Novel Reductive Amination of Nitriles: An Efficient Route to 5-Hydroxypiperidone-Derived *N,N*-Acetals

Mandy K. S. Vink,[a] Christien A. Schortinghuis,[b] Antonina Mackova-Zabelinskaja,[c] Martin Fechter,[c] Peter Pöchlauer,[d] A. Marianne C. F. Castelijns,[e] Jan H. van Maarseveen,[a] Henk Hiemstra,[a] Herfried Griengl,[c] Hans E. Schoemaker,[e] Floris P. J. T. Rutjes[b,]*

[a] Institute of Molecular Chemistry, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands
[b] Department of Organic Chemistry, NSRIM, University of Nijmegen, Toernooiveld 1, 6525 ED Nijmegen, The Netherlands
Fax: (+31)-24-365-3393, e-mail: rutjes@sci.kun.nl
[c] Institute of Organic Chemistry, Technical University Graz, Stremayrgasse 16, 8010 Graz, Austria
[d] DSM Fine Chemicals Austria, St. Peterstrasse 25, 4021 Linz, Austria
[e] DSM Research, Life Science Products, PO Box 18, 6160 MD Geleen, The Netherlands

Received: November 8, 2002; Accepted: January 9, 2003

Abstract: 5-Hydroxypiperidin-2-one is a versatile building block for the preparation of potentially biologically active compounds. We detail an enantioselective biocatalytic approach towards its synthesis using (*S*)-hydroxynitrile lyase (HNL)-mediated cyanohydrin formation, followed by hydrogenation. By adjusting the conditions of the latter step, we were able to obtain 5-hydroxypiperidinone-derived (bicyclic) *N,N*-acetals *via* an unprecedented reductive amination of the nitrile group, as well as form *N*-alkylated 5-hydroxypiperidinone in a single step from the same cyanohydrin intermediate.

Keywords: cyanohydrin; (*S*)-*Hb*HNL; hydroxylactam; nitrile hydrogenation; *N,N*-acetals

3-Hydroxypiperidines constitute a class of piperidine alkaloids that contain a conformationally restricted β-amino alcohol moiety. Representative examples that are encountered in nature include the plant alkaloids febrifugine[1] and pseudoconhydrine (Figure 1).[2] In addition, this structural moiety also occurs in pharmaceuticals[3] and may be used as a scaffold for combinatorial functionalization to give biologically relevant compound libraries.

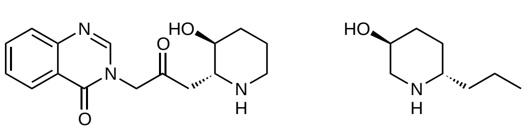
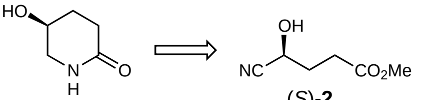

febrifugine pseudoconhydrine

Figure 1.

We envisaged that both natural products are accessible in enantiomerically pure form *via* regioselective functionalization of hydroxylactam **1** (Equation 1) using *N*-acyliminium ion-mediated addition reactions. The basis for such an approach was inspired by our recently developed stereodivergent sequence to functionalize 4-hydroxypiperidin-2-one.[4] We anticipated that we would have facile access to large quantities of lactam **1** *via* hydrogenation of the enantiopure cyanohydrin **2**. The latter compound, in turn, may be prepared *via* a hydroxynitrile lyase (HNL)-mediated enantioselective addition of HCN to the corresponding aldehyde. While investigating whether this pathway could be used to synthesize the aforementioned natural products, we came across a novel reductive amination reaction of nitriles that we wish to detail in this contribution.



1 (*S*)-**2** (1)

Hydroxynitrile lyases (or oxynitrilases) can be obtained from different sources. Perhaps the most widely used oxynitrilase is readily obtained from almonds and shows generally good to excellent (*R*)-selectivity in the addition of HCN to aldehydes.[5] In contrast to the almond oxynitrilase, the less frequently used hydroxynitrile lyase from *Hevea brasiliensis* (*Hb*HNL) shows excellent (*S*)-selectivity on a wide range of aromatic and aliphatic aldehydes and ketones.[6] Gratifyingly, by using the (*S*)-*Hb*HNL-catalyzed addition of HCN to aldehyde **3**,[7] we

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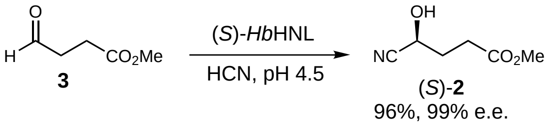
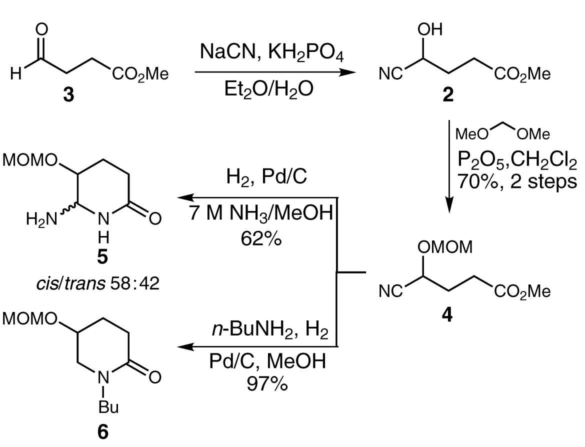
were able to obtain the cyanohydrin **2** in virtually enantiomerically pure form in 96% yield (Equation 2).[8,9]



(2)

Considering the ready availability of both starting material and enzyme, we now have an excellent starting point for an enantiomerically pure route to the aforementioned natural products. In order to establish suitable procedures for the conversion of cyanohydrin **2** into the desired lactam **1**, we used the racemic cyanohydrin, which was prepared from aldehyde **3** according to a modified literature procedure (Scheme 1).[10] In contrast to the originally described reaction, we used KH_2PO_4 to suppress ester saponification. In view of the lability of the cyanohydrin, we chose to protect the hydroxy function with a stable MOM-protective group to develop proper conditions for the hydrogenation. The MOM-ether was prepared under acidic conditions with dimethoxymethane and P_2O_5[11] in 70% yield over two steps. Hydrogenation of the cyano group was initially attempted using platinum oxide in methanol under hydrogen pressure (1–4 bar), but was unsuccessful. Much to our surprise, hydrogenation (1 bar) with palladium on carbon in a 7 M solution of ammonia in methanol gave, instead of the anticipated lactam, a diastereomeric mixture of the amino-substituted lactams **5** in 62% yield. The configuration of the major isomer was determined to be *cis* using ^{1}H NMR NOE experiments.

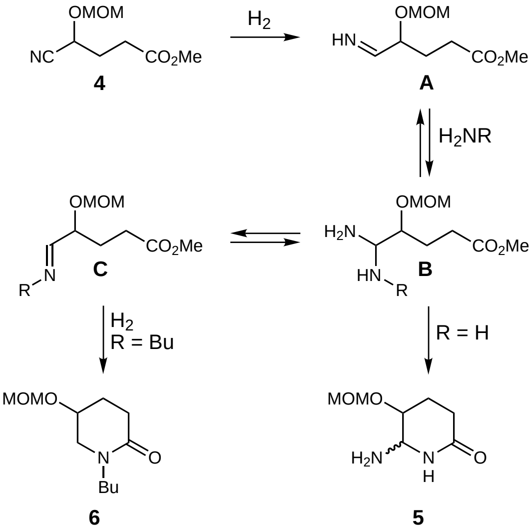
This unexpected outcome prompted us to investigate the generality of this reaction and thus develop a straightforward access to 6-aminopiperidones. We therefore performed the hydrogenation in the presence of butylamine (1.5 equivs., 0.4 M). Addition of butylamine did not lead to the expected *N*,*N*-acetal, but instead to the *N*-alkylated lactam **6** in excellent yield. However, the use of larger amounts of butylamine led to a complex mixture of products.



Scheme 1.

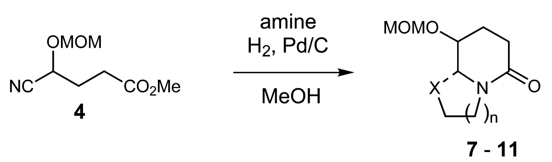
Hence, we proposed a mechanism to explain these results (Scheme 2). Supposedly, first the nitrile is partially hydrogenated to an imine intermediate (**A**), which upon attack of the amine forms the *N*,*N*-acetal **B**. This aminal readily expels ammonia to form imine **C**. When the reaction is performed in the presence of an excess of ammonia, the equilibrium between acetal **B** and imine **C** is primarily on the side of **B** and cyclization of one of the amine groups onto the ester leads to the formation of aminolactam **5**. In the presence of an equimolar amount of butylamine, however, the transimination product **C** will be the predominant intermediate, which after further hydrogenation and subsequent ring closure will give rise to *N*-butyllactam **6**. The fact that these reactions proceed in such high yields may be due to the fact that the adjacent substituent significantly slows down the rate of the imine hydrogenation, thus giving rise to quantitative formation of aminal intermediate **B**.[12]

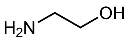
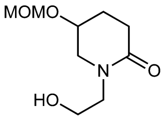
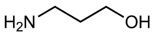
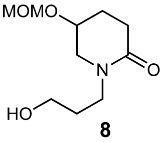
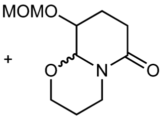
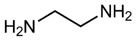
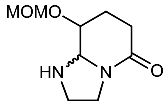
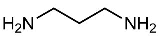
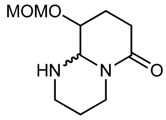
In order to further determine the scope of this reaction, we expected that the use of dinucleophilic species such as amino alcohols would eventually lead to bicyclic *N*,*O*-acetals as a result of intramolecular attack of the hydroxy function onto the imine intermediate **C**. Surprisingly, in the case of ethanolamine, the only product was the *N*-alkylated lactam **7** (95%, Table 1). With the homologous 3-aminopropanol, a small amount of bicyclic system **9** was isolated, while the major product was alcohol **8**. Evidently, the hydroxy group is insufficiently nucleophilic to cyclize onto the imine intermediate **C** prior to hydrogenation to the saturated species. Nonetheless, these results once more show the ability to efficiently prepare *N*-alkylated lactams in a

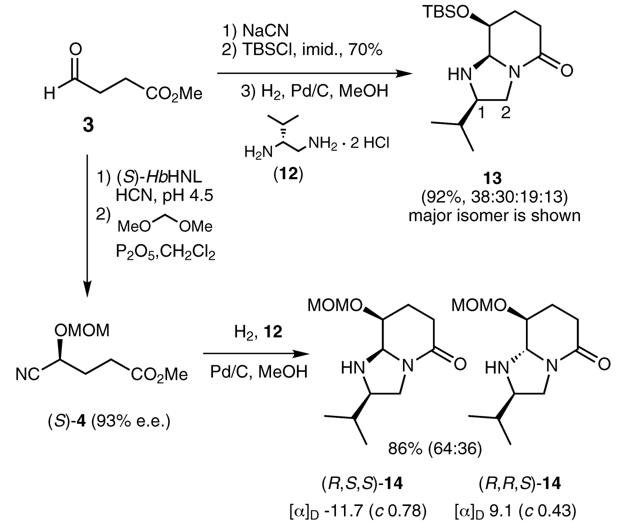


Scheme 2.

Table 1.



Entry	Amino alcohol	Product(s) (yield [%], *cis/trans*)
1		 **7** (95%)
2		 **8** (81%) +  **9** (19%, 56:44)
3		 **10** (94%, 63:37)
4		 **11** (98%, 67:33)



Scheme 3.

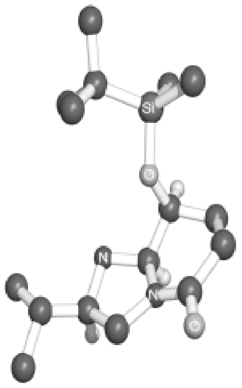


Figure 2.

single step from the corresponding cyano esters in excellent yields, thereby confirming the suggested mechanism.

Encouraged by the small amount of cyclization product **9**, we turned to more nucleophilic diamines in order to investigate whether the preparation of bicyclic *N,N*-acetals was feasible. Indeed, the use of 1.5 equivs. of the linear diamines 1,2-ethylenediamine and 1,3-propylenediamine (entries 3 and 4) under the same hydrogenation conditions led to the formation of the bicyclic *N,N*-acetals **10** and **11** in excellent yield, with the major isomer possessing the *cis*-configuration as was established *via* ^{1}H NMR NOE measurements.

In addition, the (*R*)-valine-derived diamine **12** afforded, when subjected to similar reaction conditions in the presence of the racemic TBS-protected cyanohydrin, bicycle **13** in 92% yield as a 38:30:19:13 mixture of four different isomers (Scheme 3).

The major product proved to be the all *cis*-compound – the isopropyl group being exclusively attached to C1 – as was determined by X-ray crystallography (Figure 2).[13] Presumably, this regiochemical outcome is a result of cyclization of the least hindered amino group onto the ester function. The relative stereochemistry of the other three diastereoisomers (*cis*- and *trans*-substitution at the piperidinone ring) so far could not be unambiguously assigned using NMR techniques, which was partly due to the fact that chromatographic separation appeared impossible.

In order to reduce the number of diastereoisomers, the optically active MOM-protected cyanohydrin (*S*)-**4** was subjected to diamine **12** under identical hydrogenation conditions. Indeed, in this case a mixture of only two diastereoisomers was found in 86% yield (*cis*/*trans* 64:36), which could be readily separated by column chromatography. This latter result clearly shows, that by using different combinations of the enantiomers of both reaction components virtually any product isomer is accessible in enantiomerically and diastereomerically pure form in a smooth and efficient manner.

The formation of *N,N*-acetals out of a cyano group can be considered as a reductive amination of the cyano function, which to the best of our knowledge, is an unprecedented transformation. The most related examples of *N*,*N*-acetal formation are those where amino amides or diamines react with ω-oxo-esters.[14] An advantage of our approach though, is that in combination with the HNL-mediated enantiopure cyanohydrin synthesis, we have facile access to the corresponding enantiomerically pure *N*,*N*-acetals. Beside the novel reductive amination of nitriles, by adjusting the reaction conditions and working with equimolar amounts of simple amines, we have also single step access to enantiomerically pure *N*-alkylated lactams from the same precursors.

Currently, we are further investigating the scope of the amine nucleophiles to arrive at differently substituted (bicyclic) 5-hydroxy-6-aminolactams. In addition, the synthesis of modest libraries of compounds based on functionalization of these scaffolds will be reported in the near future.

Experimental Section

1-Butyl-5-methoxymethoxypiperidin-2-one (6)

A suspension of the MOM-protected cyanohydrin **4**, (100 mg, 0.53 mmol) *n*-butylamine (79 μL, 0.80 mmol) and 10% Pd/C (28 mg, 0.027 mmol Pd) in MeOH (2 mL) was subjected to hydrogen (1 atm) for 2 h. The reaction was filtered over Celite® and the solvent was evaporated under reduced pressure. Flash chromatography afforded lactam **6** as a white oil; yield: 105 mg (0.49 mmol, 92%); ^{1}H NMR (400 MHz): δ = 4.72 (d, *J* = 7.0 Hz, 1H), 4.68 (d, *J* = 7.0 Hz, 1H), 4.00–3.95 (m, 1H), 3.45–3.29 (m, 4H), 3.38 (s, 3H), 2.56 (dt, *J* = 17.6, 7.5 Hz, 1H), 2.35 (dt, *J* = 17.6, 6.3 Hz, 1H), 1.97–1.93 (m, 2H), 1.55–1.34 (m, 2H), 1.32–1.27 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz): d = 168.8, 95.0, 69.3, 55.4, 51.9, 46.7, 28.9, 28.2, 26.4, 19.9, 13.7; IR: ν = 3417, 2933, 2360, 1738, 1640, 1038 cm^{-1}; HRMS (FAB): calcd. for $C_{11}H_{21}NO_3$ (MH$^+$): 215.1521; found: 215.1532.

9-Methoxymethoxyoctahydropyrido[1,2-*a*]pyrimidin-6-one (11)

A suspension of the MOM-protected cyanohydrin **4** (100 mg, 0.53 mmol), 1,3-diaminopropane (68 μL, 0.80 mol) and 10% Pd/C (29 mg, 0.027 mmol) in MeOH (2 mL) was subjected to hydrogen (1 atm) for 2 h. The reaction was filtered over Celite® and the solvent was evaporated under reduced pressure. Flash chromatography afforded the bicyclic *N*,*N*-acetal **11** as a pale yellow oil; yield: 112 mg (0.52 mmol, 98%); ^{1}H NMR (400 MHz, CD_3OD): δ = 4.80–4.72 (m, 2H *cis* + *trans*), 4.70–4.65 (m, 1H *cis* + *trans*), 4.39 (d, *J* = 3.8 Hz, 1H *cis*), 4.24 (d, *J* = 3.9 Hz, 1H *trans*), 4.02–3.99 (m, 1H cis), 3.77-3.73 (m, 1H, trans), 3.42 (s, 3H cis), 3.39 (s, 3H trans), 3.21-3.15 (m, 1H *cis* + *trans*), 2.96–2.82 (m, 1H *cis* + *trans*), 2.78–2.71 (m, 1H *cis* + *trans*), 2.63–2.47 (m, 1H *cis* + *trans*), 2.37–2.57 (m, 1H *cis* + *trans*), 2.18–2.06 (m, 1H *cis* + *trans*), 1.94–1.81 (m, 1H *cis* + *trans*), 1.69–1.56 (m, 2H *cis* + *trans*). ^{13}C NMR (100 MHz, CD_3OD): δ = 171.4, 170.6, 97.4, 96.9, 76.2, 75.3, 73.1, 72.6, 56.4, 56.0, 46.3, 45.1, 43.2, 42.1, 29.1, 28.4, 27.1, 27.0, 24.5, 24.5, 21.9. IR: ν = 3461, 3289, 2944, 1717, 1604, 1470, 1037 cm^{-1}; HRMS (FAB): calcd. for $C_{10}H_{18}N_2O_3$ (MH$^+$): 214.1317; found: 214.1320.

Acknowledgements

*These investigations are supported (in part) by the Netherlands Foundation for Chemical Research (CW) with financial aid from the Netherlands Technology Foundation (STW). DSM Fine Chemicals Austria is gratefully acknowledged for providing methyl 4-oxobutyrate. J. Fraanje and K. Goubitz (Institute of Molecular Chemistry, University of Amsterdam) are thanked for the X-ray structure determination of compound **13**.*

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