The combination of great effectiveness and ready availability should make the new phthalazine cinchona derivatives 1 and 2 the AD's workhorse ligands for some time to come. Nevertheless, terminal olefins are the most common and important members of the olefin family and since most representatives are still below the 90% ee level (Table I, entries 7–12), the search for new ligands continues.

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Supplementary Material Available: Experimental procedures and spectral data (^1H and ^{13}C NMR, IR, HRMS, and combustion analyses) for compounds 1 and 2, an improved preparation for 1,4-dichlorophthalazine, the preparation of AD-mix, and analytical data (HPLC, GLC retention times of the diols or their MTPA esters and the optical rotations of the diols) (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Highly Diastereoselective Alkylations of Chiral Amide Enolates: New Routes to Hydroxyethylene Dipeptide Isostere Inhibitors of HIV-1 Protease

D. Askin,* M. A. Wallace, J. P. Vacca,† R. A. Reamer, R. P. Volante, and I. Shinkai

Department of Process Research, Merck Sharp & Dohme Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065, and Department of Medicinal Chemistry, Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486

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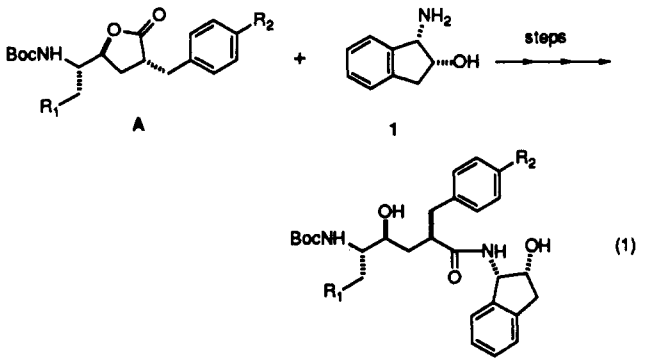
Summary: The nonchelate enforced chiral amide enolates derived from 4–7 react with alkyl iodide and protected α-amino epoxide electrophiles to produce the HIV protease inhibitors 10 and 16–19 with high diastereoselectivity.

The hydroxyethylene dipeptide isostere (HDI) transition-state mimetics have been found to be potent and selective inhibitors of aspartic acid proteases such as renin.[1] More recently, inhibition of the aspartic acid protease of HIV-1[2] has been recognized as an attractive target for therapeutic intervention in AIDS since inactivation of the protease results in cessation of the posttranslational processing of the viral *gag* and *gag-pol* gene products.

In previous reports from these laboratories, HDIs bearing the cyclic phenylglycine surrogate (−)-*cis*-(1*S*,2*R*)-1-aminoindan-2-ol (1) have been demonstrated to be potent and selective inhibitors of HIV-1 protease.[3] Initial synthetic routes to these compounds (eq 1) proceeded from a "trans"-lactone intermediate[4] A and 1 via the four-step sequence of lactone saponification, hydroxyl group protection, amide bond formation, and hydroxyl deprotection.[5] However, a more concise and practical route was desired. Herein we disclose novel chemistry leading to an efficient, highly diastereoselective coupling of chiral amide and epoxide partners to afford HDIs, as well as a rapid entry into a novel pseudo-C_2-symmetrical inhibitor, each derived from aminoindanol 1. Although many elegant approaches to HDIs have been reported,[6] we



16 R_1 = Ph, R_2 = H

17 R_1 = Ph, R_2 = OCH_2CH_2N⟨O⟩

18 R_1 = Ph, R_2 = OH

19 R_1 = cyclohexyl, R_2 = OCH_2CH_2OH

† Medicinal Chemistry.

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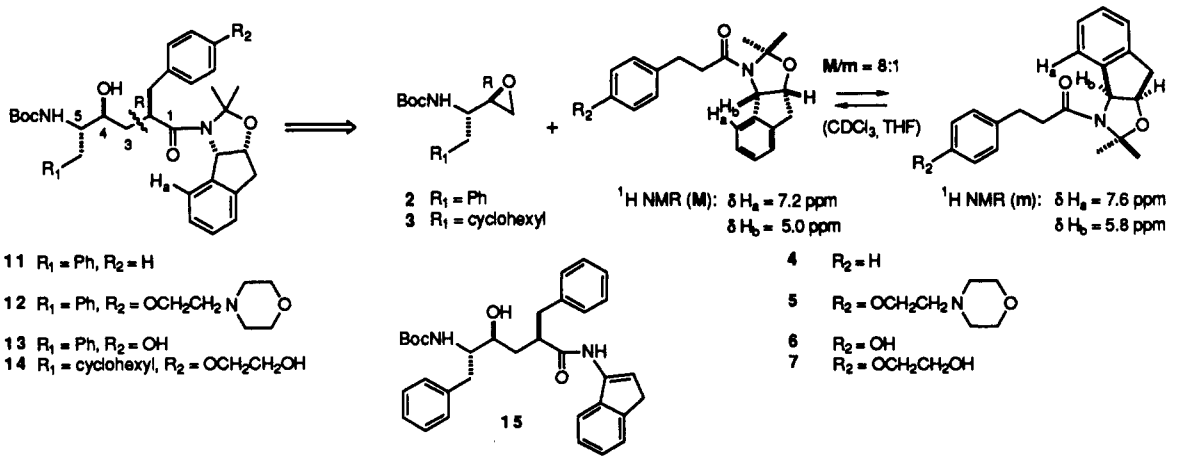
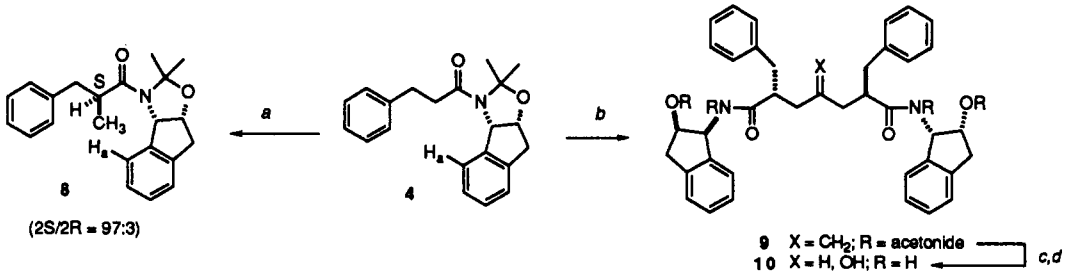
Scheme I



Scheme II[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF, −78 °C; then CH_3I; (b) *n*-BuLi, THF, −78 °C; then 3-iodo-2-(iodomethyl)-1-propene; (c) O_3, then $NaBH_4$; (d) Camphorsulfonic acid, methanol.

are unaware of methods which involve the direct coupling of protected α-amino epoxides and amide enolates as an entry into this compound class.

At the outset, three criteria had to be met for this route to be practical: (a) ready availability of the *R*-epoxides (Scheme I), (b) a diastereoselective condensation to afford the desired (2*R*) product, and (c) suitable protecting groups on the amide partner to allow both enolate formation and final deprotection of the desired HDIs.

The *R*-epoxides **2** and **3** were available from the olefin corresponding to **2** via selective, carbamate-derived epoxidation with peracid.[7] The amides **4–7** were prepared in a straightforward manner[8] from **1** and existed as an 8:1 mixture of major (**M**) and minor (**m**) rotamers in THF-d_8 and $CDCl_3$. We reasoned that formation of the *Z*-enolate of amides **4–7** followed by attack of an epoxide from the apparently least hindered enolate face of rotamer **M** should afford the desired 2(*R*)-diastereomeric product HDIs.

Treatment of amide **4** with *n*-BuLi at −78 °C resulted in the instantaneous formation of predominantly a single species, as analyzed by ^1H NMR. Treatment of the enolate with methyl iodide at −78 °C afforded virtually a single diastereomer of **8** (76%, diastereoselectivity = 97:3 by HPLC analysis of the crude reaction, Scheme II). It was confirmed independently that the major product possessed the *S*-stereochemistry resulting from approach of the electrophile from the least hindered face of the **M**-enolate rotamer.[9]

The above results led to speculation that a pseudo-C_2 symmetrical inhibitor could be selectively prepared by exposure of 2 equiv of the enolate to a bifunctional electrophile. Subjection of the lithium enolate of **4** to 0.5 equiv of 3-iodo-2-(iodomethyl)-1-propene[8] afforded a 74% yield of the double adduct **9**. Ozonolysis of the olefin followed by reductive workup gave an alcohol which was deblocked to afford the pseudo-C_2 symmetrical inhibitor **10**. The X-ray crystal structure of the HIV-1 protease/**10** complex has been determined.[10]

With these encouraging results in hand, we turned our attention to the more complex couplings with epoxide electrophiles. The chloromagnesium derivative of **2** was initially chosen[11] with the hope that intramolecular Lewis acid acceleration of the normally sluggish epoxide/amide enolate coupling would occur. Treatment of the more complex amide enolate derived from **5** with the species resulting from the action of isopropylmagnesium chloride on epoxide **2** gave a coupled adduct **12** as the major product (60%) along with the chlorohydrin side product derived from **2**.[12] Comparison of **12** with the acetonide derivative of material prepared from the "trans"-lactone intermediate (eq 1) indicated that epoxide coupling had taken place with the same enolate facial selectivity as the

(7) The *R*/*S* epoxide ratio was established by HPLC analysis of the crude epoxidation mixtures: column = 4.6-mm × 25-cm Dupont Zorbax-SIL, mobile phase = 98/2 hexane/2-propanol, flow = 1.0 mL/min, detection at 210 nm, approximate retention times (min): 2(*R*) = 9.6, 2(*S*) = 12.4. We observed that the selectivity obtained with *m*-CPBA in CH_2Cl_2 (*R*/*S* = 86:14) was lower than that reported in a previous disclosure in which the diastereomer analysis was carried out by ^1H NMR (*R*/*S* = 13:1): Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487–1492. It is clear that analysis of the diastereomeric ratio by NMR leads to inaccurate information due to the presence of minor carbamate rotamers in the integrated regions of the spectrum. The *R*/*S* epoxide ratio could be enhanced by selective crystallization of the undesired *S*-epoxide (ref 6a); a homogeneous sample of the *R*-diastereomer could be obtained by careful chromatography.

(8) See supplementary material for experimental details.

(9) Armstrong, J. Manuscript submitted to *Tetrahedron Lett.*

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(12) In the reaction of Grignard reagents with epoxides halohydrins are formed to the exclusion of alkyl group addition: Herr, R. W.; Johnson, C. R. *J. Am. Chem. Soc.* **1970**, *92*, 4979–4981.

alkyl iodide cases (Scheme II). This result is contrasted by the reversal of enolate facial attack of alkyl iodide and epoxide electrophiles upon reaction with amide enolates bearing metallo-alkoxy groups.[13]

In order to eliminate chlorohydrin formation, the coupling of the amide enolate was attempted with the lithium carbamate salt derivative of **2**. This variation had the potential advantage of operational simplicity provided that the lithium derivative of **2** was sufficiently electrophilic. *Addition of 2 equiv of n-BuLi to a solution of 1 equiv of epoxide 2 and 1 equiv of amide 4 at −78 °C followed by warming to −25 °C for 2 h and subsequent workup afforded the coupled product 11 in >90% yield.* The diastereoselectivity of the coupling was determined by preparation of the undesired 2*S* diastereomer from the "cis"-lactone corresponding to **A** (eq 1). *HPLC analysis of the crude reaction mixture and comparison with a sample spiked with the undesired 2S epimer indicated that the diastereoselectivity in the coupling was >99:1 in favor of the desired 2R diastereomer.* Interestingly, it was found that the amide linkage of adduct **11** was unreactive toward a second enolization with *n*-BuLi. For example, when **11** was subjected to 3 equiv of *n*-BuLi at −78 °C followed by quenching with methanol at −30 °C, unepimerized starting material was recovered as well as the indeneamide **15** derived from benzylic deprotonation. Apparently, the α-proton is orthogonal to the carbonyl group in the coupled product, resulting in poor kinetic acidity.[14] The remarkably mild one-pot process was extended to the coupling of hydroxyl-containing amides **6** and **7** with epoxides **2** and **3**, respectively (3 equiv of nBuLi required for deprotonation), to afford the coupled products **13** and **14** in satisfactory yields and similar diastereoselectivity. Deblocking of the adducts **11**–**14** was effected with camphorsulfonic acid in methanol to afford the HDIs **16**–**19**, which were identical to material prepared from the "trans"-lactone route.

It is clear from the foregoing discussion that the facial selectivity of the chiral amide enolates with both halide and epoxide electrophiles is much greater than would have been predicted from the amide solution rotamer argument.[15] Attempts to extend this method to other amide and epoxide partners are under investigation.

Supplementary Material Available: Experimental procedures and characterization data for new compounds (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(13) Askin, D.; Volante, R. P.; Ryan, K. M.; Reamer, R. A.; Shinkai, I. *Tetrahedron Lett.* **1988**, *34*, 4245–4248.

(14) A major change in the conformation about the C_1–C_2 bond appears to take place upon substitution at C_2. The ortho-aromatic protons (H_a) of the products **8** and **11**–**14** show dramatic upfield shifts (δ 6.3) relative to the starting amides **4**–**7** (δ 7.2), implying a conformation with the aromatic ring of the side chain at C_2 shielding H_a of the indane moiety.

(15) By analogy with Porter et al. in a related system, the unexpectedly high selectivity may be explained by electrophile attack of the **m**-enolate rotamer from the same enolate face as the **M**-rotamer due to non-bonded interactions of the incoming electrophile with the pseudoaxial methyl of the isopropylidine protecting group: Porter, N. A.; Bruhnke, J. D.; Wu, W.-X.; Rosenstein, I. J.; Breyer, R. A. *J. Am. Chem. Soc.* **1991**, *113*, 7788–7790.