ORGANIC LETTERS

2007
Vol. 9, No. 2
267−270

Directed Reductive Amination of β-Hydroxy-ketones: Convergent Assembly of the Ritonavir/Lopinavir Core

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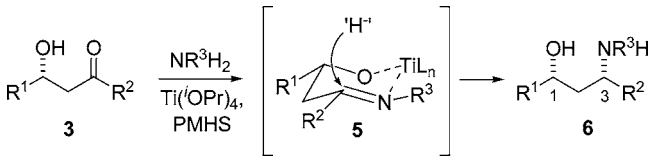
Received November 7, 2006

ABSTRACT



An efficient procedure for the directed reductive amination of β-hydroxy-ketones (3) for the stereoselective preparation of 1,3-*syn*-amino alcohols (6) is reported. The operationally simple protocol uses Ti(ⁱOPr)$_4$ for coordination of the intermediate imino alcohol (5) and PMHS as the reducing agent. The method was expanded to an asymmetric aldol reductive amination sequence to allow a highly convergent synthesis of the hydroxy-amine core of the HIV-protease inhibitors ritonavir and lopinavir.

The chiral 1,3-amino alcohol functionality presents a key element in many bioactive structures, and its synthesis is a high priority from the perspective of medicinal chemistry and drug discovery.[1,2] The direct reductive amination of a carbonyl in a one-pot fashion with an amine and a reducing agent is recognized as a very important, direct, and thus synthetically economical means to synthesize chiral amines.[3,4] However, despite this importance, so far, only few examples of asymmetric versions have been described.[5,6] In particular, the development of substrate-controlled direct asymmetric reductive aminations presents an important research goal.[7,8]

Herein, we report the design, synthetic development, and application of a procedure for the direct reductive amination of β-hydroxy ketones to give in an operationally simple

(1) For examples of bioactive 1,3-amino alcohols, see: (a) Wang, Y.-F.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465. (b) Benz, G.; Henning, R.; Stasch, J.-P. *Angew. Chem., Int. Ed.* **1991**, *30*, 1702. (c) Boyd, S. A.; Fung, A. K. L.; Baker, W. R.; Mantei, R. A.; Armiger, Y.-L.; Stein, H. H.; Cohen, J.; Egan, D. A.; Barlow, J. L.; Klinghofer, V.; Verburg, K. M.; Martin, D. L.; Young, G. A.; Polakowski, J. S.; Hoffman, D. J.; Garren, K. W.; Perun, T. J.; Kleinert, H. D. *J. Med. Chem.* **1992**, *35*, 1735. (d) Jacobi, P. A.; Murphree, S.; Rupprecht, F.; Zheng, W. *J. Org. Chem.* **1996**, *61*, 2413. (e) Steinmetz, H.; Glaser, N.; Herdtweck, E.; Sasse, F.; Reichenbach, H.; Höfle, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4888.

(2) For previous approaches to the chiral 1,3-amino alcohol functionality, which are however not as short and convergent as the one described herein, see: (a) Pilli, R. A.; Russowsky, D.; Dias, L. C. *Chem. Commun.* **1987**, *14*, 1053. (b) Pilli, R. A.; Russowsky, D.; Dias, L. C. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1213. (c) Ghosh, A. K.; Bilcer, G.; Schiltz, G. *Synthesis* **2001**, 2203. (d) Keck, G. E.; Truong, A. P. *Org. Lett.* **2002**, *4*, 3131. (e) Benedetti, F.; Berti, F.; Norbedo, S. *J. Org. Chem.* **2002**, *67*, 8635. (f) Adamo, I.; Benedetti, F.; Berti, F.; Campaner, P. *Org. Lett.* **2006**, *8*, 51.

(3) For reviews, see: (a) Martens, J. *Methods of Organic Chemistry (Houben-Weyl)*; Georg Thieme Verlag: Stuttgart, 1995; Vol. E21d, p 4199. (b) Baxter, E. W.; Reitz, A. B. *Organic Reactions*; Wiley: New York, 2002; Vol. 59, p 1. (c) Gomez, S.; Peters, J. A.; Maschmeyer, T. *Adv. Synth. Catal.* **2002**, *344*, 1037.

(4) More recent examples are described in: (a) Apodaca, R.; Xiao, W. *Org. Lett.* **2001**, *3*, 1745. (b) Allegretti, M.; Berdini, V.; Candida Cesra, M.; Curti, R.; Nicolini, L.; Topai, A. *Tetrahedron Lett.* **2001**, *42*, 4257. (c) Gross, T.; Seayad, A. M.; Ahmad, M.; Beller, M. *Org. Lett.* **2002**, *4*, 2055. (d) Miriyala, B.; Bhattacharyya, S.; Williamson, J. S. *Tetrahedron* **2004**, *60*, 1463. (e) Itoh, T.; Nagata, K.; Miyazaki, M.; Ishikawa, H.; Kurihara, A.; Ohsawa, A. *Tetrahedron* **2004**, *60*, 6649. (f) Menche, D.; Hassfeld, J.; Li, J.; Menche, G.; Ritter, A.; Rudolph, S. *Org. Lett.* **2006**, *8*, 741.

(5) For a review of direct asymmetric reductive aminations, see: Tararov, V. I.; Börner, A. *Synlett* **2005**, 203.

(6) For auxiliary-mediated variants, see: (a) Blaser, H.-U.; Buser, H.-P.; Jalett, H. P.; Pugin, B.; Spindler, F. *Synlett* **1999**, 867. (b) Kadyrov, R.; Riermeier, T. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5472. (c) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Fischer, C.; Börner, A. *Adv. Synth. Catal.* **2004**, *346*, 561. (d) Chi, Y. X.; Zhou, Y. G.; Zhang, X. M. *J. Org. Chem.* **2003**, *68*, 4120. (e) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84.

10.1021/ol062715y CCC: $37.00
Published on Web 12/23/2006

manner 1,3-*syn*-amino alcohols. Furthermore, the efficiency of this method was expanded to an asymmetric aldol reductive amination sequence for the rapid assembly of the hydroxy-amine core of the pharmaceutically used[9] HIV-protease inhibitors ritonavir (**1**)[10] and lopinavir (**2**)[11] (Figure 1).

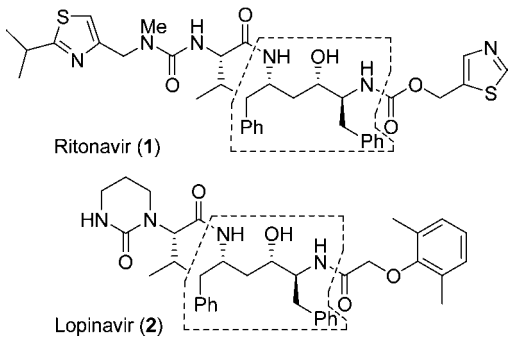
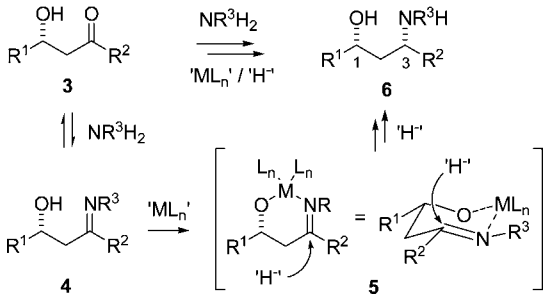


Figure 1. 1,3-*syn*-Amino alcohol functionality: a key element of the HIV-protease inhibitors ritonavir (**1**) and lopinavir (**2**).

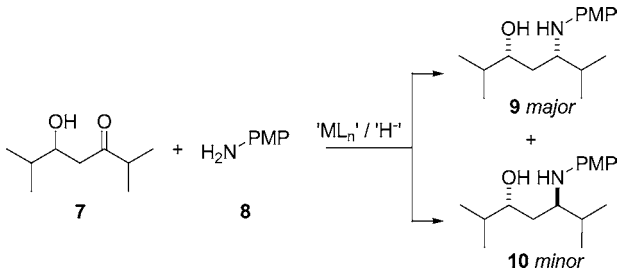
As outlined in Scheme 1, the 1,3-amino alcohol functionality may be obtained in a retro-synthetic sense by reductive amination of hydroxy-ketone **3**, itself readily available by aldol coupling. To access the 1,3-syn array **6**, a chelation-controlled intermolecular reduction was envisioned. As the intermediate imino alcohol **4** was expected to strongly coordinate to Lewis acids, reduction should then proceed in a Zimmerman−Traxler-type transition state (**5**), where R^2 adopts an equatorial position, leading to the desired 1,3-syn product. It should be noted that this synthetic design relies on selective activation of imine **4** as one of the intermediates in the reductive amination of carbonyls.[5,6c]

Scheme 1. Synthetic Concept for Accessing 1,3-*syn*-Amino Alcohols by Directed Reductive Amination



To test our notion for such a directed C−N bond formation, the amination of hydroxy-ketone **7** was studied with *para*-anisidine (**8**), which may be readily cleaved under oxidative conditions (see below), in the presence of various Lewis acids and hydride reagents. Representative results are summarized in Table 1. Although various conditions[12] (e.g., entries 1−5) failed to give the desired amino alcohols in preparatively useful yields, leading mainly to retro-aldol processes (entries 1, 2, and 4), elimination (entry 3), or low conversion (entry 5), the best results in the first screen were obtained with the reagent combination $Ti(^iOPr)_4/NaBH_4$ (entry 6) giving the desired amine **9** in promising yield and

Table 1. Directed Reductive Amination of β-Hydroxy-ketone **7**[a]



entry	ML_n	H^-	conditions	dr **9**/**10**[b]	yield [%][c]
1	$NiCl_2$	$LiBH_4$	THF, rt	–	<5
2	$ZnCl_2$	$NaBH_4$	THF, rt	78:22	27
3	$Sc(OTf)_3$[d]	Hantzsch ester	toluene, 60 °C	–	<5
4	HOAc	$NaCNBH_3$	THF, rt	83:17	22
5	thiourea[d]	Hantzsch ester	toluene, 60 °C	52:48	14
6	$Ti(^iOPr)_4$	$NaBH_4$	THF, rt	81:19	45
7	$Ti(OEt)_4$	$NaBH_4$	THF, rt	70:30	32
8	$Ti(Binol)(^iOPr)_2$	$NaBH_4$	THF, rt	82:18	16
9	$TiCl(^iOPr)_3$	$NaBH_4$	THF, rt	80:20	28
10	$Ti(^iOPr)_4$	PMHS	THF, rt	83:17	66
11	$Ti(^iOPr)_4$ (1.4 equiv)	PMHS (2.2 equiv)	CH_3CN, −20 °C, 48 h	89:11	81

[a] Typical reaction conditions: 24 h on a 1 mmol scale with 1.25 equiv of Lewis acid (ML_n), 2 equiv of reducing agent (H^-), and 2 equiv of amine **8**. [b] Ratio was determined by RP-HPLC (Nucleosil 100-5 C_{18}) (see Supporting Information). [c] Isolated yield after flash chromatography. [d] Reaction was run with 0.2 equiv of Lewis acid in the presence of 5 Å MS. PMP: *para*-methoxy-phenyl.

(7) Asymmetric aminations of cyclic ketones have been reported: (a) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849. (b) Williams, G. D.; Pike, R. A.; Wade, C. E.; Wills, M. *Org. Lett.* **2003**, *5*, 4227. (c) Nugent, T. C.; Seemayer, R. *Org. Process Res. Dev.* **2006**, *10*, 142. (d) Enders, D.; Paleek, J.; Grondal, C. *Chem. Commun.* **2006**, 655.

(8) Asymmetric reductive aminations with chiral amines are reported by: Nugent, T. C.; Ghosh, A. K.; Wakchaure, V. N.; Mohanty, R. R. *Adv. Synth. Catal.* **2006**, *348*, 1289.

(9) (a) Abbenante, G.; Fairlie, D. P. *Med. Chem.* **2005**, *1*, 71. (b) Kaplan, S. S.; Hicks, C. B. *Expert Opin. Pharmacother.* **2005**, *6*, 1573.

(10) Kempf, D. J.; Sham, H. L.; Marsh, K. C.; Flentge, C. A.; Betebenner, D.; Green, B. E.; McDonald, E.; Vasavanonda, S.; Saldivar, A.; Wideburg, N. E.; Kati, W. M.; Ruiz, L.; Zhao, C.; Fino, L.; Patterson, J.; Molla, A.; Plattner, J. J.; Norbeck, D. W. *J. Med. Chem.* **1998**, *41*, 602.

(11) Sham, H. L.; Kempf, D. J.; Molla, A.; Marsh, K. C.; Kumar, G. N.; Chen, C. M.; Kati, W.; Stewart, K.; Lal, R.; Hsu, A.; Betebenner, D.; Korneyeva, M.; Vasavanonda, S.; McDonald, E.; Saldivar, A.; Wideburg, N.; Chen, X.; Niu, P.; Park, C.; Jayanti, V.; Grabowski, B.; Granneman, G. R.; Sun, E.; Japour, A. J.; Leonard, J. M.; Plattner, J. J.; Norbeck, D. W. *Antimicrob. Agents Chemother.* **1998**, *42*, 3218.

(12) For related conditions for direct reductive aminations of carbonyls, see: (a) entry 1, ref 4a. (b) Entry 2: Bhattacharyya, S. *Synth. Commun.* **1997**, *27*, 4265. (c) Entry 3: ref 4e. (d) Entry 4: Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897. (e) Entry 5: ref 4f. (f) Entry 6: Bhattacharyya, S.; Neidigh, K. A.; Avery, M. A.; Williamson, J. S. *Synlett* **1999**, 1781.

diastereoselectivity.[12,13] Although this result could not be further improved by modifying the ligand (entries 7−9), use of polymethylhydrosiloxane as the hydride source[14] gave increased conversion and slightly improved selectivity (entry 10). After optimizing the reaction conditions (equivalents, solvent, temperature, reaction time), the 1,3-*syn*-amino alcohol **9** was obtained in good diastereoselectivity and yield (entry 11).[15]

As shown in Figure 2, various additional 1,3-*syn*-amino

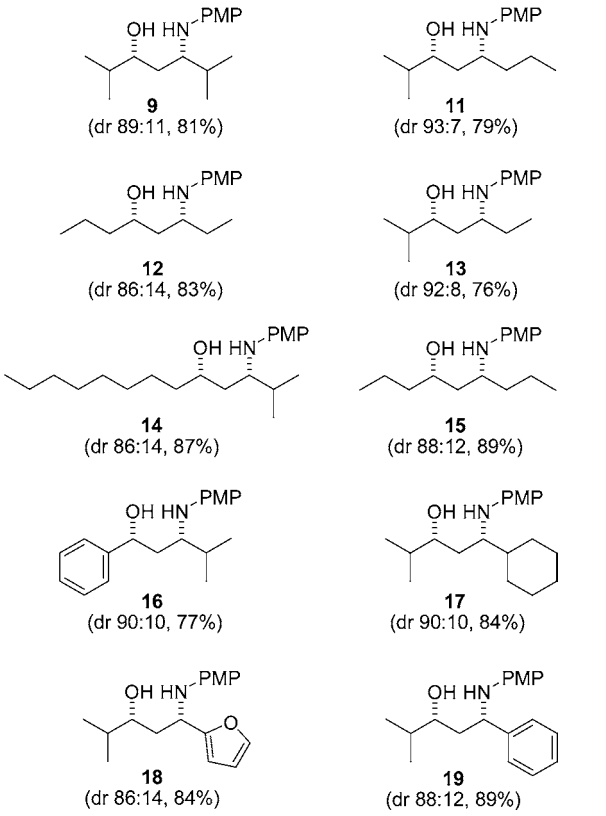
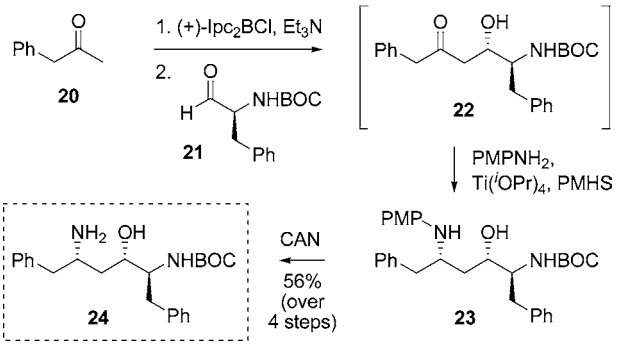


Figure 2. Selected applications of the method for the synthesis of 1,3-*syn*-amino alcohols with the indicated yields and diastereoselectivities.[15]

alcohols were readily obtained under these conditions by amination of the respective *β*-hydroxy-ketones. In all cases, preparatively useful yields and selectivities resulted, without the need for further adaptation of the reaction conditions for specific substrates. In detail, aliphatic (**9**−**15**), cyclic (**17**), as well as aromatic (**16**, **19**) and heteroaromatic substrates (e.g., **18**) are accepted, demonstrating the general usefulness of the protocol.[15] Notably, a similar asymmetric induction was observed also for sterically less-hindered substrates, which may be due to steric requirements of the presumed intermediate **5** (Scheme 1).

The starting materials in our procedure, chiral *β*-hydroxy-ketones, are easily prepared by well-established asymmetric aldol methodology, which adds to the usefulness of our method for a rapid and general access to 1,3-*syn*-amino alcohols. To demonstrate this aspect, a convergent assembly of hydroxy-amine **24**, the key building block of ritonavir and lopinavir, was realized (Scheme 2). Our approach

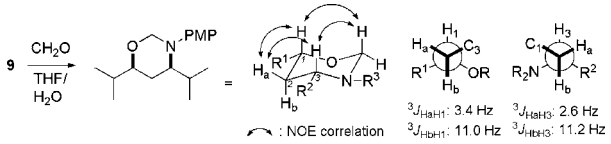
Scheme 2. Asymmetric Aldol Directed Amination Sequence: Convergent Assembly of the Hydroxy-Amine Core (24) of Ritonavir/Lopinavir



involved a diastereoselective aldol coupling of phenylacetone (**20**) with phenylalanine-derived aldehyde **21**, both readily available starting materials, and a subsequent amination of intermediate ketone **22**. Using chiral Ipc-boron-mediated enolate methodology,[16] the hydroxyl-bearing stereogenic center of **22** was readily set up in a straightforward fashion. In a one-pot-type sequence, this crude intermediate was then directly submitted to our conditions of a directed amination to give, after deprotection of the PMP group of **23**, the ritonavir/lopinavir core **24** in good yields. It should be noted that this approach presents the shortest route to **24** reported so far.[2c,e,f]

In summary, we have developed an efficient and operationally simple method for the directed reductive amination of *β*-hydroxy-ketones to give 1,3-*syn*-hydroxy amines in good chemical yields and diastereoselectivities. This approach presents one of the first examples of a general one-pot directed reductive amination of acyclic ketones. The efficiency of this protocol was demonstrated in the synthesis of diverse amines. Furthermore, this procedure was expanded to an asymmetric aldol reductive amination sequence, allowing the so far shortest synthesis of the hydroxy-amine core of the HIV-protease inhibitors ritonavir and lopinavir. It is expected that this protocol will find applications in medicinal chemistry and drug research and will stimulate the development of further methods for asymmetric reductive aminations.

(13) Stereochemical assignment of **9** and **10** was based on *J*-based configurational analysis and confirmed by NMR analysis of a cyclic derivative (see Supporting Information):



(14) Chandrasekhar, S.; Reddy, C. R.; Ahmed, M. *Synlett* **2000**, 1655.

(15) For experimental details, spectral data, HPLC traces, and copies of NMR spectra for all new compounds, see Supporting Information.

(16) For a review on asymmetric boron-mediated aldol reactions, see: Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1.

Acknowledgment. This work was supported by the Fonds der Chemischen Industrie ('Liebig-Stipendium' to D.M., 'Doktorandenstipendium' to F.A.) and the Deutsche Forschungsgemeinschaft (grant ME 2765/2-1). We thank Antje Ritter and Tatjana Arnold (both from Gesellschaft für Biotechnologische Forschung) for technical support.

Supporting Information Available: Experimental details, spectral data, HPLC traces, and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062715Y