ORGANIC LETTERS

2009
Vol. 11, No. 2
369−372

Catalytic Asymmetric Synthesis of an HIV Integrase Inhibitor

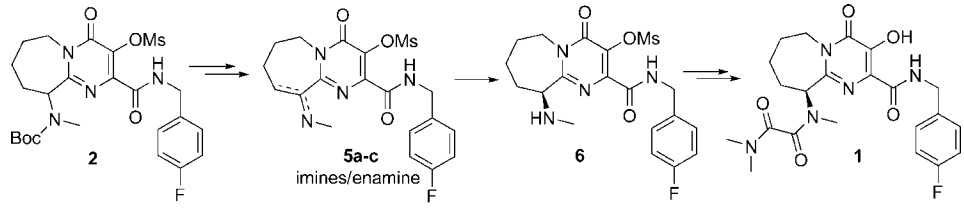
Yong-Li Zhong,* Shane W. Krska,* Hua Zhou, Robert A. Reamer, Jaemoon Lee, Yongkui Sun, and David Askin

Department of Process Research, Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065

yongli_zhong@merck.com; shane_krska@merck.com

Received November 11, 2008

ABSTRACT

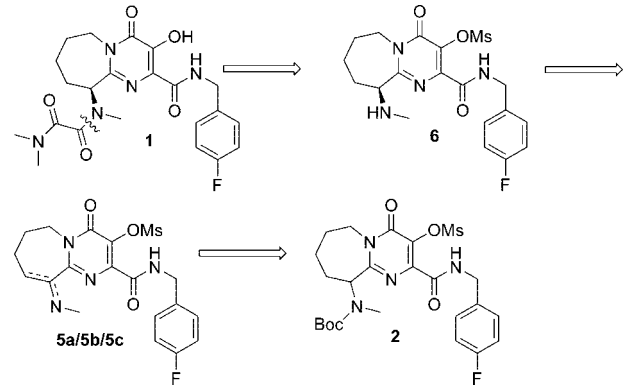


An efficient synthesis of HIV integrase inhibitor (*S*)-(−)-1 via a unique asymmetric hydrogenation of a mixture of imines/enamine 5a−5b/5c is described. Hydrogenation of the imines/enamine by a Rh(I)−Josiphos complex afforded 6 in 90% yield and 90% ee. Amide formation completed the synthesis of 1 in 58% overall yield from 2, which is readily available from 3,4-dihydro-2*H*-pyran in a seven-step sequence. A deuterium labeling study suggests the asymmetric hydrogenation proceeds predominantly via the enamine tautomer.

In our previous article,[1] we described a practical synthesis of the (−)-HIV integrase inhibitor **1**[2] via classical resolution. To support further clinical trials with this candidate, the development of a more efficient synthesis of **1** was required. Herein, we report the asymmetric synthesis of **1** via a unique catalytic asymmetric reduction of a highly functionalized mixture of imines (**5a**−**5b**) and enamine (**5c**).

The key strategic bond disconnections and retrosynthesis of **1** are shown in Scheme 1.[3] We envisioned the installation of the chiral methylamino group in **6** relying upon the efficient catalytic asymmetric hydrogenation of imines/enamine **5a**−**5b/5c**, which could be accessed in three steps from bicyclic hydroxypyrimidinone **2** through Boc-deprotection, N-chlorination, and elimination. Compound **2** is readily available from 3,4-dihydro-2*H*-pyran by a seven-step sequence.[1] The key asymmetric hydrogenation step could potentially proceed via either the imine or enamine tautomer.

Scheme 1. Retrosynthesis of **1**



(1) Zhong, Y.-L.; Pipik, B.; Lee, J.; Kohmura, Y.; Okada, S.; Igawa, K.; Kadowaki, C.; Takezawa, A.; Kato, S.; Conlon, D.; Zhou, H.; King, A. O.; Reamer, R. A.; Gauthier, D. R., Jr.; Askin, D. *Org. Process Res. Dev.* **2008**, *12*, 1245–1252.

(2) (a) Crescenzi, B.; Gardelli, C.; Donghi, M.; Ferrara, M.; Pace, P.; Kinzel, O.; Muraglia, E.; Rowley, M.; Fiore, F.; Gonzalez Paz, O.; Fonsi, M.; Stillmock, K. A.; Witmer, M. V.; Hazuda, D. J.; Summa, V. Abstracts of Papers, *232nd ACS National Meeting*, San Francisco, CA, USA,Sept. 10−14, 2006. (b) Ferrara, M.; Crescenzi, B.; Donghi, M.; Muraglia, E.; Nizi, E.; Pesci, S.; Summa, V.; Gardelli, C. *Tetrahedron Lett.* **2007**, *48*, 8379.

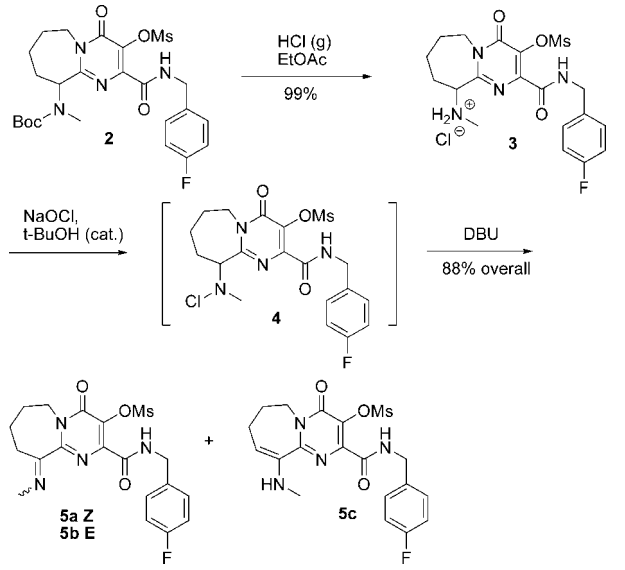
(3) According to our colleague's results (ref 2b), partial racemization happened in the rearrangement to construct the hydroxypyrimidinone core which requires high temperature. Installing the chiral center after the formation of the bicyclic hydroxypyrimidinone avoids this issue.

10.1021/ol802604v CCC: $40.75
Published on Web 12/19/2008

Studies from these laboratories[4] and others[5,6] have shown that primary[4,6] and secondary[5] acyclic enamines derived from β-ketoesters and amides are viable substrates for asymmetric hydrogenation, although no examples of asymmetric hydrogenation of cyclic secondary enamines have been reported. Exocyclic *N*-alkyl imines have been reduced with good enantioselectivity using Ru-catalyzed transfer hydrogenation[7] and Ti-catalyzed hydrosilylation.[8] However, the enantioselective hydrogenation of acyclic imines remains a significant challenge, and no general catalyst systems have been reported.[9]

Thus, treatment of compound **2**[10] with hydrogen chloride in dry ethyl acetate led to ammonium chloride **3**, which was directly crystallized from the reaction mixture in 99% yield (Scheme 2). Subsequent treatment of **3** with 2.5 N sodium hydroxide aqueous solution in isopropyl acetate and water, followed by addition of 10 mol % of *tert*-butanol, acetic acid, and sodium hypochlorite,[11] gave a quantitative assay yield of N−Cl intermediate **4**. Without isolation, compound **4** was directly exposed to DBU to afford a mixture of imines (**5a**−**5b**) and enamine (**5c**) (ratio of **5a**:**5b**:**5c** ca. 66:21:13)[12] as a light yellow crystalline solid in 88% isolated yield.

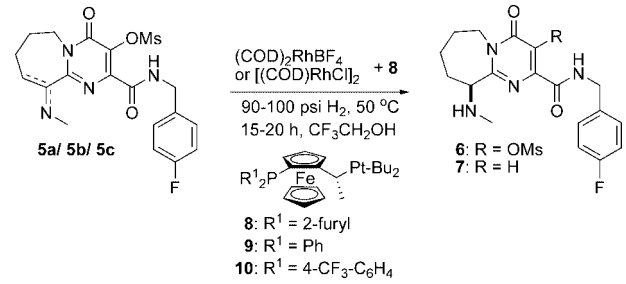
Scheme 2. Preparation of Imines and Enamine



Attempts to reduce the mixture of isolated imines (**5a**−**5b**)/enamine (**5c**) using chiral Ru, Rh, and Ir transfer hydrogenation catalysts gave low levels of enantioselectivity (<30% ee). However, screening this substrate mixture against a library of chiral bis(phosphine) Rh and Ir complexes in a variety of solvents yielded a catalyst system consisting of Josiphos **8** in conjunction with $(COD)_2RhBF_4$ that gave the desired product in reasonable conversion and enantioselectivity (Table 1, entry 1). Interestingly, the substitution pattern of the best ligand **8** was very similar to that of the two ligands (**9** and **10**) found to be effective in the asymmetric hydrogenation of β-enamine amides and esters.[4a] In addition, as was observed in certain cases for the hydrogenations of unprotected primary and secondary enamines,[4,5] the use of 2,2,2-trifluoroethanol (TFE) was found to be key to achieving high reactivity and enantioselectivity in this reaction. Interestingly, product **7**, formally derived from hydrogenolytic cleavage of a mesylate group from **6**, was detected as a byproduct in most of the screening reactions. The other major byproduct of the reaction, the corresponding alcohol derived from hydrolysis of **5a/5b/5c** to the ketone followed by reduction, could be minimized by rigorous drying of the reaction mixture with 4 Å molecular sieves.

Although the Josiphos/Rh catalyst system gave the desired chiral amine in useful enantioselectivity, it ex-

Table 1. Optimization of Asymmetric Hydrogenation Conditions



entry	precursor[a]	S/C[b]	[SM][c]	TFA[d] (equiv)	% convn[e]	6:7[e]	er[f]
1	BF_4	37	50	0	>99	47:1	94:6
2	BF_4	63	100	0	99	49:1	95:5
3	Cl	185	100	0	72	100:0	94:6
4	Cl	185	100	0.2	86	85:1	95:5
5	Cl	185	100	0.5	99	31:1	95:5
6	Cl	185	100	0.8	99	8:1	95:5
7	Cl	250	200	0.5	98	23:1	95:5

[a] The Rh catalysts were preformed by stirring the metal precursor and the ligands at ambient temperature in TFE. [b] Sustrate to catalyst ratio. [c] Concentration of **5a/5b/5c** in mg/mL. [d] Equivalents of trifluoroacetic acid (TFA) relative to substrate. [e] HPLC area percent, uncorrected for absorption factor. [f] Enantiomeric ratio of desired:undesired product, determined by chiral HPLC analysis.

(4) (a) Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, J. D., III; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918–9919. (b) Hansen, K. B.; Rosner, T.; Kubryk, M.; Dormer, P. G.; Armstrong, J. D., III *Org. Lett.* **2005**, *7*, 4935–4938. (c) Kubryk, M.; Hansen, K. B. *Tetrahedron: Asymmetry* **2006**, *17*, 205–209.

(5) Dai, Q.; Yang, W.; Zhang, X. *Org. Lett.* **2005**, *7*, 5343–5345.

(6) Bunlaksananusorn, T.; Rampf, F. *Synlett* **2005**, 2682–2684.

(7) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916–4917.

(8) (a) Verdaguer, X.; Lange, U. E. W.; Reding, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 6784–6785. (b) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11703–11714. (c) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952–8965.

(9) For a recent example, see: (a) Cheemala, M. N.; Knochel, P. *Org. Lett.* **2007**, *9*, 3089–3092. (b) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: Weinheim, 2000; p 1.

(10) For the preparation of compound **2**, please see ref 1.

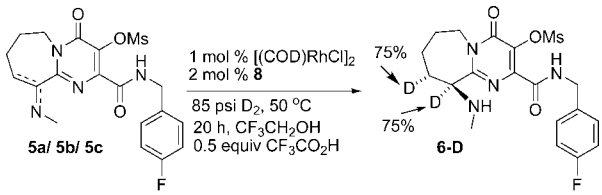
(11) Zhong, Y.-L.; Zhou, H.; Gauthier, D. R., Jr.; Lee, J.; Askin, D.; Dolling, U. H.; Volante, R. P. *Tetrahedron Lett.* **2005**, *46*, 1099.

(12) The ratio of **5a**:**5b**:**5c** varied from 66:21:13 to 14:21:65 depending on the temperature and solvents. It was subsequently found that this ratio had no impact on the performance of the asymmetric hydrogenation.

hibited rather low activity, requiring 1.6 mol % catalyst to reach full conversion even when run under relatively concentrated conditions (Table 1, entry 2). Reasoning that the secondary amine product might be inhibiting the catalyst activity,[4b] various acid additives were screened in an attempt to disrupt product coordination to the metal via protonation of the basic N lone pair.[13] Indeed, addition of increasing amounts of trifluoroacetic acid (TFA) to the reaction mixture gave a marked increase in reaction rate, however at the expense of increased formation of byproduct **7** (Table 1, entries 3−6).[14] Using an optimal charge of 0.5 equiv of TFA and running the reaction at high concentration (0.46 M) resulted in full conversion in 18 h reaction time using only 0.4 mol % catalyst, giving the desired methanesulfonate product **6** in 90% ee and 90% HPLC assay yield, with a manageable level of the side product **7** (4%, Table 1, entry 7). These conditions were successfully demonstrated on a 500 g scale.[15]

Intrigued by the success of this reaction, we sought to examine its mechanism more closely. In particular we were interested to know if this reaction followed the pattern observed with β-enamine amides in which the hydrogenation appears to proceed predominantly through the imine tautomer.[4a] Running the asymmetric hydrogenation under a D_2 atmosphere resulted in significant (75%) incorporation of deuterium into both the *ipso* and *alpha* positions of the secondary amine product **6-D** in roughly equal proportion (Scheme 3). More telling was the fact

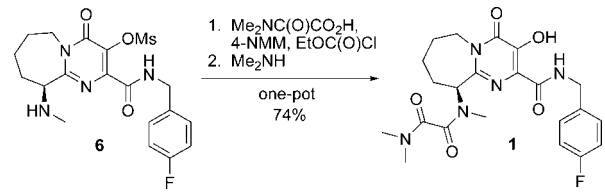
Scheme 3. Deuterium Asymmetric Hydrogenation of Imine/Enamines **5a**-**5b/5c**



that the two deuterons were exclusively cis based on NMR spectroscopy. These observations strongly suggest that, despite the similarities in catalyst and reaction conditions to our prior report of hydrogenation of β-enamine amides, the present reaction proceeds predominantly through the *enamine* tautomer. At present we have no rationale to explain this difference.

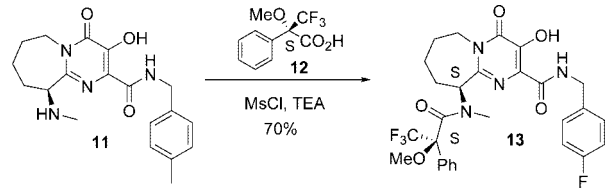
We have previously reported that the methanesulfonate ester **6** was cleaved by benzylamine at 70 °C to give hydroxyl chiral amine (−)-**11**.[1] An alternative method involves installation of the side chain followed by cleavage of the methanesulfonate ester in one pot to afford **1**. Thus, as shown in Scheme 4, the chiral amine (−)-**6** was coupled with the mixed-anhydride of *N*,*N*-dimethyloxamic acid generated in situ using ethyl chloroformate, followed by cleavage of the methanesulfonate ester with *N*,*N*-dimethylamine to afford **1** in 74% overall yield and >99% ee after isolation by crystallization.

Scheme 4. Synthesis of **1**



The Mosher's amide **13** was prepared by treatment of the chiral amine (−)-**11** with the mixed-anhydride generated in situ by treatment of Mosher's acid **12** and methanesulfonyl chloride (Scheme 5).[16] Thus, the absolute configuration of

Scheme 5. Synthesis of Mosher's Amide **13**



the chiral center of **1** was determined as *S* by X-ray crystallography of the Mosher's amide **13** (Figure 1).[17]

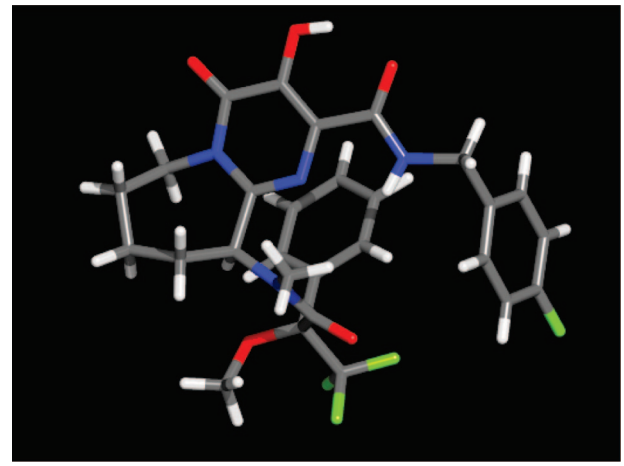


Figure 1. Structure of **13** in the crystal.

In summary, we have developed a practical, scaleable, and efficient asymmetric synthesis of the potent HIV integrase inhibitor **1** in 58% overall yield from intermediate **2**. The synthesis is highlighted by a unique catalytic asymmetric hydrogenation of a highly functionalized mixture of imines/enamine (**5a**−**5b/5c**) to give chiral amine (−)-**6** in 90% assay yield and 90% ee. The absolute configuration of the chiral center of **1** was determined as

S by X-ray crystallography of the Mosher's amide **13**.[18] This chromatography-free asymmetric synthesis of **1** was used successfully to prepare large quantities of the HIV integrase inhibitor **1**.

(13) Addition of Boc_2O to the reaction mixture as per ref 4b in an attempt to trap the product as the N-Boc secondary amine resulted in rapid formation of the N-Boc enamide which was inert to hydrogenation.

(14) Acids with more strongly coordinating counterions, such as benzoic, tartaric, oxalic, methanesulfonic, chloroacetic, and camphorsulfonic, gave lower conversions and enantioselectivities. Tetrafluoroboric acid (as the etherate) gave equivalent results to TFA.

(15) Interestingly, during scale-up runs in metal (stainless steel and Hastelloy C) reactors, the hydrogenation of **5a/5b/5c** proceeded in the absence of added catalyst to varying extents depending on the vessel—in some cases full conversion was observed in 20 h. When a TFE solution of the substrate was exposed to fresh clippings of pristine Hastelloy C wire in the presence of H_2, low but detectable amounts of product **6** were formed according to HPLC. In the absence of the wire, no product was formed.

(16) (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Choi, H.-S.; Fong, K.-C.; He, Y.; Yoon, W.-H. *Org. Lett.* **1999**, *1*, 883. (b) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S.; Jung, J.; Choi, H.-S.; Yoon, W. H. *J. Am. Chem. Soc.* **2002**, *124*, 2202.

(17) The X-ray crystallography confirmed the assignment of the absolute configuration of the chiral center of **1** (ref 2b).

(18) CCD Deposition Code: CCDC 707825.

Acknowledgment. We would like to thank the following individuals from Merck Research Laboratories: Dr. T. J. Novak (HRMS); Dr. Richard G. Ball, Ms. Jennifer R. Foley, and Ms. Nancy N. Tsou (X-ray); Ms. M. Biba (chiral HPLC); Drs. Ulf H. Dolling, Donald R. Gauthier, Jr., David L. Hughes, and Shigemitsu Okada for helpful scientific discussions.

Supporting Information Available: Full experimental details, spectral data for new compounds (PDF), and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL802604V