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Highly Diastereoselective Reaction of a Chiral, Non-Racemic Amide Enolate with *(S)*-Glycidyl Tosylate. Synthesis of the Orally Active HIV-1 Protease Inhibitor L-735,524

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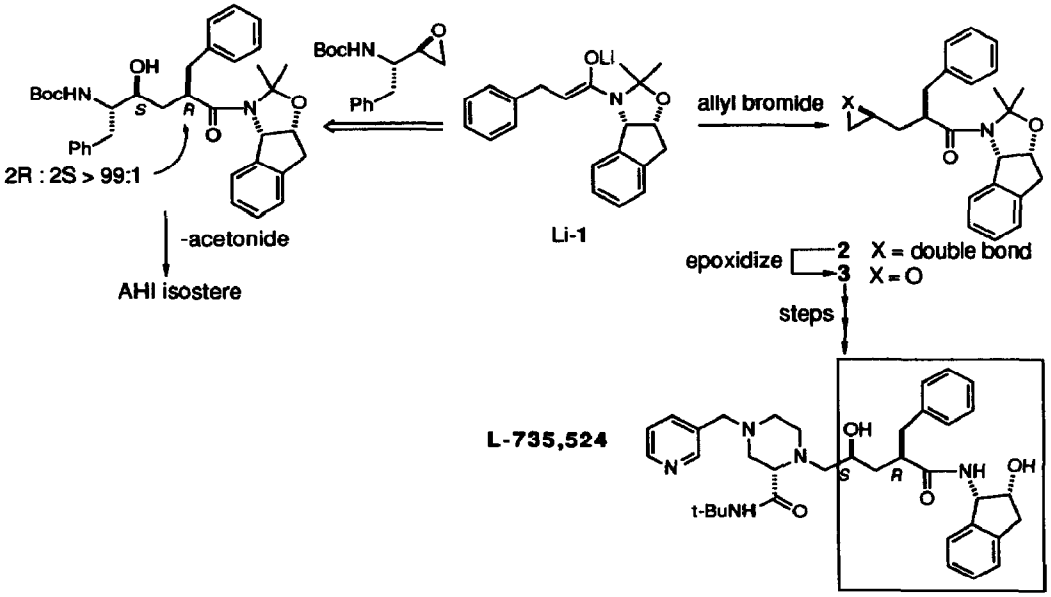
Summary: *Reaction of chiral amide enolate* ***Li-1*** *with (S)-glycidyl tosylate* ***11*** *affords the epoxide* ***3*** *in 72% yield with high diastereoselectivity. Epoxide* ***3*** *is converted to the orally-active HIV-1 protease inhibitor L-735,524 in 71% isolated yield.*

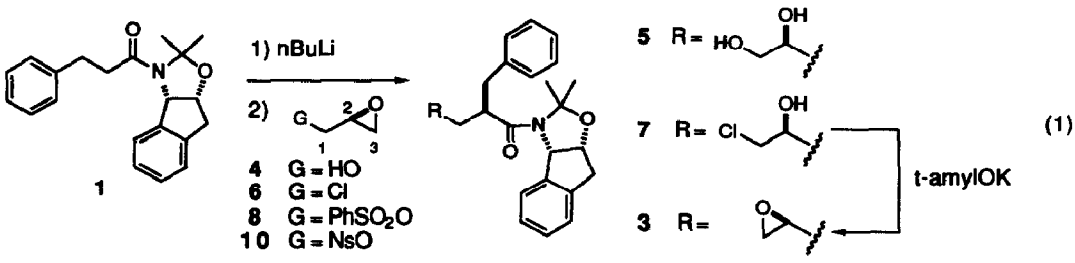
Hydroxyethylene dipeptide isosteres which contain the 1S,2R-1-amino-2-hydroxy-indanamide (AHI) moiety can be potent inhibitors of HIV-1 protease.[1] A highly diastereoselective route to the 2(R)-aryl-4(S)-hydroxy AHI isosteres was recently developed via alkylation of (N-Boc)-α-amino-epoxides with the n-BuLi generated enolate **Li-1** (Scheme I).[2]

Scheme I

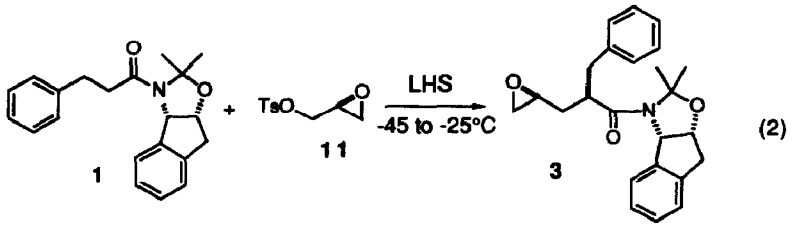


The orally active HIV protease inhibitor **L-735,524**[3] comprises the same 2(R)-aryl-4(S)-hydroxy AHI array (see box) as found in earlier inhibitors. Synthesis of epoxide **3**, a key intermediate for L-735,524, was initially carried out by diastereoselective allylation of **1** to afford **2** followed by epoxidation.[4] We now report a practical, one-step transformation of **1** to **3** which circumvents the more general problem of diastereoselective epoxidation of γ,δ-unsaturated amides with iodine.[5]

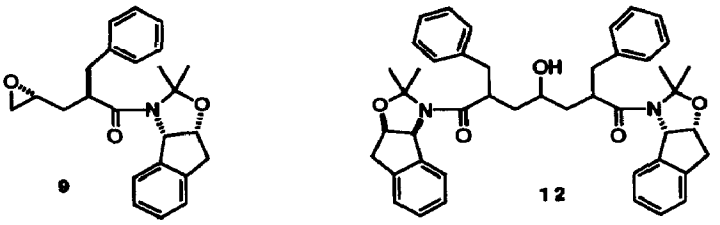
Attempted condensation of **1** with commercially available (R)-glycidol **4** via the *in-situ* enolate generation method (2 equiv. of nBuLi added to solution of **1** and **4**)[2] failed to give any isolable coupled product **5** (eq 1). This lack of reactivity was surprising in view of the enhanced electrophilicity of alkoxy-epoxides towards nucleophilic attack.[6] Condensation of Li-**1** with (S)-epichlorohydrin **6** at -30°C gave chlorohydrin **7** as the major product in addition to epoxide **3** (**7**:**3** ≈ 2.5:1). Treatment of the mixture with base gave a 70% overall yield of **3**.



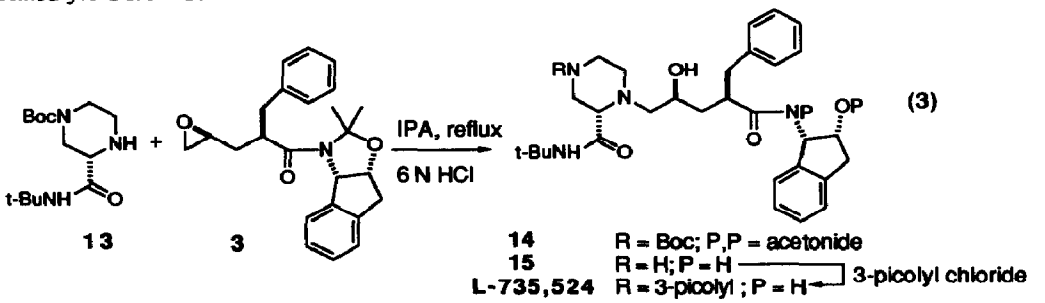
We next explored the condensation of **1** with activated glycidol derivatives as a direct route to **3**.[7] Alkylation of enolate Li-**1** with the oily benzenesulfonate **8**[7c] directly afforded **3** as the major product. Epoxide **3** is derived from attack of Li-**1** at the C_3 (oxirane) terminus of **8**. The intermediate alkoxy-benzenesulfonate could not be detected during the course of the reaction. Also present in the crude reaction mixture was the epimeric epoxide **9** (**3**:**9** ≈ 7-8:1 by ^{1}H NMR analysis). Epoxide **9** is derived from *ent*-**8** in the starting material, and any lack of regiochemical specificity in nucleophilic attack on **8**. To improve the diastereomeric purity of the product and eliminate an extra step necessary to prepare **8**, we desired a commercially available reagent of very high optical purity.



Attempted alkylation of Li-**1** with 99% ee (S)-glycidyl nosylate **10** gave a dark orange colored reaction mixture and recovered starting materials, indicative of electron transfer complications. However, *condensation of amide* ***1*** *with (S)-(+)-glycidyl tosylate* ***11***[8] *of 99 % ee (1.2 equiv.) in the presence of lithium hexamethyldisilazide (LHS) gave a 72% yield of the desired epoxide* ***3*** *(eq 2).* There was also produced minor amounts of the epimeric **9**[9] derived from enolate attack on the C_1 terminus of **11**. *Thus, in a single step, two new stereocenters are introduced in extremely high diastereoselectivity.* The use of the less reactive base LHS allows the coupling to be carried out by direct addition of base to a solution of **1** and **11** at -50 followed by warming to -25°C. Under these conditions, approximately 19 % of the dimeric product **12** is obtained. Crystallization of the crude mixture results in a 85% recovery of epoxide **3** in 99 % diastereomeric purity[10]. Not surprisingly, alkylation of **1** with (R)-glycidyl tosylate afforded the epoxide **9** as the major component.



To complete the synthesis of L-735,524, epoxide **3** and piperazine **13**[11] are subjected to a one-pot coupling/deprotection to afford **15** (eq 3). Alkylation of **15** with 3-picolyl chloride then affords L-735,524 in 71% isolated yield from **3**.



In summary, we have achieved an efficient coupling of chiral amide enolate **Li-1** and (S)-glycidyl tosylate **11** to afford the epoxide **3** in a single step with extremely high diastereoselectivity. This method provides a practical route to the orally active HIV protease inhibitor, L-735,524.[12]

References and Notes

(1) Lyle, T.A.; Wiscount, C.M.; Guare, J.P.; Thompson, W.J.; Anderson, P.S.; Darke, P.L.; Zugay, J.A.; Emini, E.A.; Schleif, W.A.; Quintero, J.C.; Dixon, R.A., Sigal, I.S.; Huff, J.R. *J. Med. Chem.* **1991**, *34*, 1228-1230.

(2) Askin, D.; Wallace, M.A.; Vacca, J.P.; Reamer, R.A.; Volante, R.P.; Shinkai, I. *J. Org. Chem.* **1992**, 57, 2771-2773. The amide **1** is available from 1S,2R-1-amino-2-hydroxy-indane in an improved one-pot procedure in 90% isolated (crystallized) yield via treatment with hydrocinnamoyl chloride and triethylamine (THF) followed by 2-methoxypropene/MsOH.

(3) (a) Vacca, J.; Dorsey, B.; Levin, R.; McDaniel, S.; Darke, P.; Zugay, J.; Schleif, W.A.; Quintero, J.; Sardana, V.; Lin, J.; Chen, I-W.; Ostovic, D.; Anderson, P.S.; Emini, E.A.; Huff, J.R. *Proceedings of the National Academy of Sciences*, submitted. (b) Poster presentations at the IX International Conference on AIDS; Berlin, Germany, June 6-11, 1993 and the 206th ACS National meeting, MEDI-6, Chicago, Illinois, August 22-27, 1993.

(4) Low yields (25-35%) of epoxide **3** were obtained via per-acid treatment of olefin **2** due to non-selective epoxidation (B. Dorsey, unpublished results). A three-step epoxidation method has also been developed via asymmetric dihydroxylation of olefin **2** followed by activation and cyclodehydration (B. Dorsey, J. Vacca, to be submitted to *J. Med. Chem.*).

(5) Attempted diastereoselective epoxidation of **2** via iodination/iminolactone formation leads to lactonization and amide bond cleavage, cf: Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079-1085.

(6) Marshall, J.A.; Andrews, R.C. *J. Org. Chem.* **1985**, *50*, 1602-1606.

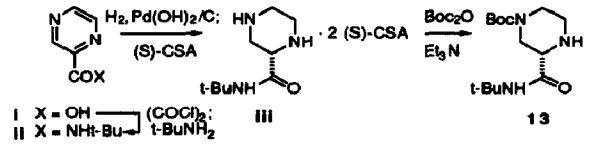
(7) (a) Klunder, J. M.; Onami, T.; Sharpless, K.B. *J. Org. Chem.* **1989**, *54*, 1295-1304. (b) Hanson, R.M. *Chem. Rev.* **1991**, *91*, 437-475. (c) Derived ($PhSO_2Cl$, Et_3N/CH_2Cl_2) from 83% ee **4**. The benzenesulfonate was initially chosen due to the acidity of the toluenesulfonyl-methyl group. As an approximation, the pKa of p-$PhSO_2C_6H_4CH_3$ is 30 as measured in DMSO solution: Bordwell, F.G. *Acc. Chem. Res.* **1988**, *21*, 456-463.

(8) Available in bulk quantities in 95 % ee from D.S.M. Andeno (Netherlands) or 99% ee from DAISO (Japan). For a recent example of boron trifluoride assisted condensation of (S)-glycidyl tosylate with a lithiated sulfone, see: Baldwin, J.E.; Adlington, R.M.; Bebbington, D.; Russell, A.T. *J. Chem. Soc., Chem. Commun.* **1992**, 1249-1251.

(9) The ratio of epoxides in the crude mixture derived from 99 % ee *(S)*-**11** was 98:2 (**3**:**9**) as measured by normal phase HPLC: 4.6 mm x 25 cm dupont Zorbax-NH_2 column, hexane/2-propanol (98/2) mobile phase, 3.8 mL/min flow rate, 220 nm detection, approximate retention times (min) : **1** = 2.0, **3** = 2.3, **9** = 3.2. Interestingly, a similar level of regiochemical control of C_3 (oxirane):C_1 attack was noted for the condensation of malonate with non-racemic epichlorohydrin: Pirrung, M.C.; Dunlap, S.E.; Trinks, U.P. *Helv. Chim. Acta* **1989**, *72*, 1301-1310.

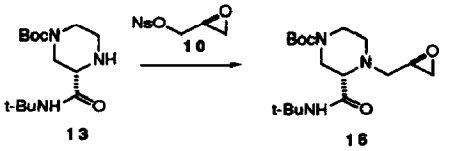
(10) Typical experimental procedure: A solution of amide **1** (1000 g, 3.11 mol) and 98 % ee 2(S)-glycidyl tosylate **11** (853 g, 3.74 mol, 1.2 equiv.) in 15.6 L of THF (KF = 22 mg/L) was degassed with nitrogen and cooled to -56°C. LHS in THF (2.6 L, 1.38 M, 1.15 equiv.) was added over 2 h, while keeping the temperature between -50 to -45°C. The reaction mixture was stirred at -45 to -40°C for 1 h and then allowed to warm to -25°C over 1 h and aged between -25 to -22°C for 4 h. The reaction was quenched with 6.7 L of water at -15°C, extracted with ethyl acetate (10 L) and washed with a solution of 1% aqueous $NaHCO_3$ (5 L) and saturated NaCl (0.5 L). Nominal assay yield for **3** is 72% by quantitative HPLC analysis: (25 cm C_{18} Machery-Nagel "nucleosil" column, pH 6.8 phosphate buffer/CH_3OH, 35/65 (v/v), 0-20 min, isocratic, then gradient over 20 min to 10/90 (v/v), 40°C, 220 nm detection, retention times: **3** = 32.4 min., **9** = 27.7 min. The ethyl acetate extract was concentrated *in vacuo* and solvent switched to MeOH and further concentrated to a final volume of 3.2 L and cooled to 5°C. The white slurry was filtered and the wet cake was washed with cold methanol (2 x 250 mL). The washed cake was dried under vacuum (26 in. Hg) at 25°C to afford 727 g of epoxide **3** (61 % isolated yield, 98.7 area % **3**, 1.3 area % **9** by HPLC analysis). Spectral data for **3**: ^{13}C NMR (300 MHz, CDCl3) δ 171.1, 140.6, 140.5, 139.6, 129.6, 128.8, 128.2, 127.2, 126.8, 125.6, 124.1, 96.8, 79.2, 65.8, 50.0, 48.0, 44.8, 39.2, 37.4, 36.2, 26.6, 24.1; for **9**: ^{13}C NMR (300 MHz, CDCl3) δ 171.0, 140.5, 139.9, 129.7, 128.8, 128.2, 127.2, 126.8, 125.6, 124.1, 96.8, 79.1, 65.5, 50.5, 47.7, 45.9, 37.8, 37.1, 36.2, 26.6, 23.8.

(11) (a) Piperazine **13** was prepared in 26% overall yield from 2-pyrazinecarboxylic acid by the 4-step procedure:



(b) Felder, von E.; Maffei, S.; Pietra, S.; Pitrè, D. Helv. Chim. Acta **1960**, *43*, 888-896.

(12) An alternate route to L-735,524 would involve initial connection of the non-racemic glycidyl unit with the piperazine **13**. Attempted coupling of **13** with tosylate **11** afforded a complex reaction mixture in which the major product did not contain an epoxide moiety. However, coupling of **13** with the more C_1-reactive (S)-glycidyl nosylate **10** afforded the desired piperazine-epoxide **16** in 72% isolated yield. Unfortunately, the coupling of Li-**1** and **16** afforded intermediate **14** in only 20% yield.



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