Pergamon

Tetrahedron Letters 39 (1998) 6823–6826

TETRAHEDRON LETTERS

An Efficient Asymmetric Hydrogenation Approach to the Synthesis of the Crixivan® Piperazine Intermediate

K. Rossen*, P.J. Pye*, L.M. DiMichele, R.P. Volante and P.J. Reider

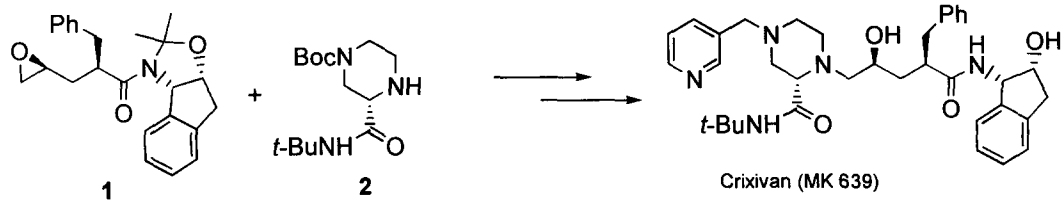
Department of Process Research Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065.
E-mail: kai_rossen@merck.com or philip_pye@merck.com

Received 6 May 1998; accepted 10 July 1998

Abstract: The Crixivan® HIV protease inhibitor piperazine intermediate **2** was prepared by a four step sequence using a chiral hydrogenation of the tetrahydropyrazine **9** to establish the absolute stereochemistry.

Asymmetric catalytic reactions are in principle the most attractive approaches for the synthesis of chiral molecules as only a small amount of catalyst is required to prepare larger amounts of product. However, for such a synthesis to be practical and viable, not only must the chiral center be established in high enantiomeric excess and high yield, but two often overlooked criteria must also be met: the starting material for the reaction has to be accessible in an efficient manner and the product of the asymmetric reaction must be converted into the desired product without racemization of the chiral center.

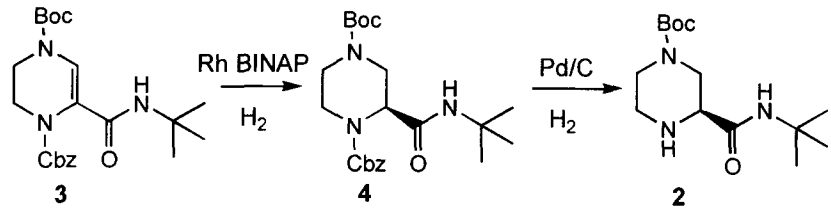
A key step in the assembly of the Merck HIV protease inhibitor Crixivan® (Indinavir™, MK 639) is the coupling of the enantiomerically pure piperazine **2** with the enantiomerically pure epoxide **1** to afford the backbone of this important drug for the treatment of HIV infection.[1]



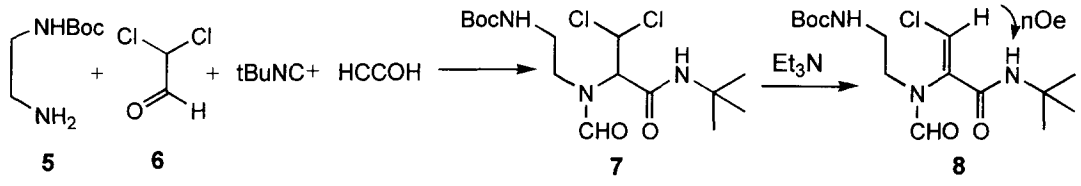
1 **2** Crixivan (MK 639)

We previously reported the preparation of piperazine **2** using a chiral hydrogenation of the tetrahydropyrazine **3**.[2] While the chiral hydrogenation occurs in high yield and high ee using the Rh-BINAP catalyst, the synthesis of the hydrogenation substrate **3** requires five steps and thus makes this route less attractive than the classical resolution approach.[1c]

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01484-1

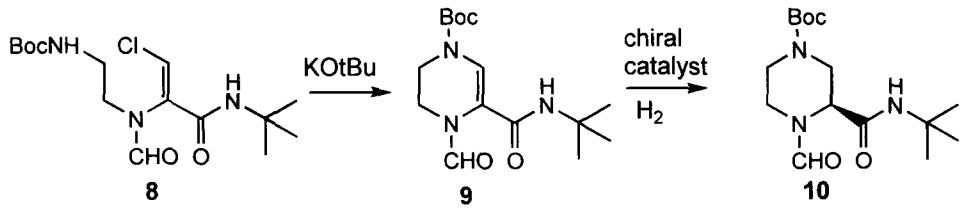


In order to overcome the shortcomings of this chiral hydrogenation route we decided to explore an alternative synthesis of the tetrahydropyrazine that would rapidly assemble this heterocycle from readily available starting materials.[3] To this end, we combined N-Boc-ethylenediamine (**5**) with dichloroacetaldehyde (**6**) to form the imine and then added *tert*-butylisocyanide and formic acid. The resulting Ugi adduct **7** can be isolated; however, the desired vinylchloride **8** is obtained more conveniently in essentially quantitative overall yield by the Et_3N induced HCl elimination from **7**. Interestingly, **8** exists as a single diastereomer and examination of the nOe in **8** show it to be the Z-isomer.[4]

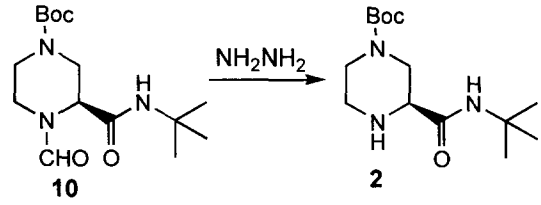


The subsequent cyclization of **8** to **9** proved difficult. Amine bases (including DBU) led to no reaction, while use of LDA or n-BuLi, even at low temperatures, produced a polymeric material. The most promising results were obtained with alkoxide bases and increasing conversions were observed by going from LiO*t*Bu to NaO*t*Bu and KO*t*Bu. An acceptable yield (60%) in the cyclization was realized by careful control of the amount of base (1.6 equiv. of KO*t*Bu), concentration (0.05M) and solvent (addition of KO*t*Bu in *t*-butanol to THF solution of **8**).

With a short synthesis of the tetrahydropyrazine **9** in hand, we examined the chiral hydrogenation of this substrate. Tetrahydropyrazine **9** differs from the frequently examined N-acyl dehydroaminoacid hydrogenation substrates not only by the positioning of the double bond in the ring between two nitrogen atoms, but also by the scarcely precedented use of the formyl group for the protection of N-1. A screen of various Rh and Ru based catalysts under a standard set of conditions (3.5 atm H_2, 18 h, MeOH, 2 mol% catalyst) was undertaken.[6]



The best activity and enantioselectivity is obtained using the Rh-BINAP catalyst and complete conversion of **9** to **10** could be achieved at 100 atm H_2 pressure at 40°C in MeOH with 7 mol% catalyst to give the product with 97% ee.[7]



In the last step the formyl group in **10** must be removed without the racemization of the newly formed chiral center. Since the N-1 protecting group is derived from the acid used in the Ugi condensation, the use of a carbamate protecting group, such as Cbz, is precluded. We envisioned that only easily deprotected amides, such as formamide, might allow for the required mild deprotection. Indeed, treatment of **10** with dilute aqueous NaOH cleanly removed the formyl group, but with concomitant racemization: the ee of **2** was reduced to 80% from the 99% of the starting material even when the deprotection was performed at 0°C! Remarkably, heating **10** with 35% aqueous hydrazine led to a clean deprotection to give **2** (91% yield) while leaving the enantiomeric purity essentially unchanged at 98%![8]

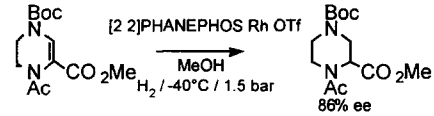
In summary, we have developed a short alternative synthesis of the piperazine intermediate of the Merck HIV protease inhibitor Crixivan®. It consists of a novel, two step preparation of a tetrahydropyrazine, its chiral hydrogenation and the subsequent formamide deprotection without concomitant racemization.

References and Notes

1. (a) Vacca, J.P.; Dorsey, B.D.; Schleif, W.A.; Levin, R.B.; McDaniel, S.L.; Darke, P.L.; Zugay, J.; Quintero, J.C.; Blahy, O.M.; Sardana, V.V.; Schlabach, A.J.; Graham, P.I.; Condra, J.H.; Gotlib, L.; Holloway, M.K.; Lin, J.; Chen, I.-W.; Vastag, K.; Ostovic, D.; Anderson, P.S.; Emini, E.A.; Huff, J.R. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4096. (b) *Idem., J. Med. Chem.* **1994**, *37*, 3443. (c) Askin, D.; Eng, K.K.; Rossen, K.; Purick, R.M.; Wells, K.M.; Volante, R.P.; Reider, P.J. *Tetrahedron Lett.* **1994**, *35*, 673. (d) Maligres, P.E.; Upadhyay, V.; Rossen, K.; Cianciosi, S.J.; Purick, R.M.; Eng, K.K.; Reamer; R.A. Askin, D.; Volante, R.P.; Reider, P.J. *Tetrahedron Lett.* **1995**, *36*, 2195. (e) Maligres, P.E.; Weissman, S.A.; Upadhyay, V.; Cianciosi, S.J.; Purick, R.M.; Eng, K.K; Reamer, R.A.; Sager, J.; Rossen, K.; Askin, D.; Volante, R.P.; Reider, P.J. *Tetrahedron* **1996**, *52*, 3327. (f) Rossen, K.; Reamer, R.A.; Volante, R.P.; Reider, P.J. *Tetrahedron Lett.*, **1996**, *37*, 6843. (g) Rossen, K.; Volante, R.P.; Reider, P.J. *Tetrahedron Lett.* **1997**, *38*, 777.

2. Rossen, K.; Weissman, S.A.; Sager, J.; Reamer, R.A.; Askin, D.A.; Volante, R.P.; Reider, P.J. *Tetrahedron Lett.* **1995**, *36*, 6419.
3. (a) Rossen, K.; Sager, J.; DiMichele, L.M. *Tetrahedron Lett.* **1997**, *38*, 3183. (b) Ugi, I.; Lohberger, S.; Karl, R. in *Comprehensive Organic Chemistry: Selectivity for Synthetic Efficiency*, Vol. 20. (Eds. B.M. Trost, C.H. Heathcock), Pergamon, Oxford **1991**, P. 1083.

4. Preparation of **8**: A solution of N-Boc-ethylenendiamine (7.07 g, 44.1 mmol) and dichloroacetaldehyde hydrate (6.30 g, 48 mmol) in 100 mL of toluene is heated to 50°C for 4 h and evaporated to dryness. The residual product is dissolved in 100 mL of MeOH and tert-butylisocyanide (8.0 mL, 71 mmol) and formic acid (96%, 2.0 mL, 51 mmol) are added at 0°C. The reaction mixture is stirred at 23°C for 2 days, and Et_3N (12.5 mL, 90 mmol) is added. After stirring for 3 h at 23°C, the reaction mixture is diluted with 500 mL of EtOAc and 500 mL of hexane and washed twice with 5% aqueous citric acid, 5% aqueous $NaHCO_3$, water and brine. The organic phase is dried over Na_2SO_4, treated with Darco G60 and filtered through a plug of SiO_2 to give after evaporation 15.44 g (100%) of **8** as a red, semisolid material. ^1H and ^{13}C spectra of **8** and **9** were recorded in CD_3CN on a Bruker AM 400 at a frequency of 400.13 and 100.61 MHz respectively. The spectra were run at T=-20°C to resolve the major and minor rotamers. Compounds **8** and **9** are 60:40 and 55:45 rotameric mixtures respectively. **8** Major rotamer-^1H NMR δ 7.96_7 (s, 1H), 7.13 (s, 1H), 6.84 (br s, 1H), 5.59 (t, J=6.0, 1H), 3.46 (t, J=6.3, 2H) 3.07 (q, J=6.3, 2H), 1.35 (s, 9H), 1.30 (s, 9H), minor rotamer 7.97_4 (s, 1H), 6.99 (s, 1H), 6.89 (br s, 1H), 6.31 (t, J=6.3, 1H), 3.58 (t, J=5.4, 2H), 3.09 (om, 2H), 1.37 (s, 9H), 1.29 (s, 9H). Major rotamer-^{13}C NMR δ 164.3, 162.2, 156.4, 137.5, 126.2, 79.1, 52.5, 43.7, 38.9, 28.2(6C), minor rotamer-164.0, 163.8, 156.4, 136.3, 125.0, 79.7, 52.4, 47.5, 39.0, 28.2(6C). The Z- stereochemistry of **8** is base on the observed nOe (represented by the curved arrow) from the vinyl proton to the *t*-butyl amide proton. Dichloroacetaldehyde hydrate is commercially available from TCI, N-Boc-ethylenediamine is commercially available from Aldrich, but is readily prepared in high yield from ethylenediamine.
5. Preparation of **9**: To a solution of **8** (1.00 g, 2.88 mmol) in 50 mL of dry THF under N_2 is added KO*t*Bu (1 M solution in *tert*-butanol, 4.5 mL) at 23°C. After 3 h, the reaction mixture is diluted with 400 mL of EtOAc, washed with 5% aqueous citric acid, H_2O and brine. The organic phase is dried ($MgSO_4$), treated with Darco G60, and filtered through a plug of SiO_2. The residue after evaporation is chromatographed on SiO_2 (60% EtOAc in hexanes increasing to 70%) to give 540 mg of **9** (60% yield) as a tan solid. **9** Major rotamer-^1H NMR δ 8.21 (s, 1H), 7.16 (s, 1H), 6.81 (br s, 1H), 3.65-3.49 (om, 4H), 1.43 (s, 9H), 1.30 (s, 9H), major rotamer-^{13}C NMR δ 163.7, 161.9, 151.7, 118.0, 116.2, 82.5, 52.0, 43.5, 35.8, 28.4 (3C), 27.8 (3C),
6. Preparation of **10**: To a solution of 100 mg of **9** in 4 mL of degassed MeOH is added 2 mol% of the catalyst. The mixture is then hydrogenated at 50 psi H_2 for 24 h. Conversion and ee are determined using a Hewlett Packard SFC instrument with a YMC column (PN:A-903-5NP)followed by 2 Chiracel AS columns with 8% isocratic MeOH as eluent (1 mL / min). RT **9**: 14.1 min, RT (R)-**10**: 15.5 min, (S)-**10**: 17.0 min. Complete conversion of **9** to **10** is obtained with 7 mol% of [(R)-BINAP (COD) Rh] OTf at 100 atm H_2 and 40°C for 24 h to give (S)-**10**. The absolute stereochemistry is determined by preparation of authetic (S)-**10** from (S)-**2** of known absolute stereochemistry (EDC, HCOOH).
7. The following results were obtained at 3.5 atm H_2: [(R)-pTolBINAP Rh (COD)]OTf 3% conv., 80% ee; [(4R,5R)-DIOP Rh (COD)]OTf 3% conv., 50% ee; [CHIRAPHOS Rh (COD)] OTf 0% conv.; [(R,R) DIPAMP Rh (COD)] BF_4 1% conv., <1% ee; (R)-(S) JOSIPHOS Rh (COD)] OTf 3% conv., <1% ee; [3,5-DiMethyl[2.2]PHANEPHOS Rh (COD)] OTf 2% conv., 37% ee; [3,5-DiMethyl-4-Methoxy[2.2]PHANEPHOS Rh (COD)]OTf 3% conv., 41% ee; [TolBINAP Ru Cl_2] Et_3N adduct <1% conv., ,1% ee; [[2.2]PHANEPHOS Ru $(CF_3CO_2)_2$] with nBu_4NI, <1% conv., 21% ee. The poor performance of the [2.2]PHANEPHOS ligand is suprising, since the ligand gives a highly active hydrogenation catalyst for a closely related tetrahydropyrazine: Pye, P.J.; Rossen, K.; Reamer, R.A.; Tsou, N.N.; Volante, R.P.; Reider, P.J. *J. Am. Chem. Soc.* **1997**, *119*, 6207.



8. Preparation of **2**: A solution of 330 mg (1.06 mmol) of (S)-**10** (99%ee) in 5 mL of 35% aqueous hydrazine is heated at 100°C for 9 hours. The reaction mixture is diluted with 100 mL of H_2O and the product is extracted into 100 mL of EtOAc. The organic phase is washed three times with H_2O, dried over $MgSO_4$ and evaporated to dryness to give 273 mg of **2** (91%) as a white crystalline material. An aliquot of the product was formylated (EDC, HCOOH) and its ee was determined as 98% using the SFC.