isomer **9**, although with somewhat

disappointing selectivity (4:1 ratio, **9**:**8**).[10] The 4:1 ratio could be enhanced to 10:1 with the simple expedient of precipitating the more crystalline *trans* isomer **8** from cold hexanes. Finally, the carbamate protecting group of the *cis* isomer **9** was removed using hydrogen chloride in ethyl ether providing chiral **3** as its hydrochloride salt; mp.225-227°C(d); $[\alpha]_D^{25}$ -1.7 (c=1.5, EtOH).[11]

Scheme 2



The sequence illustrated in Scheme 2 was accomplished without recourse to a single chromatographic purification. Further, each synthetic operation was carried out in excess of 70% yield[12]. The homochiral ketone 7 can be prepared with ease in 10-20g quantities and should serve as an excellent branch point for further functionalization of the cyclopentane nucleus. We are currently exploring routes to alternative substitution patterns of optically active aminocyclopentanols. Incorporation of these structures into aspartyl protease inhibitors and the disclosure of their biological activity will be the subject of our full report which will appear elsewhere.

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3. R.K. Dieter, J.W. Dieter, *J. Chem. Soc. Chem. Commun.* **1983,** 1378. We have prepared the ethyl derivative analogous to **2** using similar chemistry.
4. (a) C. Gennari, L. Colombo, G. Bentoli *J. Am. Chem. Soc.* **1986,** *108*, 6395. (b) D.A. Evans, T.C. Britton, R.L. Dorow, J.F. Dellaria *J. Am. Chem. Soc.* **1986,** *108*, 6396. (c) J.C. Vederas, L.A. Trimble *J. Am. Chem. Soc.* **1986,** *108*, 6397.
5. We are unable to quantify the full extent of this reduction process due to the presence of rotamers in the ^{1}H NMR spectrum. The10:1 isomer ratio for this step represents the lower limit for this step.
6. Additional examples can be found in J.W. Scott,"Asymmetric Synthesis"J.D. Morrison; J.W. Scott; Eds. Academic Press: New York, 1984 Vol.4, pp.1.
7. The procedure of Marx and Norman (J.N. Marx, L.R. Norman, *J.Org. Chem.* 1975, *40*, 1602) consistently yielded a 1:1 mixture of *cis* and *trans* ethylpulegenates. Saponification of this mixture using LiOH(aq.)/MeOH produced only the *trans* isomer as determined chromatographically and spectroscopically (HPLC, ^{1}HNMR). The distilled material was a yellow oil and this slight discoloration may account for the discrepancies in the measured optical rotation values. For a discussion of the Favorskii rearrangement of pulegone see S.A. Achmad, G.W.K. Cavill *Aust. J. Chem.* **1963,** *16*, 858, J. Wolinsky, D. Chan *J.Org. Chem.* **1965,** *30*, 41 and references therein.
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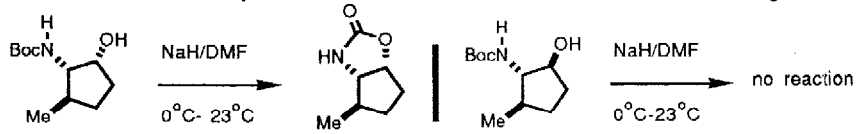
9. M.E. Duggan, J.S. Imagire *Synthesis* **1989,** 131.
10. The *cis* stereochemistry was firmly established by treating both **8** and **9** with NaH in DMF. The *cis* isomer **9** furnished the cyclic carbamate while **8** was recovered unchanged.



9 8

11. Conversion of recrystallized **3** (EtOH/Et$_2$O) to Mosher's amide and inspection of the crude product by HPLC and 300MHz ^{1}HNMR confirmed material to be >95% enantiomerically pure.
12. All reported yields are unoptimized. An additional 5-10% can be obtained by chromatographic purification of the mother liquors.

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