Reductive and Oxidative Transformations of the *N*-(Cyanomethyl)oxazolidine System to Expand the Chiral Pool of Piperidines

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Two new reactions have been exploited to modify piperidine scaffolds containing the chiral, non-racemic *N*-(cyanomethyl)oxazolidine system. A Raney nickel mediated decyanation was studied first, followed by an oxidative process using potassium permanganate to furnish enantiopure lactams including oxopipecolic acid derivatives.

Introduction

Contemporary organic chemists face the challenge of inventing and developing simple methodologies for easing access to a wide range of biologically relevant compounds, notably six-membered nitrogen-containing heterocycles. Among these, the piperidine ring system is one of the most common structural subunits found in alkaloids, pharmaceuticals, and synthetic intermediates. Because of the rich chemistry and biology of this class of compounds, the synthesis of diversely substituted enantiopure piperidine derivatives has been a central and important theme in organic chemistry in recent years. The variety of functionalities and substitution patterns found in piperidine targets continues to drive the search for new methodologies.[1]

In continuance of our efforts to expand the chiral pool in the piperidine series, we report in this article an efficient and straightforward route to substituted piperidines and piperidones by taking advantage of the functionalizations of the known and commercially available 3-phenylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridine-5-carbonitrile (**1**). The synthetic potential of this chiral, non-racemic starting material has already been demonstrated in numerous applications.[2] Among its structural features, this building block contains an *N*-(cyanomethyl)oxazolidine system and, accordingly, possesses two non-equivalent reactive sites on the piperidine ring system: an α-amino nitrile at the C-2 position and an α-amino ether at the C-6 position. We focus in this paper on two original reactions that we have observed with regard to the *N*-(cyanomethyl)oxazolidine system: namely the reduction of the α-amino nitrile and the oxidation of the α-amino ether.

Piperidin-6-ones have generally been regarded as precursors to the corresponding piperidines,[3] but these two methodologies can be used, from a synthetic viewpoint, as new routes to functionalized piperidin-6-one structures from their piperidine counterparts.

Results and Discussion

Reductive Decyanation

The reductive decyanation of α-amino nitriles involves selective replacement of a cyano group by a hydrogen atom. The nature of this reaction, either ionic or radical, is dictated by the choice of the reducing agent. The standard procedure involves reduction of the α-amino nitrile with an alkali metal, usually lithium[4] or sodium,[5] in a mixture of liquid ammonia and THF at low temperatures. It has also been reported that α-amino nitriles can be decyanated with systems such as $AgBF_4/Zn(BH_4)_2$ [6] or with classical hydride donors ($NaBH_4$,[7] $LiAlH_4$,[8] BH_3,[9] $NaBH_3CN$[10]). However, these methods have one or more limitations: (i) metal/liquid ammonia requires a strongly basic medium, and (ii) hydrides lack selectivity if the molecule has reducible moieties. Furthermore, in some cases, the use of hydrides has produced unsuccessful results[11] or has resulted in the reduction of the cyano group into an amine.[12] The outcome is highly dependent on the substitution pattern. Overall, each of these methods represents a different balance of yield, toxicity, expense, and technical convenience. Further, these methods frequently result in competitive side reactions, notably in the presence of benzylamines and α-

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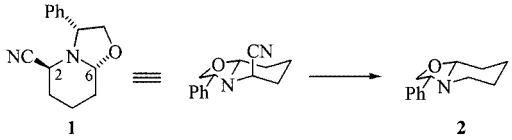
amino ethers, groups that are readily hydrogenolysable and reducible, respectively. Previous studies have shown, for example, that α-amino ether moieties are not tolerated by DIBALH, $LiAlH_4$,[13] or $NaBH_4$.[14] Given the structural features of our compounds, it is necessary to find reaction conditions that are selective for the removal of the cyano group without opening of the oxazolidine ring and/or without cleavage of the chiral auxiliary.

Although a decyanation with metal/liquid ammonia or with $AgBF_4/Zn(BH_4)_2$ could theoretically be considered in our case, we sought to develop a new practical method that would complement existing methodologies. Earlier, we reported the first example of reductive decyanation on the 3-phenylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridine-5-carbonitrile building block **1** [the key element of the CN(*R*,*S*) strategy[2]] with Raney nickel (Scheme 1).[15] We were pleased to observe that the process took place under extremely mild conditions, without causing the reduction of any reducible or hydrogenolysable substituents. Despite the widespread use of Raney nickel in reductive applications, its use in decyanation has not received any attention and therefore its potential is unknown. This prompted us to investigate the generality and scope of this method further with various cyclic α-amino nitriles.

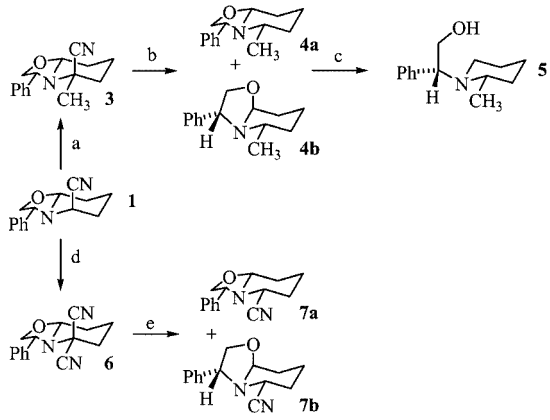


Scheme 1. Decyanation of building block **1**; reagent and conditions: Raney nickel (excess), THF, reflux, 24−48 h (90%)

This study aims to address the following inquiries: (i) what is the facial selectivity for quaternary α-amino nitriles, (ii) what is the behavior of an α,α-dicyanopiperidine, and (iii) with the support of these answers, can we put forward a mechanism?

The stereoselectivity outcome of the reaction was first addressed with quaternary α-amino nitriles. On the C-2 methyl derivative **3**, prepared from **1**,[6a] Raney nickel mediated decyanation was quantitative and afforded compounds **4** as a mixture of two isomers, which were determined to be epimers at the 6-position without any racemization of the C-2 methyl group. This was confirmed by reduction of the mixture of **4a** and **4b** with sodium borohydride to a single diastereomer **5** (Scheme 2).[16]

Preference for an axial decyanation was demonstrated when dicyano compound **6**, obtained from **1**,[15] was treated under our conditions and afforded a 75:25 mixture of two compounds in a moderate non-optimized yield. Mass analysis of the mixture showed a single peak, $m/z = 229$ [M + H^+], signifying the elimination of a single cyano group. Careful NMR studies resulted in a complete understanding of the composition of the mixture. The major compound was assigned with certainty as **7b**, possessing an axial oxazolidine system, the minor compound being **7a** with an



Scheme 2. Decyanation of building block **1** derivatives; reagents and conditions: (a) (i) LDA (3 equiv.), THF, −78 °C, 20 min, (ii) MeI (2 equiv.), −78 °C → room temp. (95%); (b) Raney nickel (excess), THF, room temp., 1.5 h (quant., **4a/4b** = 1.8); (c) $NaBH_4$ (5 equiv.), MeOH, room temp., 20 min (92%); (d) (i) LDA (3 equiv.), THF, −78 °C, 20 min, (ii) TsCN (2 equiv.), −78 °C, 4 h (67%); (e) Raney nickel (excess), THF, reflux, 3 h (20%, not optimized, **7b/7a** = 3)

equatorial oxazolidine ring (Scheme 2). Some of these NMR spectroscopic data are noteworthy as they indicate the stereochemistry at C-2 and C-6 (Figure 1). The two most significant ^1H NMR signals of the **7a/7b** mixture are a doublet of doublets (J = 10 Hz and 3.5 Hz) at δ = 3.66 ppm attributable to the C-2 proton of the major diastereomer **7b** and a doublet of doublets (J = 11 Hz and 3 Hz) at δ = 3.23 ppm attributable to the C-2 proton of the minor isomer **7a**. The coupling constant and signal patterns are characteristic of axial orientations for 2-H in **7a** and **7b** and consequently reveal that the cyano groups are located equatorially in these compounds. Moreover, close similarities in the NMR spectra of **4a** and **7a** as well as those of **4b** and **7b** allowed us to assign the stereochemistry at C-6 in **7a** and **7b**. For example, the ^{13}C chemical shifts of C-6 for **7b** (δ = 87.4 ppm) and C-2 for **4b** (δ = 89.1 ppm) are both nearly identical and upfield with respect to those of the corresponding carbon atoms in **7a** (δ = 94.3 ppm) and **4a** (δ = 95.7 ppm). These comparisons and correspondences can be accounted for by an axial position for 6-H in **7a** and an equatorial one in **7b**. Also, the orientation of 6-H in **7a** was secured from the observation of a doublet of doublets (J = 10 Hz and 2.5 Hz) at δ = 3.73 ppm. This is in agreement with an axial orientation, whereas the analogous hydrogen atom in **7b** appears as an undefined multiplet (δ = 4.51−4.53 ppm). Moreover, the correlations between 2-H^b and 7-H^b and between 2-H^a and the axial protons 6-H^a

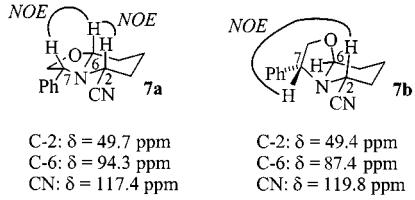


Figure 1. Selected NMR spectroscopic data for compounds **7a** and **7b**

and 7-H[a] in the NOESY experiments confirmed the relative configurations of C-2 and C-6 with respect to 7-H (Figure 1). Thus, compound **7a** has a *cis* relationship of the hydrogen atoms at C-6 and C-7 (*cis*-oxazolidine), whereas **7b** has a *trans* relationship for the same protons (*trans*-oxazolidine).

To summarize, compounds **7a** and **7b** are stereomers of the parent cyanopiperidine **1** and, more interestingly, they display an antianomeric equatorial cyanopiperidine feature.

The reaction was also carried out on the highly hindered polyhydroxylated piperidine **8**.[17] Despite a low yield due to purification problems relating to the high polarity of the compounds, a single stereomer **9** was obtained in a very clean reaction, giving access to a new building block for the design of glycosidase inhibitors (Scheme 3).

Scheme 3. Decyanation of polyhydroxylated building block **8**; reagents and conditions: Raney nickel (excess), THF, reflux, 30 min (30%)

This new decyanation method was shown to be highly stereoselective and easy to use in the laboratory, despite epimerization at the C-6 position (oxazolidine moiety) in some cases. This drawback was not so problematic, since these compounds constitute synthetic intermediates and nucleophilic substitutions could eventually take place at this position via the iminium salt form (potential iminium reactivity).

A reasonable mechanism, based on principles of stereoelectronic control, is outlined below (Figure 2).[18] The initial step could proceed by the expected generation of a prochiral iminium ion, which could be explained in terms of a "push-pull" mechanism. The most favored conformation of the iminium ion is shown in Figure 2. The reduction by the hydrogen present in Raney nickel permits the subsequent reduction of the iminium carbon atom from the upper face. It should be noted that the delivery of the hydrogen is the result of a stereoelectronically controlled process. The delivery occurs so that maximum orbital overlap is maintained between the incoming hydrogen atom and the developing lone-electron pair on the nitrogen atom, thereby resulting in molecules in which the generated sp^3-hybridized orbitals are anticoplanar. Oxazolidine epimerization, as observed in compounds **4** and **7**, for example, probably occurs during workup of the reaction mixtures.

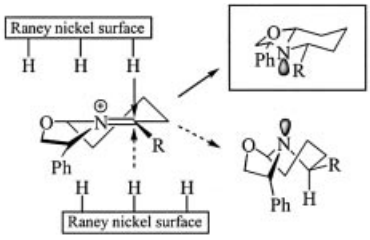


Figure 2. Mechanistic considerations for Raney nickel decyanation

Regioselective Oxidation of the Oxazolidine System with Potassium Permanganate − Easy Access to Enantiopure Lactams

The 2-substituted piperidin-6-one pattern is noteworthy, as it is found as a part of some natural products (e.g., cadiamine[19] and other natural products from Leguminosae), as well as in some biologically interesting peptidomimetic molecules (e.g., conformationally restrained peptides as potent integrin antagonists[20]). Concerning oxopipecolic acid derivatives more particularly, they constitute, for example, a part of posatireline,[21] a TRH-like drug prescribed for the treatment of senile dementia. They have also been used as synthetic intermediates for access to *C*-glycosylated amino acids[22] or γ- or δ-substituted α-amino acids.[23] Various esters of *N*-protected 6-oxopipecolic acids have also been used as key compounds in the synthesis of dual metalloprotease inhibitors,[24] and recently for the preparation of prototypical piperidone libraries and constrained analogues of adipic acid.[25]

Interest in such compounds has prompted us to develop a general approach to a large variety of *N*-protected 2-substituted piperidin-6-ones (Figure 3). To this end, it appears that building block **1** possesses two essential features. On the one hand, the N,O-acetal system can be regarded as the precursor of a lactam function after oxidation. On the other hand, the presence of the cyano group might allow us to accomplish some transformations in order to provide a general and versatile route into the pipecolic series.

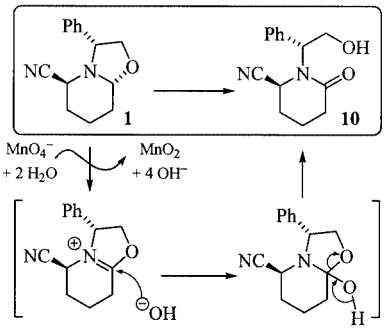
Figure 3. Looking for an oxidation process

However, the synthetic methods that permit the oxidation of the N,O-acetal without alteration of the CN group are still limited. Our group has already shown that the α-amino ether functions of (phenyloxazolo)piperidines could be oxidized to the corresponding δ-lactams.[26] Despite favorable yields, this method, by use of bromine followed by basic treatment, was not very versatile with regard to the substituents at the 2-position on the piperidine ring. In fact, it was impossible to oxidize **1** to the corresponding lactam. Indeed, only 2,2-disubstituted (i.e., a cyano and an alkyl group) or 2-alkyl-substituted molecules could be oxidized, not allowing access to oxopipecolate derivatives.

We therefore looked for a new, convenient, and reliable oxidation method with an appropriate oxidant that would respect the integrity of the cyano group and could also be a cornerstone reaction for the preparation of lactams. Screening for an inexpensive and less toxic oxidizing agent, we chose potassium permanganate. Many oxidations of tertiary amines by use of potassium permanganate in aqueous media have been reported: notably, the observed oxidation occurred with monocyclic[27] or bicyclic systems.[28] Conse-

quently, we set out to study the behavior of **1** and its derivatives with this oxidant.

The key step of our scheme was the preparation of compound **10** in 80% yield and on multigram scales from **1** (Scheme 4).[29] Most importantly, neither degradation nor racemization at the CN group was observed. The presumed mechanism for the reaction path is depicted in Scheme 4. Firstly, permanganate ion oxidized the α-amino ether function to produce an iminium intermediate. The reduction of permanganate ion to manganese dioxide in an aqueous medium liberated hydroxy ions, which could trap the iminium species. Finally, the opening of the oxazolidine and the subsequent creation of the lactam function could explain the formation of **10**. Regioselective discrimination between the two masked potential iminium functions was observed in this reaction, with oxidation only on the oxazolidine side of the nitrogen atom.

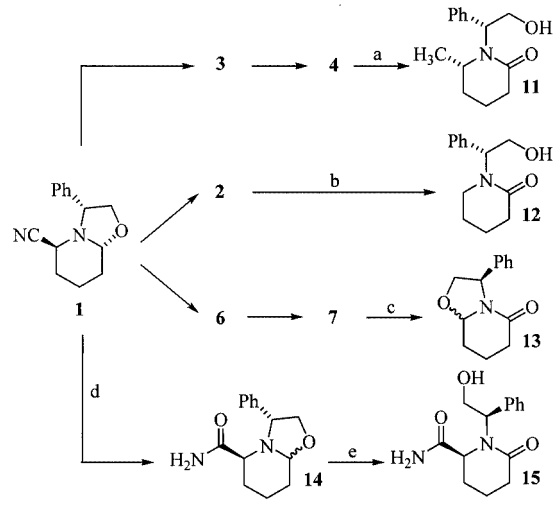


Scheme 4. Oxidation of building block **1** with potassium permanganate and plausible mechanism; reagents and conditions: $KMnO_4$ (7 equiv.), acetone/H_2O (8:2), room temp., 2 d (80%)

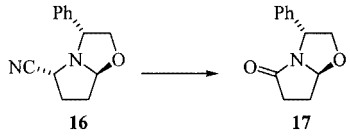
Having performed this reaction successfully, we decided to continue the study of $KMnO_4$'s oxidative capacity with a range of 2-substituted piperidin-6-ones and to try to establish its scope and limitations (Scheme 5). The decyanated compound **2** was oxidized into lactam **12** in 75% yield.[30] A better yield (90%) was observed when lactam **11**[26] was targeted from decyanated derivative **4**. Treatment of the equatorial cyano derivatives **7a** and **7b** gave lactam **13**.[31] It seems that an equatorial or pseudo-equatorial cyano group does not behave like its axial counterpart in the oxidative process; this was confirmed when the known pyrrolidine building block **16**[32] was oxidized by potassium permanganate to afford compound **17** in high yield (Scheme 6). The cyano group of **1** can be converted into an amide function as described previously,[33] and oxidation of **14** gave, albeit in moderate yield, the interesting lactam **15**.

It then appeared that compound **10** was rich in synthetic potential. We now describe our first studies concerning the nitrile transformation possibilities of **10** (Scheme 7).

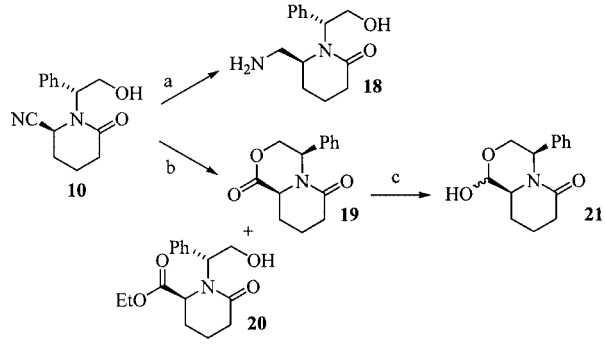
Firstly, reactivity studies suggested the synthesis of amine **18** by high-pressure PtO_2 catalytic hydrogenation of **10** (yield: 70%). Treatment of **10** with HCl/ethanol at room temperature afforded a slow but non-racemizing hydrolysis of the CN group, providing lactone **19** in 65% yield, ac-



Scheme 5. Lactams derived from building block **1**; reagents and conditions: (a) $KMnO_4$ (4 equiv.), acetone/H_2O (7:3), room temp., 20 h (90%); (b) $KMnO_4$ (3 equiv.), acetone/H_2O (1:1), room temp., 24 h (75%); (c) $KMnO_4$ (3 equiv.), acetone/H_2O (1:1), room temp., 12 h (60%); (d) H_2O_2 (1.2 equiv.), K_2CO_3, DMSO, 60 °C, 1 h (70%); (e) $KMnO_4$ (4 equiv.), acetone/H_2O (1:1), room temp., 24 h (50%)



Scheme 6. Lactam formation in the pyrrolidine series; reagents and conditions: $KMnO_4$ (4 equiv.), acetone/H_2O (1:1), room temp., 12 h (94%)



Scheme 7. Lactams derived from building block **10**; reagents and conditions: (a) H_2 (11 bar), PtO_2 (1 equiv., w/w), EtOH, room temp., 5 d (70%); (b) HCl/EtOH, room temp., 20 d (**19**: 65%; **20**: < 5%, conversion 80%); (c) $NaBH_4$ (1.2 equiv.), MeOH, room temp., 30 min (93%)

companied by small amounts (< 5%) of ethyl ester **20** and 20% of recovered **10**. We then decided to investigate the possibility of obtaining an aldehyde (or equivalent) function. The reduction of the lactone function with sodium borohydride at room temperature in methanol afforded lactol **21** (93% yield);[34] again, no racemization at C-2 occurred. This lactol, as a protected aldehyde, is of great interest for future exploration.

We have shown that a small, discrete library of mono- or bicyclic chiral, non-racemic lactams could easily be ob-

tained from oxazolidine oxidation through the use of an inexpensive, commercially available starting material and potassium permanganate, and in a maximum of three steps from **1**. All compounds are enantiomerically pure (*de* > 96%, NMR) at crucial stereocenters (this point contrasts with some of the other known methods for lactam synthesis[35]). Compound **10**, which is obtained in one step and high yield from **1**, possesses several structural elements required for an efficient and versatile building block (Figure 4 examines its potential as a synthetic equivalent: i.e., cationic or anionic synthons). It is particularly and notably an example of a potential endocyclic *N*-acyliminium ion.[36] The high flexibility of our approach is currently being studied, with functionalization of, for example, the other positions on the piperidine ring system of building blocks **10**.[37] Finally, by starting from (*S*)-phenylglycinol, all compounds are available in the enantiomeric series.

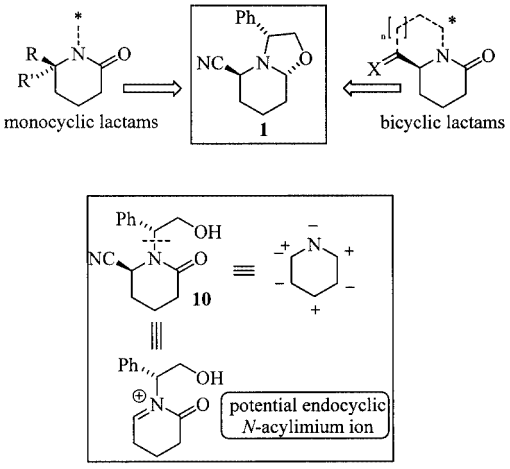


Figure 4. Lactams obtained from **1**

Conclusion

We have shown two simple methods for the rapid construction of enantiopure scaffolds from easily obtainable compounds. This work provides reliable, convenient, and high-yielding reductive and oxidative methods with economical reagents to modify the *N*-(cyanomethyl)oxazolidine system selectively.

Experimental Section

General: For general techniques, see ref.[15]

Raney Nickel Decyanations: The preparation of piperidine **2** is representative (see ref.[15]) of individual conditions and yields; see Schemes 1−3.

(3*R*,5*R*,8a*R*)-3-Phenylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridine-5-carbonitrile (7a, minor) and (3*R*,5*R*,8a*S*)-3-Phenylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridine-5-carbonitrile (7b, major): Inseparable mixture of diastereomers: Colorless oil. R_f = 0.2 (cyclohexane/diethyl ether, 7:3). $[\alpha]_D^{20}$ = −21 (*c* = 1, $CHCl_3$). IR ($CHCl_3$, film): $\tilde{\nu}$ = 2244 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.6−2.1 (m), 3.23 (dd, ^3J = 11, ^3J = 3 Hz), 3.66 (dd, ^3J = 10, ^3J = 3.5 Hz), 3.73 (dd, ^3J = 10, ^3J = 2.5 Hz), 3.75−3.8 (m), 3.93 (dd, ^2J = 8.3, ^3J = 4.3 Hz), 4.24 (t, ^2J = ^3J = 6.5 Hz), 4.39 (t, ^2J = ^3J = 8 Hz), 4.48−4.54 (m), 7.25−7.5 (m) ppm. **7a:** ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4, 29.0, 30.7, 49.7, 66.9, 73.8, 94.3, 117.4, 126.8−128.6, 139.8 ppm. **7b:** ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.4, 26.0, 28.4, 49.4, 66.2, 69.0, 87.4, 119.8, 126−128.6, 138.7 ppm. MS (CI, isobutane): *m*/*z* = 229 $[M + 1]^+$. HRMS (CI, CH_4): *m*/*z* calcd. for $C_{14}H_{17}N_2O$ 229.1341 $[M + 1]^+$, found 229.1340.

(3*R*,6*S*,7*R*,8*S*,8a*S*)-3-Phenylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]-pyridine-6,7,8-triol (9): Hygroscopic, colorless crystals. R_f = 0.25 (CH_2Cl_2/MeOH, 9:1). $[\alpha]_D^{20}$ = −165 (*c* = 1, MeOH). ^1H NMR (300 MHz, CD_3OD): δ = 2.14 (t, ^2J = ^3J = 10.5 Hz, 1 H), 2.94 (dd, ^3J = 5.5, ^2J = 10.5 Hz, 1 H), 3.33 (t, ^3J = 8.5 Hz, 1 H), 3.56 (dd, ^3J = 8.5, ^3J = 8 Hz, 1 H), 3.67 (ddd, ^3J = 10.5, ^3J = 5.5, ^3J = 1 Hz, 1 H), 3.71−3.83 (m, 2 H), 3.84 (d, ^3J = 8 Hz, 1 H), 4.35 (t, ^2J ^3J = 6 Hz, 1 H), 7.2−7.4 (m, 5 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 50.7, 67.3, 72.3, 75.6, 75.7, 79.4, 97.5, 128.7, 129.1, 129.7, 139.5 ppm. MS (CI, NH_3): *m*/*z* = 252 $[M + 1]^+$. HRMS (CI, CH_4): *m*/*z* calcd. for $C_{13}H_{18}NO_4$ 252.1236 $[M + 1]^+$, found 252.1240.

Oxidation with Potassium Permanganate: The preparation of lactam **10** is representative. For individual conditions ($KMnO_4$ equivalents, solvents, time) and yields, see Schemes 5 and 6.

(2*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-6-oxopiperidine-2-carbonitrile (10): Building block **1** (1 g, 4.38 mmol) was dissolved in a mixture of acetone and water (8:2, 250 mL), and $KMnO_4$ (4.84 g, 30.6 mmol, 7 equiv.) was added in small portions over 4 h. The mixture was stirred at room temp. for 2 d. The resulting suspension was filtered and the filtrate was concentrated under reduced pressure. The resulting aqueous phase was diluted with a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 times). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to yield lactam **10** as a colorless oil (850 mg, 80%) that crystallized slowly; recrystallization from diethyl ether is possible. Colorless crystals. R_f = 0.3 (CH_2Cl_2/MeOH, 98:2). $[\alpha]_D^{25}$ = −41 (*c* = 1, $CHCl_3$). M.p. 116−119 °C (diethyl ether). IR ($CHCl_3$, film): $\tilde{\nu}$ = 1631, 2337, 3370 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.8−2.2 (m, 4 H), 2.45−2.6 (m, 1 H), 2.6−2.75 (m, 1 H), 3.4 (br. s, 1 H), 4.1 (br. s, 2 H), 4.48 (dd, ^3J = 2, ^3J = 4.5 Hz, 1 H), 5.57 (dd, ^3J = 6.5, ^3J = 5.5 Hz, 1 H), 7.2−7.5 ppm (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6, 27.4, 31.5, 46.4, 60.8, 61.8, 117.6, 128.5, 128.7, 128.9, 135.1, 170.7 ppm. MS (CI, NH_3): *m*/*z* = 245 $[M + 1]^+$.

(2*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-6-oxopiperidine-2-carboxamide (15): Colorless oil (141 mg from 267 mg of **14**). R_f = 0.3 (CH_2Cl_2/MeOH, 91:9). $[\alpha]_D^{20}$ = +81 (*c* = 1, $CHCl_3$). IR ($CHCl_3$, film): $\tilde{\nu}$ = 1622, 1681, 3404 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.65−1.85 (m, 3 H), 2.3−2.6 (m, 3 H), 3.8−3.95 (m, 2 H), 4.34 (dd, ^3J = 11, ^3J = 6 Hz, 2 H), 4.81 (t, ^2J ^3J = 11 Hz, 1 H), 7.2−7.4 (m, 5 H), 8.0 ppm (s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.3, 26.9, 32.9, 62.5, 63.7, 68.7, 127.7, 128.2, 128.7, 136.3, 172.6, 174.3 ppm. MS (CI, NH_3): *m*/*z* = 263 $[M + 1]^+$. HRMS (CI, CH_4): *m*/*z* calcd. for $C_{14}H_{19}N_2O_3$ 263.1396 $[M + 1]^+$, found 263.1397.

(6*S*)-6-(Aminomethyl)-1-[(1*R*)-2-hydroxy-1-phenylethyl]piperidin-2-one (18): Cyanolactam **10** (150 mg, 0.614 mmol) was dissolved in EtOH (10 mL) and hydrogenated in the presence of PtO_2 (100 mg) under a pressure of 11 bar over 5 d. The catalyst was removed by filtration, and the solution was concentrated under reduced press-

ure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 85:15) to furnish the lactam **18** (106 mg, 70%). Colorless oil. R_f = 0.3 (CH_2Cl_2/MeOH, 85:15). $[\alpha]_D^{28}$ = +38 (*c* = 1, $CHCl_3$). IR ($CHCl_3$, film): $\tilde{\nu}$ = 1616 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.65−2.00 (m, 4 H), 2.43 (m, 2 H), 2.6−2.9 (m, 3 H), 3.3−3.4 (m, 1 H), 4.0 (dd, ^2J = 12, ^3J = 6 Hz, 1 H), 4.41 (dd, ^2J = 12, ^3J = 8 Hz, 1 H), 4.71 (dd, ^3J = 6, ^3J = 8 Hz, 1 H), 7.2−7.4 ppm (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3, 24.8, 32.0, 43.6, 59.4, 63.3, 65.6, 127.4, 128.4, 137.5, 172.1 ppm. MS (CI, NH_3): *m*/*z* = 249 [M + 1]$^+$. HRMS (CI, CH_4): *m*/*z* calcd. for $C_{14}H_{20}N_2O_2$ 248.1525 [M + 1]$^+$, found 248.1523.

(4*R*,9a*S*)-4-Phenylhexahydropyrido[2,1-*c*][1,4]oxazine-1,6-dione (19) and Ethyl (2*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl)-6-oxopiperidine-2-carboxylate (20): A solution of cyanolactam **10** (200 mg −0.985 mmol) in saturated HCl/ethanol (4 mL) was stirred at room temp. for 20 d. The reaction mixture was diluted with a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 times). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH, 98:2) first gave ester **20** (0−12 mg, 0−5%, unstable, spontaneous cyclization into **19**), followed by lactone **19** (120−130 mg, 60−65%) and recovered **10** (30−40 mg, 15−20%). **Lactone 19:** Colorless crystals. $[\alpha]_D^{25}$ = −20 (*c* = 1, $CHCl_3$); m.p. 156−158 °C (diethyl ether). R_f = 0.3 (CH_2Cl_2/MeOH, 97:3). IR ($CHCl_3$, film): $\tilde{\nu}$ = 1763, 1629 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.7−1.85 (m, 1 H), 1.85−2.0 (m, 1 H), 2.15−2.35 (m, 2 H), 2.35−2.55 (m, 2 H), 4.33 (dd, ^3J = 7.5, ^3J = 6 Hz, 1 H), 4.45−4.65 (m, 2 H), 5.71 (t, ^3J = 7.5 Hz, 1 H), 7.2−7.5 ppm (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4, 24.5, 32.1, 52.0, 54.3, 68.4, 126.2, 128.6, 129.0, 136.0, 168.4, 169.2 (2 C) ppm. MS (CI, NH_3): *m*/*z* = 246 [M + 1]$^+$. HRMS (CI, CH_4): *m*/*z* calcd. for $C_{14}H_{15}NO_3$ 245.1052 [M + 1]$^+$, found 245.1051. **Ester 20:** Colorless oil. R_f = 0.5 (CH_2Cl_2/MeOH, 97:3). IR ($CHCl_3$, film): $\tilde{\nu}$ = 3417, 1734, 1636 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.03 (t, ^3J = 7 Hz, 3 H), 1.6−1.8 (m, 3 H), 1.9−2.1 (m, 2 H), 2.5 (dd, ^2J = 10, ^3J = 7 Hz, 1 H), 2.56 (dd, ^2J = 7, ^3J = 4 Hz, 1 H), 3.6−3.8 (m, 2 H), 4.0−4.2 (m, 3 H), 5.83 (t, ^3J = 7 Hz, 1 H), 7.2−7.4 ppm (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 17.3, 26.5, 31.2, 43.0, 56.4, 58.3, 61.1, 128.3, 129.1, 135.2, 170.6, 171.2 (2 C) ppm. MS (CI, NH_3): *m*/*z* = 292 [M + 1]$^+$.

(1*RS*,4*R*,9a*S*)-1-Hydroxy-4-phenylhexahydropyrido[2,1-*c*][1,4]-oxazin-6-one (21): Lactone **19** (90 mg, 0.37 mmol) was dissolved in methanol (5 mL) and reduced with sodium borohydride (18 mg, 0.44 mmol, 1.2 equiv.) at room temp. After 0.5 h, the mixture was concentrated under reduced pressure and the residue was dissolved in CH_2Cl_2. The solution was washed with a saturated solution of $NaHCO_3$, dried (Na_2SO_4), and concentrated to furnish, after trituration in diethyl ether, lactol **21** (6:4 mixture of epimers, 85 mg, 93%). Amorphous white powder. R_f = 0.2 (CH_2Cl_2/MeOH, 97:3). IR ($CHCl_3$, film): $\tilde{\nu}$ = 3320, 1616 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): major isomer: δ = 1.35−2.15 (m, 4 H), 2.2−2.5 (m, 2 H), 3.31 (q, ^3J = 8 Hz, 1 H), 3.9 (dd, ^2J = 12, ^3J = 4 Hz, 1 H), 4.35 (br. d, ^2J = 12 Hz, 1 H), 4.54 (d, ^3J = 8 Hz, 1 H), 5.64 (br. t, ^3J = 4 Hz, 1 H), 7.2−7.5 ppm (m, 5 H); minor isomer: δ = 1.21 (td, ^2J ^3J = 7, ^3J = 1 Hz, 1 H), 1.35−2.15 (m, 3 H), 2.2−2.5 (m, 2 H), 3.4−3.55 (m, 1 H), 4.07 (d, ^2J = 12 Hz, 1 H), 4.43 (dd, ^2J = 12, ^3J = 3.5 Hz, 1 H), 4.85 (s, 1 H), 5.78 (d, ^3J = 3.5 Hz, 1 H), 7.2−7.5 ppm (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): major isomer: δ = 17.9, 24.3, 32.3, 50.4, 55.9, 65.2, 97.3, 127.2, 127.5, 128.4, 138.2, 170.3 ppm; minor isomer: δ = 18.0, 23.9, 32.5, 49.6, 53.2, 59.1; 91.2, 127.2, 127.6, 128.4, 138.4, 171.0 ppm. MS (CI, NH_3): *m*/*z* = 248 [M + 1]$^+$. HRMS (CI, CH_4): *m*/*z* calcd. for $C_{14}H_{17}NO_3$ 247.1208 [M + 1]$^+$, found 247.1208.

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