ORGANIC LETTERS

2006
Vol. 8, No. 1
51−54

Stereoselective Hydroazidation of Amino Enones: Synthesis of the Ritonavir/Lopinavir Core

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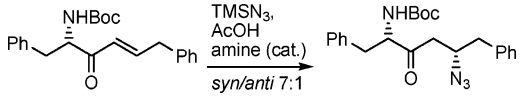
Received October 5, 2005

ABSTRACT



The base-catalyzed hydroazidation of α′-amino α,β-unsaturated ketones with in situ generated hydrazoic acid was found to proceed with high stereoselectivity in favor of the *syn* product. The stereoselectivity is controlled by the configuration of the enone and *syn*/*anti* ratios up to 7:1 were obtained with secondary and tertiary amines at low temperature. By this route the diamino alcohol core of HIV-PR inhibitors ritonavir and lopinavir was synthesized in 37% yield from phenylalanine.

The conjugate addition of a nitrogen nucleophile to an α,β-unsaturated carbonyl compound (the aza-Michael reaction) is a classical synthetic method, giving access to important classes of compounds, such as β-amino acids[1] and ketones,[2] β-lactams,[3] and 1,3-amino alcohols.[4] A variety of nitrogen compounds can be used as nucleophiles in this reaction, including aliphatic and aromatic amines, lithium amides, hydroxylamines, oximes, carbamates, and other nitrogen donors.[1−5] For the introduction of a primary amino group, azide offers several advantages over other nucleophiles as this reagent is simple and inexpensive and does not require catalysts due to its high reactivity, and the conversion of the product into primary amine is relatively atom economic and can be carried out with a variety of reducing agents and conditions.[6] The hydroazidation of α,β-unsaturated compounds has been carried out with hydrazoic acid,[7] but this highly toxic and explosive reagent can be replaced by safer azide donors[8] or, alternatively, can be generated in situ from trimethylsilyl azide ($TMSN_3$) and a carboxylic acid.[9]

Asymmetric aza-Michael reactions have recently attracted much attention, and stereoselection has been achieved with chiral catalysts[5] and by asymmetric induction from chiral reagents or auxiliaries.[10] In this communication we report on the hydroazidation of amino acid derived α,β-unsaturated ketones to give β-azido carbonyl compounds in which the

(1) (a) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodiversity* **2004**, *1*, 1111−1239. (b) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991−8035. (c) Sharma, G. V. M.; Reddy, V. G.; Chander, A. S.; Reddy, K. R. *Tetrahedron: Asymmetry* **2002**, *13*, 21−24. (d) Taillefumier, C.; Lakhrissi, Y.; Lakhrissi, M.; Chapleur, Y. *Tetrahedron: Asymmetry* **2002**, *13*, 1707−1711. (e) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, 117−128.

(2) (a) Bartoli, G.; Bartolacci, M.; Giuliani, A.; Marcantoni, E.; Massaccesi, M.; Torregiani, E. *J. Org. Chem.* **2005**, *70*, 169−174. (b) Kobayashi, S.; Kakumoto, K.; Sugiura, M. *Org. Lett.* **2002**, *4*, 1319−1322. (c) Xu, L. W.; Xia, C. G. *Tetrahedron Lett.* **2004**, *45*, 4507−4510.

(3) Caracciolo Torchiarolo, G.; D'Onofrio, F.; Margarita, R.; Parlanti, L.; Piancatelli, G.; Bella, M. *Tetrahedron* **1998**, *54*, 15657−15666.

(4) (a) Kolarovic, A.; Berkes, D. A.; Baran, P.; Povazanec, F. *Tetrahedron Lett.* **2005**, *46*, 975−978. (b) Takashiro, E.; Nakamura, Y.; Miyamoto, S.; Ozawa, Y.; Sugiyama, A.; Fujimoto, K. *Bioorg. Med. Chem.* **1999**, *7*, 2105−2114.

(5) (a) Xu, L. W.; Xia, C. G. *Eur. J. Org. Chem.* **2005**, 633. (b) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367−391.

(6) (a) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188−5240. (b) Scriven, E. F. V.; Turnbull, K. *Chem Rev.* **1988**, *88*, 297−368.

(7) (a) Lakshmipathi, P.; Rama Rao, A. V. *Tetrahedron Lett.* **1997**, *38*, 2551−2552. (b) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959−8960.

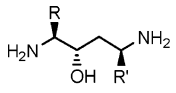
(8) Chung, B. Y.; Park, Y. S.; Cho, I. S.; Hyun, B. C. *Bull. Korean Chem. Soc.* **1988**, *9*, 269−270.

(9) (a) Guerin, D. J.; Horstmann, T. E.; Miller, S. J. *Org. Lett.* **1999**, *1*, 1107−1109. (b) Horstmann, T. E.; Guerin, D. J.; Miller, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3635−3638. (c) Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134−2136.

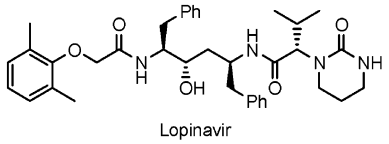
(10) See, for example: (a) Prieto, A.; Fernandez, R.; Lassaletta, J. M.; Vazquez, J.; Alvarez, E. *Tetrahedron* **2005**, *61*, 4609−4613. (b) Etxebarria, J.; Vicario, J. L.; Badia, D.; Carrillo, L. *J. Org. Chem.* **2004**, *69*, 2588−2590. (c) Molteni, M.; Volonterio, A.; Zanda, M. *Org. Lett.* **2003**, *5*, 3887−3890. (d) Sani, M.; Bruche, L.; Chiva, G.; Fustero, S.; Piera, J.; Volonterio, A.; Zanda, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2060−2063. (e) Enders, D.; Muller, S. F.; Raabe, G.; Runsink, J. *Eur. J. Org. Chem.* **2000**, 879−892.

10.1021/ol0524104 CCC: $33.50
Published on Web 12/03/2005

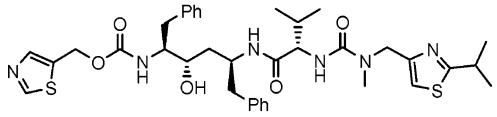
stereoselectivity is efficiently controlled by the remote stereocenter present on the substrate (1,4-asymmetric induction).



1 (**a**: R,R'=Bn)



Lopinavir

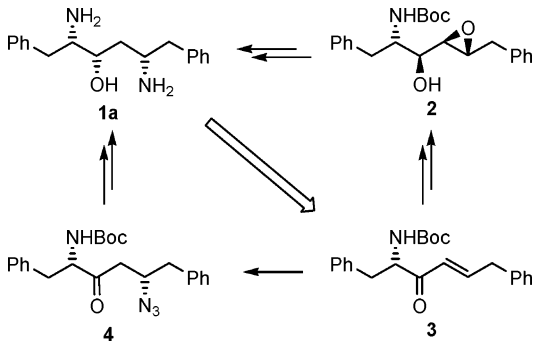


Ritonavir

Our interest in this reaction arose in connection with studies on the synthesis of dipeptide isosteres and peptidomimetic protease inhibitors.[11] Recently, considerable interest has developed in the 1,4-diamino 2-hydroxybutane scaffold **1** as core unit of peptidomimetic inhibitors of HIV-protease.[12] In particular, compound **1a**, a mimic of the Phe-Phe dipeptide, is the central element of Ritonavir[13] and Lopinavir,[14] two potent inhibitors of HIV-PR, currently used in the treatment of AIDS.[15]

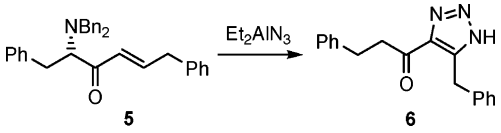
Our original approach to **1a** was based on the retrosynthetic analysis shown in Scheme 1. The pivotal α,β-unsaturated ketone **3**, readily obtained from L-phenylalanine,[16] was transformed into epoxyalcohol **2** in two steps; however, conversion of **2** into **1a** required seven steps.[10b] We reasoned that this approach would be considerably shortened if the enone **3** could be directly hydroazidated to give the azido ketone **4** in a stereocontrolled way: conversion of **4** to **1a** would then be straightforward.

Scheme 1



Our first attempt to hydroazidate ketone **3** with diethylaluminum azide[7] was frustrating, as this reaction failed to give any recognizable product, while the corresponding *N*,*N*-dibenzyl compound **5** (Scheme 2) underwent a [3 + 2] cycloaddition with the same reagent followed by an Al-promoted hydride shift and reductive elimination of dibenzylamine, giving the triazole **6**.[17]

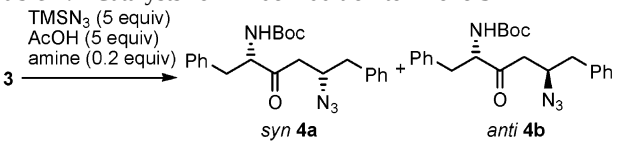
Scheme 2



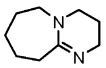
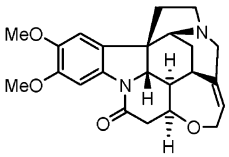
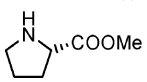
5 **6**

Recently, the β-azidation of α,β-unsaturated carbonyl compounds with a 1:1 mixture of acetic acid and $TMSN_3$ as the azide source and a catalytic amount of a tertiary amine has been reported by Miller and co-workers.[9a] Under these conditions, with tertiary or secondary amines such as triethylamine, diisopropylamine, or DBU, the ketone **3** was completely converted into products (Table 1). However, no stereoselectivity was observed, as a 1:1 mixture of *syn* and *anti* diastereoisomers **4a** and **4b** was formed (Table 1; entries 1−3). Decreasing the basicity (entries 4−6 and 8) and the amount of the catalyst (entries 9 and 10), resulted in an increase of the selectivity in favor of the *syn* isomer **4a.** The

Table 1. Catalysts for Azide Addition to Enone **3**



syn **4a** *anti* **4b**

entry	amine	time h	temp °C	yield %	*syn*/*anti*[a]
1	Et_3N	18	25	quant	1:1
2	$(i\text{-}Pr)_2NH$	18	25	93	1:1
3		18	25	quant	1:1
4		18	25	quant	2:1
5		18	25	quant	5:1
6		18	25	quant	5:1
7		18	-18	quant	6:1
8		4	25	quant	5:1
9		4	25	quant	6:1[b]
10		72	-18	96	7:1[b]

[a] By 400 MHz ^1H NMR. [b] Amine: 0.05 equiv.

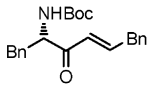
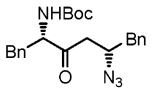
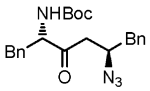
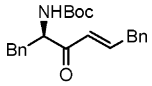
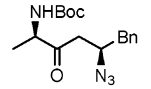
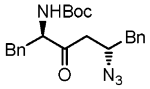
(11) (a) Benedetti, F.; Berti, F.; Garau, G.; Martinuzzi, I.; Norbedo, S. *Eur. J. Org. Chem.* **2003**, 1973−1982. (b) Benedetti, F.; Berti, F.; Norbedo, S. *J. Org. Chem.* **2002**, *67*, 8635−8643. (c) Tossi, A.; Bonin, I.; Antcheva, N.; Norbedo, S.; Benedetti, F.; Miertus, S.; Nair, A. C.; Maliar, T.; Del Bello, F.; Palù, G.; Romeo, D. *Eur. J. Biochem.* **2000**, *267*, 1715−1722.

(12) (a) Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359−1472. (b) Brik, A.; Wong, C. H. *Org. Biomol. Chem.* **2003**, *1*, 5−14.

diastereoselectivity further improved at lower temperatures (entries 7 and 10), and the best de (75%) was obtained with 5% L-proline methyl ester, at −18 °C for 72 h (entry 10).

As the chiral bases brucine (entries 6 and 7) and L-proline methyl ester (entries 8−10) proved particularly effective in this reaction, we turned our attention to the influence of the chirality of the amine on the stereoselectivity. Thus, we carried out the reaction of enantiomeric enones **3** and **7** (derived from D-phenylalanine)[16] with trimethylsilyl azide in the presence of L- and D-proline methyl ester (Table 2).

Table 2. Hydroazidation of Enantiomeric Enones **3** and **7** with L- and D-Proline Methyl Ester[a]

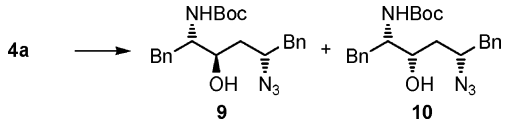
	enone	adducts *syn*	adducts *anti*	amine config	dr[b] (%)
1				L	5:1
2	**3**	*(S,S)*-**4a**	*(S,R)*-**4b**	D	4:1
3				L	4:1
4	**7**	*(R,R)*-**8a**	*(R,S)*-**8b**	D	5:1

[a] Conditions: $TMSN_3$, 5 equiv; AcOH, 5 equiv; amine 0.2 equiv; CH_2Cl_2; 25 °C. [b] *syn*/*anti* ratios; by chiral HPLC.

A comparison of matching substrate-base pairs (entries 1 and 4) and mismatching pairs (entries 2 and 3) shows only a modest drop in the stereoselectivity from 5:1 to 4:1. This clearly indicates that, with the present series of amines,[18] the chirality of the catalyst has only a minor effect on the stereoselectivity, which is chiefly controlled by the substrate through 1,4 asymmetric induction.[19]

The main diastereoisomer **4a**, obtained from the reaction of enone **3** with $TMSN_3$ (Table 1), was isolated in 70% yield by crystallization; this compound possesses the correct configuration to serve as a precursor of the target diamine **1a** (Scheme 1). *Syn* (Felkin−Anh) reduction of the α-amino carbonyl group is required for the conversion of **4a** into **1a.**

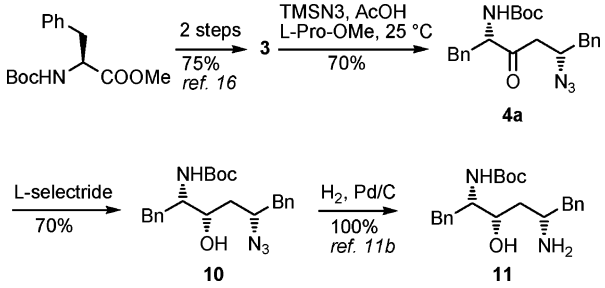
Table 3. Reduction of Amino Ketone **4a**



entry	reagent	conditions	yield (%)	*anti*/*syn*
1	$NaBH_4$	MeOH, 0 °C	90	75:25
2	$NaCNBH_3$	MeOH, 0 °C	85	50:50
3	NB-enantride	THF, −78 °C	80	50:50
4	L-selectride	MeOH, −78 °C	70	<5:95

Reduction with sodium borohydride (Table 3) gave a 3:1 mixture of *anti*,*anti* and *syn*,*syn* diamino alcohols **9**[11b] and **10**.[11b] Sodium cyanoborohydride gave a 1:1 mixture of diastereoisomers, and the same result was obtained with NB-enantride, although this reagent has been reported to give *syn*-reduction with similar substrates.[20] The desired selectivity was obtained with L-selectride,[21] which gave exlusively the *syn*,*syn* azido alcohol **10** (Table 3). This known compound can finally be converted into the mono-Boc-protected diamine **11** by catalytic hydrogenation in 95% yield (Scheme 3).[11b] By this combination of stereoselective azidation and

Scheme 3



syn-reduction, the Boc-protected Phe-Phe isostere **11** is available from **3** in three steps and 49% yield, a considerable improvement over the eight steps (8% yield) previously required.[11b]

In conclusion, we have shown that a good level of stereoselectivity in the substrate-controlled hydroazidation of α-amino enones with $TMSN_3$/AcOH can be obtained by a careful choice of the secondary/tertiary amine catalyst and of the reaction conditions. Although the scope of the reaction and its mechanism are still being investigated, particularly for the underlying stereochemical implications, its synthetic utility has been demonstrated by the conversion of the enone **3** into Boc-protected dipeptide isostere **11**. By this route the monoprotected core of Lopinavir and Ritonavir can be

(13) 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*, 602−617.

(14) 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*, 3218−3224.

(15) (a) Abbenante, G.; Fairlie, D. P. *Med. Chem.* **2005**, *1*, 71−104. (b) Kaplan, S. S.; Hicks, C. B. *Expert Opin. Pharmacother.* **2005**, *6*, 1573−1585.

(16) Benedetti, F.; Miertus, S.; Norbedo, S.; Tossi, A.; Zlatoidzky, P. *J. Org. Chem.* **1997**, *62*, 9348−9353 and references therein.

(17) Adamo, I.; Benedetti, F.; Berti, F.; Nardin, G.; Norbedo, S. *Tetrahedron Lett.* **2003**, *44*, 9095−9097.

(18) See ref 9b and 9c for examples of asymmetric azidations controlled by the amine catalyst.

(19) Accordingly, little or no enantioselectivity was observed in the L-Pro-OMe catalyzed hydroazidation of achiral enones.

(20) Vabeno, J.; Brisander, M.; Lejon, T.; Luthman, K. *J. Org. Chem.* **2002**, *67*, 9186−9191.

(21) Rodriguez, A. C.; Ramos, A. P.; Hawkes, G. E.; Berti, F.; Resmini, M. *Tetrahedron: Asymmetry* **2004**, *15*, 1847−1855.

obtained from commercial *N*-Boc phenylalanine methyl ester in only five steps and 37% yield overall, this being to date the shortest and most efficient synthesis of this important intermediate of the pharmaceutical industry.[22]

Acknowledgment. This work was supported by the Ministry for University and Scientific Research (PRIN 2003 programme and FIRB grant RBNE017F8N).

Supporting Information Available: Experimental procedures and spectral data for compounds **4a/b**, **7**, **8a**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0524104

(22) Ghosh, A. K.; Bilcer, G.; Schiltz, G. *Synthesis* **2001**, 2203−2229.