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A Stereodivergent Approach to Substituted 4-Hydroxypiperidines

Mandy K. S. Vink, Christien A. Schortinghuis,[†] Jordy Luten, Jan H. van Maarseveen, Hans E. Schoemaker,[‡] Henk Hiemstra, and Floris P. J. T. Rutjes*,[†]

Institute of Molecular Chemistry, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

rutjes@sci.kun.nl

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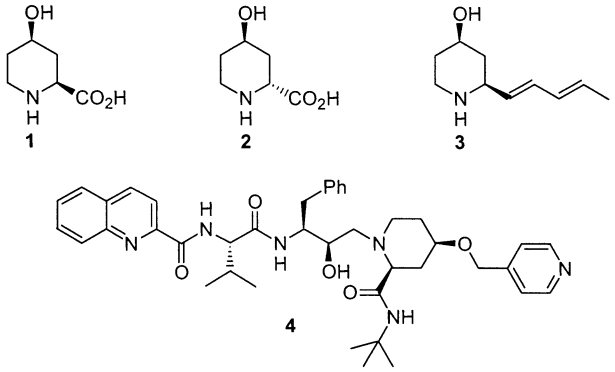
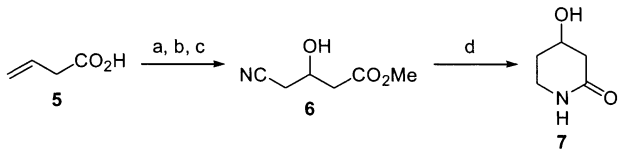
Abstract: A stereodivergent route toward both diastereomeric forms of functionalized 4-hydroxypiperidines has been successfully developed. This route involves biocatalytic generation of the enantiopure starting materials followed by functionalization via *N*-acyliminium ion-mediated CC-bond formation.

Functionalized piperidines are common substructures in natural compounds (e.g., pipecolic acid, coniine, and thalidomide)[1] and often exhibit interesting biological activity. Various methods have been developed in order to arrive at piperidines in an enantiomerically pure fashion.[1,2] In most cases, the enantiopurity originates from either chiral auxiliaries or enantiopure precursors such as amino acid derivatives. A group of piperidines that have not received much attention so far are ones containing a 4-hydroxypiperidine unit, such as the naturally occurring *cis*- and *trans*-4-hydroxypipecolic acids **1** and **2**,[3] the alkaloid SS20846A (**3**),[4] and palinavir (**4**), a highly potent inhibitor of the immunodeficiency virus (HIV).[5]



We developed a novel entry into the latter class of compounds involving the cyclization of δ-amino esters that are obtained via an enantioselective biocatalytic hydrolysis of substituted glutaronitriles. In such enzymatic conversions, generally, one of the two cyano groups is selectively converted into the acid or the amide.[6] This method is particularly useful in the case of prochiral glutaronitriles, where desymmetrization enables a yield of 100%.[7] Once at the lactam stage, *N*-acyliminium ion chemistry can be applied to functionalize the piperidones in a regioselective way.[8]

SCHEME 1. Synthesis of Racemic 4-Hydroxypiperidone[a]



[a] Reagents and conditions: (a) Oxone, H_2O, pH 6; (b) NaCN, $MgSO_4$, H_2O; (c) $SOCl_2$, MeOH (51% from **5**); (d) 50 psi H_2, PtO_2, MeOH (81%).

In this paper, we will detail the synthesis of both diastereomeric forms of substituted 4-hydroxypiperidines following two complementary routes, both involving functionalization of the key lactam **7** via *N*-acyliminium ion chemistry. Starting from commercially available vinylacetic acid (**5**), racemic 4-hydroxypiperidin-2-one (**7**) was efficiently prepared in four steps (Scheme 1). Oxone-mediated epoxidation of the double bond,[9] followed by ring opening with sodium cyanide and subsequent esterification, yielded cyano ester **6** in 51% overall yield. Upon platinum-catalyzed hydrogenation of the nitrile,[6b] spontaneous cyclization occurred to afford the desired lactam **7**.

Following a classical pathway to convert lactam **7** into a suitable *N*-acyliminium ion precursor, the amide functionality was methoxycarbonylated (**8**, Scheme 2). The use of Mander's reagent[10] resulted in higher yields than the corresponding chloroformate. Furthermore, *n*-butyl-

[†] Department of Organic Chemistry, University of Nijmegen, Toernooiveld 1, 6525 ED Nijmegen, The Netherlands.

[‡] DSM Research, Life Science Products, PO Box 18, 6160 MD Geleen, The Netherlands.

(1) Bailey, P. D.; Millwood, P. A.; Smith P. D. *Chem. Commun.* **1998**, 633−640.

(2) For a review, see: (a) Laschat, S.; Dickner, T. *Synthesis* **2000**, *13*, 1781−1813.

(3) For an entry into the synthesis of these compounds, see, e.g.: Rutjes, F. P. J. T.; Veerman, J. J. N.; Meester, W. J. N.; Hiemstra, H.; Schoemaker, H. E. *Eur. J. Org. Chem.* **1999**, 1127−1135.

(4) (a) Komoto, T.; Yano, K.; Ono, J.; Okawa, J.; Nakajima, T. JP Patent 61035788, 1986. (b) Takemoto, Y.; Ueda, S.; Takeuchi, J.; Nakmoto, T.; Iwata, C. *Tetrahedron Lett.* **1994**, *35*, 8821−8824.

(5) (a) Lamarre, D.; Croteau, G.; Bourgon, L.; Thibeault, D.; Wardrop, E.; Clouette, C.; Vaillancourt, M.; Cohen, E.; Pargellis, C.; Yoakim, C.; Anderson, P. *Antimicrob. Agents Chemother.* **1997**, 965−971. (b) Gorys, V.; Soucy, F.; Yoakim, C.; Beaulieu, P. L. Eur. Patent 560 269, 1993. (c) Anderson, P. C.; Soucy, F.; Yoakim, C.; Lavallée, P.; Beaulieu, P. L. US Patent 5 614 533, 1997; *Chem. Abstr.* **1997**, 2131185.

(6) (a) Faber, K. *Biotransformations in Organic Chemistry*, 4th ed.; Springer-Verlag: Heidelberg, 2000. (b) Cooling, F. B.; Fager, S. K.; Fallon, R. D.; Folsom, P. W.; Gallagher, F. G.; Gavagan, J. E.; Hann, E. C.; Herkes, F. E.; Phillips, R. L.; Sigmund, A.; Wagner, L. W.; Wu, W.; DiCosimo, R. *J. Mol. Catal. B: Enzymol.* **2001**, *11*, 295−306. (c) Wieser, M.; Nagasawa, T. In *Stereoselective Biocatalysis*; Patel, R. N., Ed.; Marcel Dekker: New York, 2000; Chapter 17, pp 461−486. (d) Bunch, A. W. *Antonie van Leeuwenhoek* **1998**, *74*, 89−97.

(7) (a) Wang, M.-X.; Liu, C.-S.; Li, J.-S.; Meth-Cohn, O. *Tetrahedron Lett.* **2000**, *41*, 8549−8552. (b) Beard, T.; Cohen, M. A.; Parratt, J. S.; Turner, N. J.; Crosby, J.; Moilliet, N. J. *Tetrahedron: Asymmetry* **1993**, *4*, 1085−1104. (c) Kayeka, H.; Saikai, N.; Sano, A.; Yokoyama, M.; Sugai, T.; Ohta, H. *Chem. Lett.* **1991**, 1823−1824.

(8) For a recent review, see, e.g.: Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817−3856 and references therein.

(9) Bloch, R.; Abecassis, J.; Hassan, D. *J. Org. Chem.* **1985**, *50*, 1544−1545.

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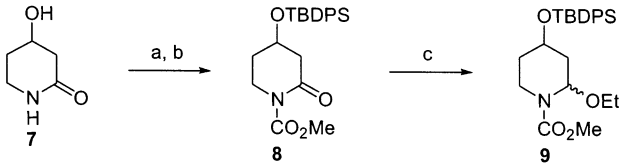
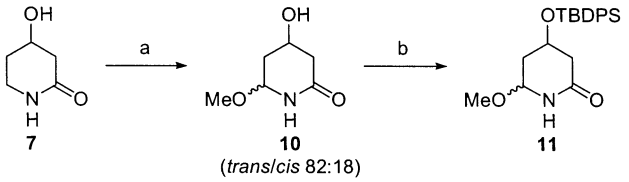
SCHEME 2. Carbamate Pathway[a]



[a] Reagents and conditions: (a) TBDPSCl, DMAP, imidazole, DMF, 80 °C (82%); (b) *n*-BuLi, MeOCOCN, THF, −78 °C, (76%); (c) $NaBH_4$, EtOH, −15 °C; then H_2SO_4/EtOH, −15 °C (96%).

SCHEME 3. Electrochemical Pathway[a]



[a] Reagents and conditions: (a) $-2e^-$ (3.0 V), $PhSO_3Na$, MeOH, 15 °C (95%); (b) TBDPSCl, DMAP, imidazole, MeCN (76%).

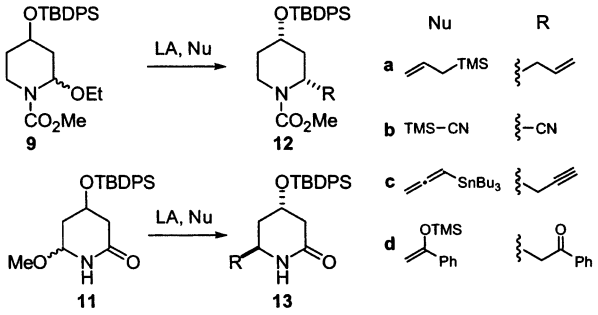
lithium afforded the best results since other bases caused partial elimination of the oxygen substituent. Reduction of the lactam carbonyl and subsequent ethanolysis then gave rise to *N*,*O*-acetal **9** in excellent yield.

A complementary approach to arrive at *N*-acyliminium ion precursors involves electrochemical oxidation of lactams such as **7** in methanol. This type of methoxylation to prepare *N*,*O*-acetals of type **10** has been reported in the literature.[11] Disappointingly, we were unable to reproduce these procedures due to overoxidation of the amide under the constant current setup described. Indeed, it proved to be more rewarding to apply a constant potential of 3.0 V (which corresponds to an initial current of approximately 15 mA). In this way, we were able to prepare *N*,*O*-acetal **10** in excellent yield (Scheme 3) in a reproducible and scalable manner. The use of various other electrolytes (NaCl, NaOMe, Et_4NOTs, NH_4NO_3, Bu_4NBF_4) resulted in lower conversions or no reaction at all.

The most significant difference between the two *N*-acyliminium ion precursors is the position of the acyl group, situated either exocyclic (**9**) or endocyclic (**11**). To alkylate via *N*-acyliminium ion chemistry, four different nucleophiles (Nu) were used (Scheme 4) in combination with two Lewis acids (LA) in different solvents.

A few general trends can be observed in Scheme 4. First of all, despite a generally moderate diastereoselectivity, it is obvious that precursor **9** predominantly produces the cis isomer, whereas precursor **11** displays a preference for the trans isomer. Furthermore, one can deduce that depending of the nature of the nucleophiles, different diastereoselectivity ratios are obtained: especially the allylsilane (Scheme 4, entries 1, 2, 13, and 14)

SCHEME 4. *N*-Acyliminium Ion-Mediated Functionalization



entry	product	Nu	LA	solvent	yield (*trans*/*cis*)[a]
1	**12**	**a**	$BF_3{\cdot}OEt_2$	CH_2Cl_2	65% (17:83)
2	**12**	**a**	$BF_3{\cdot}OEt_2$	MeCN	92% (28:72)
3	**12**	**a**	$Sc(OTf)_3$	MeCN	89% (48:52)
5	**12**	**b**	$BF_3{\cdot}OEt_2$	MeCN	79% (39:61)
6	**12**	**b**	$Sc(OTf)_3$	MeCN	92% (46:54)
7	**12**	**c**	$BF_3{\cdot}OEt_2$	CH_2Cl_2	trace
8	**12**	**c**	$BF_3{\cdot}OEt_2$	MeCN	67% (38:62)
9	**12**	**c**	$Sc(OTf)_3$	MeCN	no reaction
10	**12**	**d**	$BF_3{\cdot}OEt_2$	CH_2Cl_2	22% (25:75)
11	**12**	**d**	$BF_3{\cdot}OEt_2$	MeCN	trace
12	**12**	**d**	$Sc(OTf)_3$	MeCN	86% (26:74)
13	**13**	**a**	$BF_3{\cdot}OEt_2$	CH_2Cl_2	81% (75:25)
14	**13**	**a**	$BF_3{\cdot}OEt_2$	MeCN	100% (89:11)
15	**13**	**b**	$BF_3{\cdot}OEt_2$	CH_2Cl_2	75% (57:43)
16	**13**	**b**	$BF_3{\cdot}OEt_2$	MeCN	42% (58:42)
17	**13**	**c**	$BF_3{\cdot}OEt_2$	CH_2Cl_2	85% (59:41)
18	**13**	**c**	$BF_3{\cdot}OEt_2$	MeCN	100% (51:49)
19	**13**	**d**	$BF_3{\cdot}OEt_2$	CH_2Cl_2	trace
20	**13**	**d**	$BF_3{\cdot}OEt_2$	MeCN	50% (74:26)
21	**13**	**d**	$Sc(OTf)_3$	MeCN	88% (78:22)

[a] Isolated yields after column chromatography; the *trans*/*cis* ratio was determined from ^1H NMR data of the crude reaction mixtures.

and the silyl enol ether (Scheme 4, entries 10, 12, 20, and 21) give reasonable selectivity, the allylsilane being somewhat more selective than the silyl enol ether. The selectivity is also influenced by the nature of the Lewis acid, since $Sc(OTf)_3$ generally provides worse ratios than $BF_3{\cdot}OEt_2$. This could be a result of the significantly lower reaction rate in case of the milder Lewis acidic $Sc(OTf)_3$. On the other hand, in combination with the silyl enol ether, $Sc(OTf)_3$ proved to be the Lewis acid of choice due to the relative instability of this nucleophile in the presence of $BF_3{\cdot}OEt_2$.[12] Our results also demonstrate the positive influence of acetonitrile (in contrast with dichloromethane) on the yield of the reaction; presumably, acetonitrile to some extent stabilizes the intermediate *N*-acyliminium ion, thus avoiding possible side reactions.

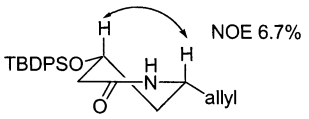
The relative configuration of compounds **12** (the major isomer: cis), and **13** (major isomer: trans) was etablished by performing ^1H NMR NOE measurements. For product **13a**, a clear NOE effect (6.7%) was observed between H4 and H6 of the cis isomer, while the trans isomer showed no spatial interaction between these two protons (Scheme 5).

(10) (a) Crabtree S. R.; Chu W. L. A.; Mander L. N. *Synlett* **1990**, 169−170. (b) Melching, K. H.; Hiemstra, H.; Klaver, W. J.; Speckamp, W. N. *Tetrahedron Lett.* **1986**, *27*, 4799−4802.

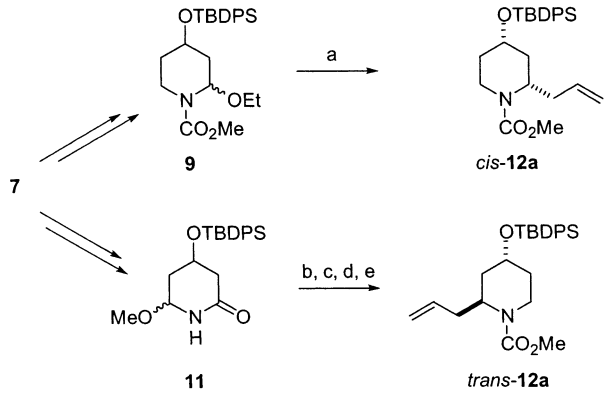
(11) (a) Lennartz, M.; Sadakane, M.; Steckhan, E. *Tetrahedron* **1999**, *55*, 14407−14420. (b) Shono, T. In *Best Synthetic Methods Electroorganic Synthesis*; Katritzky, A. R., Meth-Cohn O., Rees, C. W., Eds.; Academic Press: London, 1991. (c) Steckhan, E. In *Organic Electrochemistry*, 3rd ed.; Lund, H., Baizer, M. M., Eds.; Marcel Dekker: New York, 1990; Chapter IV, pp 581−613.

(12) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809−823.

SCHEME 5. Relative Conformation of the *Cis*-Isomer of 13a



SCHEME 6. A Stereodivergent Synthesis[a]



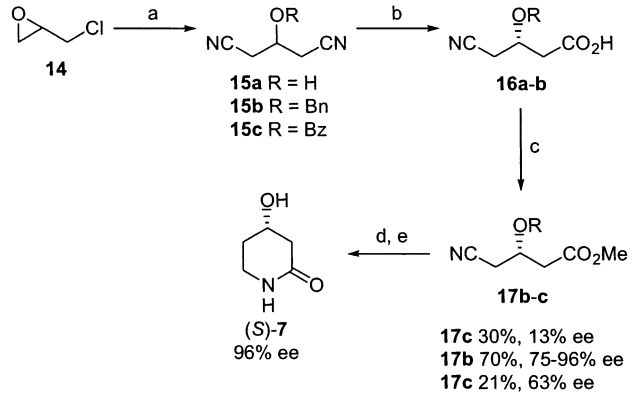
[a] Reagents and conditions: (a) allylSiMe$_3$, BF_3·OEt_2, MeCN, −50 °C to rt; (b) allylSiMe$_3$, BF_3·OEt_2, MeCN, 0 °C to rt; (c) *n*-BuLi, MeOCOCN, THF, −78 °C (96%); (d) DIBAL, THF, −78 °C; (e) Et_3SiH, TFA, TFAA, CH_2Cl_2 (16%, two steps).

The different relative orientation of the two substituents in both heterocycles was confirmed by conversion of allyllactam **13a** into the epimer of **12a** as depicted in Scheme 6; methoxycarbonylation of **13a**, followed by a two-step reduction of the lactam carbonyl, provided the trans-substituted piperidine **12a**.

The selectivity can be explained by the fact that the transition state conformations of the two *N*-acyliminium ion intermediates are slightly different. In carbamate **9**, the oxygen substituent adopts a pseudo-axial conformation, enabling its lone pairs to partially stabilize the cation, which then reacts with the nucleophile via preferred axial attack.[13] This is in agreement with the results of Woerpel and co-workers for related addition reactions onto oxycarbenium ions derived from 4-substituted tetrahydropyrans.[14] Inversely, conversion of **11** into the corresponding *N*-acyliminium ion leads to a species that has the substituent in a pseudo-equatorial conformation and upon axial attack of the nucleophile will give rise to the trans product.

Since these products were synthesized in a racemic fashion, we also explored an entry into an enantiomerically pure synthesis of the starting material **6** to eventually obtain (*S*)-4-hydroxypiperidin-2-one (Scheme 7). To this end, the bacterium *Rhodococcus erythropolis* NCIMB 11540,[15,16] which was already known to possess hydrolytic activity on nitriles (including nitrilase, nitrile hydratase, and amidase activity), was selected to investigate whether it could be used to desymmetrize the prochiral substrates 3-hydroxy-, 3-benzyloxy-, and 3-benzoyloxypentanedinitrile[7b] (**15a**, **15b**, and **15c**, respectively). In all cases, subjection of these dinitriles to the whole cells at pH 7 led to complete conversion into the cyano acids (*S*)-**16a**−**c** without detecting the corresponding cyano amides or bis-hydrolysis products. For HPLC analysis, the cyano acids were subsequently esterified to the corresponding methyl esters, and alcohol **16a** was benzoylated. With the free hydroxyl group (**15a**), there was hardly any selectivity. In contrast, high selectivity was obtained for substrate **15b** with ee's varying from 75 to 96%. The latter result demonstrates that we have identified a new strain that is able to conduct this particular transformation in an ee higher than ever previously reported.[7] Interestingly, subjection of benzoyl-protected dinitrile **15c** to the whole cells led to **16a** (together with a small amount of starting material), which after subsequent esterification and benzoylation appeared to have an ee of 63%. This shows that in the latter case nitrile hydrolysis presumably takes place prior to the hydrolysis of the benzoyl ester. Finally, a 1 g scale batch of **17b** (ee 96%) was esterified and reduced to yield the enantiopure piperidone (*S*)-**7**. Obviously, (*S*)-**7** can be readily converted into the enantiopure variants of the two *N*-acyliminium ion precursors **9** and **11** using the aforementioned procedures.

SCHEME 7. Enantioselective Biocatalytic Nitrile Hydrolysis[a]



[a] Reagents and conditions: (a) NaCN, $MgSO_4$, H_2O, −10 °C (43%); (b) *R. erythropolis* NCIMB 11540, 0.1 M KH_2PO_4/K_2HPO_4 pH 7, 30 °C, 150 rpm; (c) CH_2N_2, EtOH, Et_2O (quant); (d) $CoCl_2$, $NaBH_4$, MeOH, −10 °C (79%); (e) H_2, Pd/C, MeOH (100%).

In conclusion, the combination of biocatalytic desymmetrization of glutaronitriles, followed by two different *N*-acyliminium ion-mediated routes eventually paves the way for the synthesis of a series of enantiopure, substituted 4-hydroxypiperidines. The selective and efficient formation of regioisomeric *N*-acyliminium ion precursors from a common intermediate enables the synthesis of both diastereomeric forms of the target compounds, thereby establishing a diastereodivergent protocol.

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Supporting Information Available: Detailed experimental protocols and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; Chapter 6.
(14) Romero, J. A. C., Tabacco, S. A., Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168−169.
(15) Boesten, W. H. J.; Cals, M. J. H. US Patent 4 705 572, 1987; *Chem. Abstr.* **1987**, *105*, 170617k.
(16) Obtained as lyophilized whole cells from DSM Research, Life Science Products, Geleen, The Netherlands.