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Stereocontrolled Access to Orthogonally Protected *anti,anti*-4-Aminopiperidine-3,5-diols through Chemoselective Reduction of Enantiopure β-Lactam Cyanohydrins

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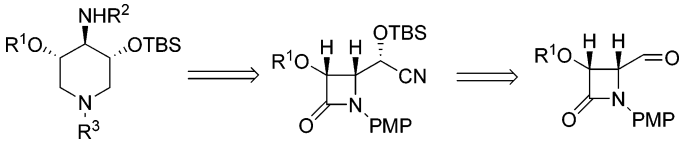

The cyanosilylation of enantiopure 4-oxoazetidine-2-carbaldehydes with *tert*-butyldimethylsilyl cyanide was promoted by either molecular sieves or catalytic amount of sodium carbonate to give O-silylated β-lactam cyanohydrins with good yield and diastereoselectivity. In contrast, Lewis acids did not effectively promote the cyanosilylation under different experimental conditions, and instead hydrocyanation took place affording the corresponding free cyanohydrins in variable yield and selectivity. Starting from β-lactam cyanohydrin hybrids, two concise, complementary stereocontrolled routes to optically pure orthogonally protected *anti*,*anti*-4-amino-3,5-piperidine diols were achieved. Key features of the first approach include chemoselective reductive opening of the β-lactam ring with $LiBH_4$ to a 3-amino-5-hydroxy pentanenitrile followed by reductive cyclization of a conveniently functionalized cyanomesylate derivative with $NaBH_4$/$NiCl_2$. The second approach involves $LiAlH_4$ reduction of protected *anti*,*anti*-4-amino-3,5-dihydroxypiperidin-2-ones, which were easily obtained by chemoselective reduction of the cyano group in the β-lactam cyanohydrin hybrids with $NaBH_4$/$NiCl_2$ and subsequent intramolecular rearrangement of the resulting amino β-lactams. Both routes make use of an oxidative N-dearylation with diacetoxyiodobenzene of a 4-methoxyphenylamino group as a common synthetic step. Specifically, the utility of this novel reaction sequence has been demonstrated by the synthesis of fully orthogonally protected sialidase inhibitors.

Introduction

The piperidine ring is a ubiquitous structural feature of many natural products and pharmacologically active compounds. Therefore, a continuous interest exists in the development of new methodologies for asymmetric synthesis of this six-membered azaheterocycle.[1] In recent years, polyhydroxylated piperidines, also called azasugars or iminosugars,[2] and their synthetic analogues have attracted a great deal of attention due to their ability to mimic sugars and selectively inhibit glycosidases and glycoprotein-processing enzymes.[3] These inhibitors have shown a great therapeutic potential as drugs for the treatment of a variety of carbohydrate-mediated diseases such as diabetes, cancer, and viral infections including HIV.[4] More

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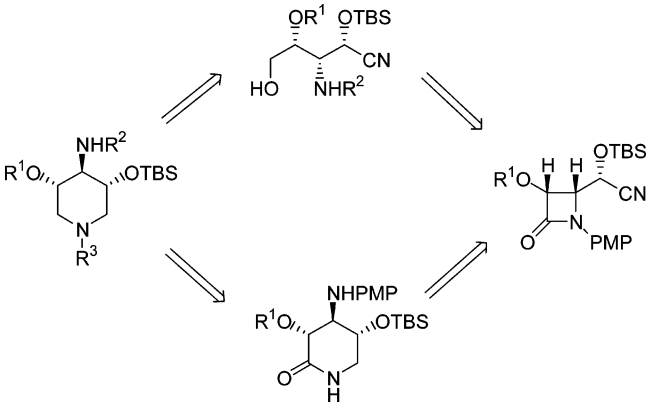
specifically, N-functionalized *trans,trans*-4-acetamido-3,5-piperidine diols have been described as a new structural class of sialidase inhibitor which combines transition state analogy with the ability to include aglycon mimicry.[5] In addition, protected piperidine-3,5-diols[6] have been used as asymmetric catalysts in organometallic additions to aldehydes,[7] and *cis*-4-amino-3-methoxypiperidine has been reported as a substructure of cisapride, a potent gastric prokinetic agent with reduced Dopamine D_2 receptor antagonistic activity.[8]

Besides the key role that β-lactams have played in the fight against pathogenic bacteria, the use of 2-azetidinones as chiral building blocks in organic synthesis is now well-established.[9] Due to ring strain, 2-azetidinones are susceptible to ring-cleavage reactions with a broad range of reagents with high or often complete regio- and stereoselectivity.[10] Selective bond cleavage of the 2-azetidinone ring coupled with further interesting synthetic transformations renders these fascinating molecules powerful synthetic building blocks in the stereocontrolled synthesis of a wide variety of nitrogen-containing compounds.[11] On the other hand, cyanohydrins are versatile synthetic intermediates for the synthesis of a variety of interesting compounds. Both the hydroxy and nitrile groups of the cyanohydrins can be further transformed into a variety of useful functional units.[12] Thus, the nitrile group can be hydrolyzed to create different types of α-hydroxy carbonyl compounds or reduced to form 1,2-amino alcohol derivatives.[13] In light of the synthetic utility of both classes of compounds, the stereoselective preparation of optically pure β-lactam cyanohydrin hybrids arises as an important endeavor since they are potential versatile precursors to functionalized azaheterocycles. We have used carbonyl β-lactams as chiral templates[14] and have recently shown their transformation to a variety of potentially bioactive products.[15] We now report two short, complementary β-lactam cyanohydrin-based routes to orthogonally protected enantiopure *anti*,*anti*-4-amino-3,5-piperidine diols, by a strategy that allows stereocontrolled construction of all three contiguous stereocenters. Our retrosynthetic strategies are outlined in Scheme 1. Specifically, the utility of this novel reaction sequence has been demonstrated by the synthesis of fully orthogonally protected sialidase inhibitors.

SCHEME 1



Results and Discussion

In light of the synthetic utility of cyanohydrins, their enantioselective preparation has been extensively investigated and comprehensively reviewed.[16] Among different reported examples, only a few papers refer to chiral protected α-aminoaldehydes.[17] Our interest in the use of 4-oxoazetidine-2-carbaldehydes as substrates for addition reactions[14a] prompted us to evaluate their cyanosilylation reaction with *tert*-butyldimethylsilyl cyanide (TBSCN). We choose TBSCN as the cyanide source instead of the simpler trimethylsilyl cyanide in order to obtain more robust O-TBS derivatives compatible with reaction conditions used in the synthetic routes, thus avoiding problems associated with the sensitive trimethylsilyloxy moiety. In this context, we began this work by investigating the effect of various Lewis acids on the cyanosilylation with TBSCN of 4-oxoaze-

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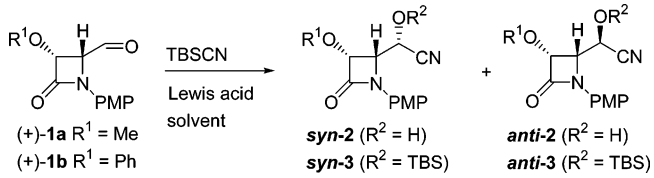
TABLE 1. Lewis Acid Mediated TBSCN Addition to β-Lactam Aldehydes 1a,b[a]



entry	R^1	Lewis acid (mol %)	solvent	*T* (°C)	*t* (h)	product	*syn*/*anti*[b]	yield[c] (%)
1	Me	$InCl_3$ (100)	CH_2Cl_2	Δ	24	*d*		
2	Me	$InCl_3$ (30)	CH_2Cl_2	rt	45	**2a**	65:35	15
3	Me	$InCl_3$ (10)	CH_2Cl_2	rt	6	**2a**	60:40	84
4	Me	$InCl_3$ (10)	CH_3CN	rt	97	**2a**	90:10	12
5	Me	$InCl_3$ (10)	CH_3CN	Δ	41	**2a**	90:10	40
6	Me	$InCl_3$ (50)	CH_3CN	Δ	6	**2a**	90:10	35
7	Me	$InCl_3$ (100)	CH_3CN	Δ	6	**2a**	90:10	54
8	Me	$InCl_3$ (100)	DMSO	rt	30	**2a**	81:19	73
9	Me	$InCl_3$ (100)	CH_3CN/H_2O	Δ	22	**2a**	74:26	32
10	Me	$SnCl_4$ (100)	CH_3CN	Δ	5	**2a/3a**	65:35	50[e]
11	Me	$ZnCl_2$ (100)	CH_3CN	Δ	21	**3a**	47:53	68
12	Me	$BiCl_3$ (20)	CH_3CN	rt	20	**2a/3a**	70:30	45[f]
13	Me	none	CH_3CN	rt	48	**2a/3a**	*g*	15[h]
14	Ph	$InCl_3$ (10)	CH_2Cl_2	rt	7	**2b**	57:43	61
15	Ph	$InCl_3$ (100)	CH_3CN	Δ	30	**2b**	90:10	15

[a] All reactions were performed using an aldehyde/TBSCN ratio of 1/1.2 mmol. [b] The ratio was determined by integration of well-resolved signals in the ^1H NMR spectra of the crude reaction mixtures before purification. [c] Combined yield of pure, isolated products (*syn*/*anti*-**2**) after silica gel chromatography with correct analytical and spectral data. [d] A complex mixture of uncharacterized products was obtained. [e] In addition, a further 5% yield of a mixture of O-silylated cyanohydrins **3a** was obtained. [f] In addition, a further 8% yield of a mixture of O-silylated cyanohydrins **3a** was obtained. [g] Undetermined mixture of *syn*/*anti*-isomers both for **2a** and **3a**. [h] In addition, a further 18% yield of a mixture of O-silylated cyanohydrins **3a** was obtained.

tidine-2-carbaldehyde **1a**,[18] which was selected as a model substrate. First, we investigated reaction of **1a** with $TiCl_4$, $BF_3 \cdot Et_2O$, and $ZnBr_2$, which are well-documented promoters for cyanosilylation of chiral aldehydes.[17,19] The reaction failed to give the corresponding cyanation products under different experimental conditions and a complex mixture of uncharacterized products being obtained in all cases. Similar results were observed for the $InCl_3$ (100 mol %)-induced reaction in dichloromethane as solvent, both at room temperature and at reflux (Table 1, entry 1).[20] However, when a catalytic amount of $InCl_3$ (10 mol %) was used, quantitative conversion to the cyanohydrin **2a** was obtained after 4 h in dichloromethane at room temperature, as a 60/40 mixture of *syn*/*anti* isomers (Table 1, entry 3). Fortunately, both diastereomers of compound **2a** could be easily separated and obtained in reasonable yield by flash chromatography on silica gel, the major isomer *syn*-**2a** being the less polar compound. We also found that on increasing the amount of $InCl_3$ (30 mol %) both the efficiency and the reaction rate decreased (Table 1, entry 2). In order to improve the selectivity of the process, the effect of altering the reaction solvent was then explored (tetrahydrofuran, acetonitrile, and DMSO). A significant solvent effect on the diastereoselectivity was observed, the more polar solvents increased the selectivity although the reaction proceeded more slowly and with diminished efficiency in acetonitrile (Table 1, entries 4 and 5). When the reaction was run in acetonitrile, the effect of the amount of $InCl_3$ and temperature on the conversion rate as well as on the selectivity was studied. It was found that the efficiency of the process did improve upon increasing the amount of catalyst while retaining the selectivity of the reaction when cyanohydrin formation was performed in refluxing acetonitrile (Table 1, entries 5−7). A similar experiment in DMSO at room temperature gave slightly improved yield but worse selectivity (Table 1, entry 8), and a poor result in terms of both selectivity and efficiency of the reaction was achieved when a 4/1 mixture of acetonitrile/water was used (Table 1, entry 9). On the basis of these results, we chose to use equimolecular amounts of different Lewis acid in acetonitrile as solvent. A mixture (90/10) of cyanohydrin **2a**, major compound, and O-silylated cyanohydrin **3a** was obtained for the $SnCl_4$ (1 equiv)-promoted reaction after 5 h, in both cases as mixtures of *syn*/*anti* isomers (Table 1, entry 10). Interestingly, the $ZnCl_2$ (1 equiv)-promoted reaction gave in good yield cyanohydrin **2a** with poor *anti*-selectivity (Table 1, entry 11). The reaction with $BiCl_3$ (1 equiv) results in a complete recovery of the starting aldehyde, while use of less $BiCl_3$ (20 mol %) in acetonitrile at room temperature afforded an 84/16 mixture of cyanohydrin **2a** and its O-silyl derivative **3a**, respectively, in both cases as a 70/30 mixture of

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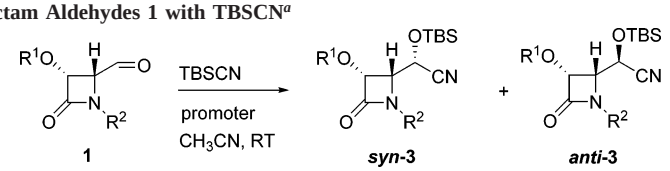
TABLE 2. Silylcyanation of β-Lactam Aldehydes 1 with TBSCN[a]



entry	aldehyde	R^1	R^2	promoter (mol %)	*t* (h)	product	*syn*/*anti*[b]	yield[c] (%)
1	(+)-**1a**	Me	PMP	MS 4 Å[d]	3.0	**3a**	82:18	87
2	(+)-**1a**	Me	PMP	Na_2CO_3 (25)	1.0	**3a**	82:18	94
3	(+)-**1a**	Me	PMP	Bu_4NCN (10)	0.4	**3a**	82:18	75
4	(+)-**1a**	Me	PMP	Et_3N (50)		**2a**/**3a**[e]	*f*	75[g]
5	(+)-**1b**	Ph	PMP	MS 4 Å[d]	3.5	**3b**	87:13	60
6	(+)-**1b**	Ph	PMP	Na_2CO_3 (25)	0.75	**3b**	88:12	81
7	(+)-**1c**	Bn	PMP	Na_2CO_3 (25)	1.5	**3c**	82:18	89
8	(+)-**1d**	Me	Bn	MS 4 Å[d]	2.0	**3d**	60:40	64
9	(+)-**1d**	Me	Bn	Na_2CO_3 (25)	0.75	**3d**	62:38	81
10	(+)-**1e**	Me	allyl	Na_2CO_3 (25)	1.5	**3e**	67:33	54

[a] All reactions were performed using an aldehyde/TBSCN ratio of 1/1.2 mmol. [b] The ratio was determined by integration of well-resolved signals in the ^{1}H NMR spectra of the crude reaction mixtures before purification. [c] Combined yield of pure, isolated products *syn*/*anti*-**3** after silica gel chromatography with correct analytical and spectral data. [d] A ratio of 4 Å molecular sieves/aldehyde = 500 mg/mmol was used. [e] A 15/85 mixture of compounds **2a**/**3a** was obtained as determined by ^{1}H NMR analysis of the crude reaction mixture before purification. [f] Compound **2a** was obtained as a 43:57 mixture of *syn*/*anti*-isomers as determined by ^{1}H NMR analysis of the crude reaction mixture before purification. Compound **3a** was obtained as a 87:13 mixture of *syn*/*anti*-isomers as determined by ^{1}H NMR analysis of the crude reaction mixture before purification. [g] In addition, a further 13% yield of a 43:57 mixture of cyanohydrins **2a** was obtained.

syn/anti isomers (Table 1, entry 12).[21] Use of $HfCl_4$ (1 equiv or 20 mol %) to promote the cyanosilylation of compound **1a** was unsuccessful, the starting aldehyde being recovered almost unchanged, after prolonged reaction times in acetonitrile both at room temperature and at reflux. Finally, a blank test using TBSCN in acetonitrile at room temperature without a Lewis acid promoter gave a 23/34/43 mixture of compounds **1a**/**2a**/**3a**, respectively, from which the *syn/anti* ratio of isomers could not be determined (Table 1, entry 13). From the above study, we could conclude that Lewis acids are unable to effectively promote the cyanosilylation under different experimental conditions, and instead hydrocyanation takes place affording the corresponding free cyanohydrin in variable yield and selectivity. In terms of yield, the best result was obtained using $InCl_3$ (10 mol %) in dichloromethane at room temperature (Method A, see Supporting Information), while use of $InCl_3$ (100 mol %) in acetonitrile at reflux was necessary for better diastereoselectivity (Method B, see Supporting Information). On the other hand, no significant steric effect on the diastereoselectivity was observed under the above optimized conditions for aldehyde **1b** having a sterically more demanding phenoxy group at C3 than aldehyde **1a**. However, the efficiency and the reaction rate decreased for **1b** (Table 1, entries 14 and 15).

Next, we focused our efforts on the cyanosilylation of aldehyde **1a** using an equimolar amount of Lewis acid in combination with an excess of 4 Å molecular sieves (MS), but this proved to be equally unfeasible. On the other hand, when the cyanosilylation was carried out in the presence of 4 Å MS[22] in acetonitrile at room temperature, and in the absence of a Lewis acid, the cyanosilyl derivative **3a** was obtained in very good yield and reasonable diastereoselectivity (Table 2, entry 1) (Method A, see Experimental Section). In this way, formation of cyanohydrin **2a** was suppressed. Switching solvents (CH_2Cl_2, THF, toluene, DMSO) had no beneficial effects. In terms of achieving good yields with reasonable selectivity of reaction, room temperature seemed to be the temperature of choice for running the experiments.

Then, we turned our attention to the use of bases such as Bu_4NCN,[23] Et_3N,[24] and Na_2CO_3.[25] As shown in Table 2, the best results were obtained using Na_2CO_3 (25 mol %) in acetonitrile at room temperature (entry 2) (Method B, see Experimental Section), affording compound **3a** in excellent yield as a 4.5/1 mixture of *syn/anti*-isomers. Next, we decided to extend the process to other β-lactam aldehydes **1b**−**e**, bearing different substituents both at C3 and at N1 (Table 2, entries 5−10). The steric properties of both the C3 and N1 substituents on the 2-azetidinone ring appear to influence the stereoselectivity of the addition, with sterically less demanding groups decreasing the diastereoisomeric ratio. In fact, when a phenoxy group was used instead of a methoxy group, the stereoselectivity increased (Table 2, entries 5 and 6). Also, placing a less bulky group at N1, such as benzyl or allyl, decreased both the efficiency and the selectivity of the addition (Table 2, entries 8−10). Fortunately, both diastereomers of compound **3** could be easily separated by flash chromatography on silica gel in all cases. Chemical correlation between cyanosilyl derivatives *syn*-**3a** and *anti*-**3a** and their corresponding cyanohydrins *syn*-**2a** and *anti*-**2a** was achieved by hydrolysis of the formers with 20% aqueous HCl in acetonitrile in moderate yield.

The *syn/anti* stereochemistry for new compounds **2** and **3** was assigned by comparison of its ^{1}H NMR data with that

(21) Bismuth(III) chloride has been reported as a versatile catalyst for cyanation of aldehydes with trimethylsilyl cyanide as well as for the synthesis of α-aminonitriles by a one-pot three-component Strecker reaction. See, for example: (a) De, S. K.; Giggs, R. A. *Tetrahedron Lett.* **2004**, *45*, 7407. (b) Wada, M.; Takahashi, T.; Domae, T.; Fukuma, T.; Miyoshi, N.; Smith, K. *Tetrahedron: Asymmetry* **1997**, *8*, 3939.

(22) For the use of molecular sieves (4 Å) in the cyanobenzoylation and hydrocyanation of aldehydes, see: Watahiki, T.; Ohba, S.; Oriyama, T. *Org. Lett.* **2003**, *5*, 2679.

(23) For the use of TBACN as catalyst for the cyanosilylation of carbonyl compounds with trialkylsilyl cyanides, see: Amurrio, I.; Córdoba, R.; Csáky, A. G.; Plumet, J. *Tetrahedron* **2004**, *60*, 10521.

(24) See, for example: (a) Denmark, S. E.; Chung, W.-J. *J. Org. Chem.* **2006**, *71*, 4002. (b) Paraskar, A. S.; Sudalai, A. *Tetrahedron Lett.* **2006**, *47*, 5759.

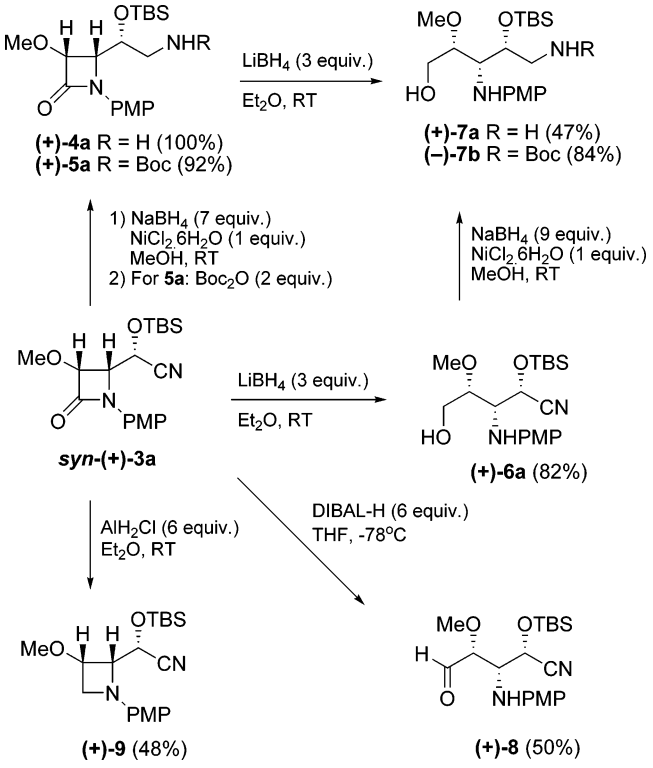
(25) He, B.; Li, Y.; Feng, X.; Zhang, G. *Synlett* **2004**, 1776.

reported in the literature for related products.[26] In this way, the vicinal coupling constant between H4 and H4′ is higher for *syn*-isomers ($J_{4,4}$ = 5.3 Hz for **2a** and $J_{4,4}$ = 7.8−6.3 Hz for compounds **3**) than for *anti*-isomers ($J_{4,4}$ = 2.7 Hz for **2a** and $J_{4,4}$ = 5.9−2.4 Hz for compounds **3**). Moreover, assignment of configuration of cyanohydrins *syn*-**2a** and *anti*-**2a**[27] has been recently reported by Riguera et al. by comparison of the corresponding ^{1}H and ^{13}C NMR spectra of their (*R*)- and (*S*)-2-methoxy-2-phenylacetates.[28] The stereochemistry for the rest of the *β*-lactams was initially assigned on the basis of the above data and was finally confirmed by chemical correlation with their corresponding piperidines (see below). The observed *syn*-diastereoselectivity for both compounds **2** and **3** might be tentatively explained by invoking the Felkin-Anh model, analogously to the related addition processes described in our laboratories.[14a]

Polyfunctional *β*-lactam cyanohydrin derivatives may be considered versatile intermediates in organic synthesis because of their inherent dual reactivity. With O-silylated *β*-lactam cyanohydrins **3** in hand, we next explored different reducing agents in order to find the best conditions for their chemoselective reduction. Since these compounds **3** may yield many different products, a number of different metal hydrides were screened using *β*-lactam cyanohydrin *syn*-**3a** as a model substrate.

First, we used $LiAlH_4$[29] that led to the disappearance of starting material, and no recognizable products were isolated after treatment with aqueous base. These results clearly point out the delicate balance of reactivity between the reducing agent and reactive functional groups in the molecule. On the other hand, $NaBH_4$[30] was revealed to be ineffective for promoting any reduction on *β*-lactam cyanohydrin *syn*-**3a**; the *β*-amino ester arising from the basic opening of the *β*-lactam ring was the only formed product after prolonged reaction time. It is well-known that the reducing behavior of sodium borohydride is dramatically improved with the addition of transition metal salts.[31] Among these, Ni(II) and Co(II) salts have drawn wide attention in the modification of $NaBH_4$ reactivity and have found application in the reduction of nitriles.[32] Therefore, we investigated the reduction of compound *syn*-**3a** with $NiCl_2 \cdot 6H_2O$ (1 equiv) and an excess of $NaBH_4$ in methanol. We were pleased

SCHEME 2



to find rapid, complete chemoselective reduction of the cyano group affording amino *β*-lactam **4a** in quantitative yield (Scheme 2).

Having developed an efficient method to selectively reduce the nitrile function on compounds *syn*-**3a**, we needed to explore other reagents that could chemoselectively react with the *β*-lactam ring. Lithium borohydride has been reported as a selective reducing agent for esters and amides, but its use has never been reported for *β*-lactams.[33] To our surprise, reduction of the model compound *syn*-**3a** with $LiBH_4$ in diethyl ether as solvent at room temperature smoothly gave the corresponding *β*-amino-*δ*-hydroxy nitrile **6a** in excellent yield and with total chemoselectivity (Scheme 2). Further reduction of compound **6a** with nickel boride under the conditions used before resulted in the formation of diamino alcohol **7a** in 47% yield. Finally, to complete the reduction processes, we subjected the Boc-protected derivative **5a** to treatment with $LiBH_4/Et_2O$ at room temperature, affording the corresponding *β*-amino-*δ*-hydroxy carbamate **7b** in excellent yield (Scheme 2). Amino alcohols such as **7a** and **7b** may serve as chelating agents as well as versatile chiral building blocks for both organic synthesis and the preparation of macrocycles.[34]

DIBAL-H has been reported to react both with a cyano and *β*-lactam ring to give aldehydes[35] and *β*-amino alcohols or azetidines,[36] respectively. In our hands, the cyano group was

(26) See, among others: (a) Andrés, J. M.; de Elena, N.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron* **1999**, *55*, 14137. (b) Ishimaru, K.; Tsuru, K.; Yabuta, K.; Wada, M.; Yamamoto, Y.; Akiba, K. *Tetrahedron* **1996**, *52*, 13137. (c) van der Zeijden, A. A. H. *Tetrahedron*: *Asymmetry* **1995**, *6*, 913. (d) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 4629.

(27) Samples of cyanohydrins *syn*-**2a** and *anti*-**2a** were supplied from our laboratory in connection with a general study on the assignment of absolute configuration of cyanohydrins by NMR.

(28) Louzao, I.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Commun.* **2006**, 1422

(29) Van Brabandt W.; Dejaegher, Y.; Van Landeghem, R.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 1101 and references cited therein.

(30) Del Buttero, P.; Molteni, G.; Roncoroni, M. *Tetrahedron Lett.* **2006**, *47*, 2209.

(31) See, for example: (a) Periasamy, M.; Thirumalaikumur, M. *J. Organomet. Chem.* **2000**, *609*, 137. (b) Carlier, P. R.; Lo, K. M.; Williams, I. D. *J. Org. Chem.* **1995**, *60*, 7511. (c) Ito, K.; Itsuno, S.; Sakurai, Y. *Synthesis* **1988**, 995. (d) Ganem, B.; Osby, J. O. *Chem. Rev.* **1986**, *86*, 763. (e) Wade, R. C. *J. Mol. Catal.* **1983**, *18*, 273. (f) Niino, Y.; Nishiki, M.; Mitsuo, N.; Miyataka, H.; Satoh, T. *Tetrahedron Lett.* **1982**, *23*, 193. (g) Chung, S.-K. *J. Org. Chem.* **1979**, *44*, 1014. (h) Nystrom, R. F. *J. Am. Chem. Soc.* **1955**, *77*, 2544.

(32) (a) Caddick, S.; Judd, D. B.; Lewis, A. K. de K.; Reich, M. T.; Williams, M. R. V. *Tetrahedron*, **2003**, *59*, 5417. (b) Khurana, J. M.; Kukreja, G. *Synth. Commun.* **2002**, *32*, 1265. (c) Caddick, S.; Haynes, A. K. de K.; Judd, D. B.; Williams, M. R. V. *Tetrahedron Lett.* **2000**, *41*, 3513.

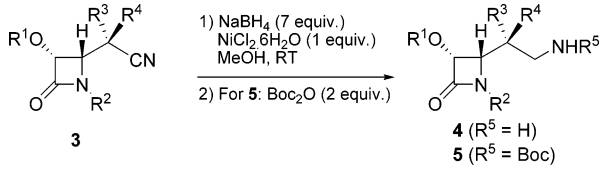
(33) See, for example: (a) Soai, K.; Ookawa, A. *J. Org. Chem.* **1986**, *51*, 4000. (b) Piers, E.; Chong, J. M. *J. Org. Chem.* **1982**, *47*, 1605.

(34) (a) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. (c) Kolb, H. C.; Sharpless, K. B. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 1998; p 243.

(35) Proudfoot, J. R.; Li, X.; Djerassi, C. *J. Org. Chem.* **1985**, *50*, 2026.

(36) (a) Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K.; Yamashita, M.; Abe, R. *J. Org. Chem.* **1991**, *56*, 5263. (b) Yamashita, M.; Ojima, I. *J. Am. Chem. Soc.* **1983**, *105*, 6339.

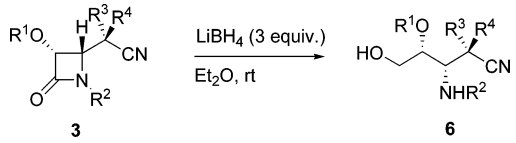
TABLE 3. Reduction of β-Lactam Cyanohydrins 3 with $NaBH_4/NiCl_2·6H_2O$: Synthesis of Amino β-Lactams 4 and β-Lactam Carbamates 5[a]



substrate	R^1	R^2	R^3	R^4	*t* (min)	product	R^2	R^5	yield[b] (%)
anti-(+)-**3a**	Me	PMP	H	OTBS	20	*anti*-(+)-**4a**	PMP	H	100[c]
syn-(+)-**3c**	Bn	PMP	OTBS	H	20	*syn*-(+)-**4b**[d]	PMP	H	56[e]
						syn-(+)-**4c**	PMP	H	14
syn-(−)-**3d**	Me	Bn	OTBS	H	25	*syn*-(−)-**4d**	Bn	H	91[c]
syn-(−)-**3e**	Me	allyl	OTBS	H	20	*syn*-(+)-**4e**[f]	Pr	H	65
anti-(+)-**3a**	Me	PMP	H	OTBS	30	*anti*-(+)-**5a**	PMP	Boc	71
syn-(−)-**3d**	Me	Bn	OTBS	H	25	*syn*-(−)-**5b**	Bn	Boc	86
syn-(−)-**3e**	Me	allyl	OTBS	H	20	*syn*-(+)-**5c**[f]	Pr	Boc	51

[a] In all cases, complete transformation to the reduced products was observed by ^1H NMR spectroscopy. [b] Yield of pure, isolated product with correct analytical and spectral data. [c] Yield of crude isolated product with no further purification necessary after workup. [d] A 4:1 ratio of products *syn*-**4b**/*syn*-**4c** was obtained as determined by integration of well-resolved signals in the ^1H NMR spectra of the crude reaction mixtures before purification. [e] The reduction product *syn*-(+)-**4b** was obtained (56%) along with the O-debenzylated product *syn*-(+)-**4c** (R^1 = H) (14%) after purification by column chromatography. [f] The *N*-propyl-β-lactam was isolated as a result of the reduction of both the nitrile group and the double bond.

TABLE 4. Reduction of β-Lactam Cyanohydrins 3 with $LiBH_4$/Et_2O: Synthesis of 3-Amino-5-hydroxypentanenitriles 6



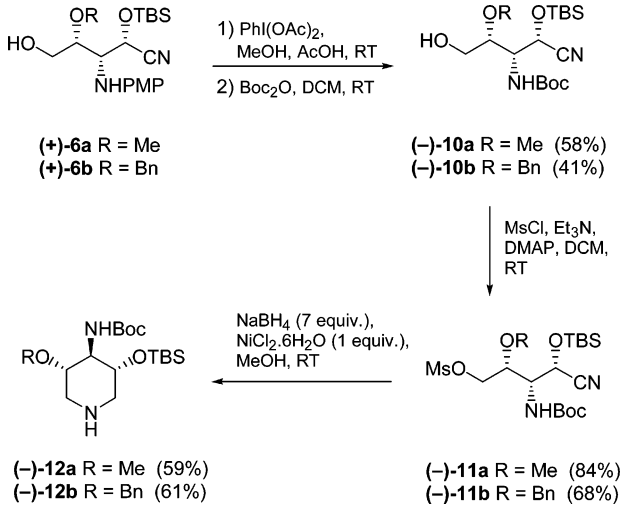
substrate	R^1	R^2	R^3	R^4	*t* (min)	product	yield[a] (%)
syn-(+)-**3c**	Bn	PMP	OTBS	H	50	(+)-**6b**	74
syn-(−)-**3d**	Me	Bn	OTBS	H	60	(+)-**6c**	54
anti-(+)-**3e**	Me	allyl	H	OTBS	90	(+)-**6d**	40

[a] Yield of pure, isolated product with correct analytical and spectral data.

unaffected when compound *syn*-**3a** was treated with DIBAL-H in THF, giving γ-formyl nitrile **8** and β-amino-δ-hydroxy nitrile **6a** in variable yield depending on the reaction conditions. Thus, aldehyde **8**[37] was the main product at −78 °C for 6 min, while compound **6a** was the sole component when reaction was conducted at room temperature for longer reaction times. Finally, monochloroalane (AlH_2Cl) was examined.[36] We found that AlH_2Cl prepared in situ from $LiAlH_4$ and $AlCl_3$ in diethyl ether gave cyano azetidine **9** in reasonable yield, without being accompanied by other reduction products (Scheme 2).

Having established chemoselective reduction methods for the model compound *syn*-**3a**, we further probed the generality of these two processes. Thus, using the $NaBH_4/NiCl_2$/methanol system, cyanohydrins *anti*-**3a** and *syn*-**3d** were efficiently reduced to their corresponding amino derivatives *anti*-**4a** and *syn*-**4d**, respectively (Table 3). Remarkably, changing the group on nitrogen from aryl to benzyl had little consequence on the isolated yield of the amino β-lactam product (Table 3). However,

SCHEME 3

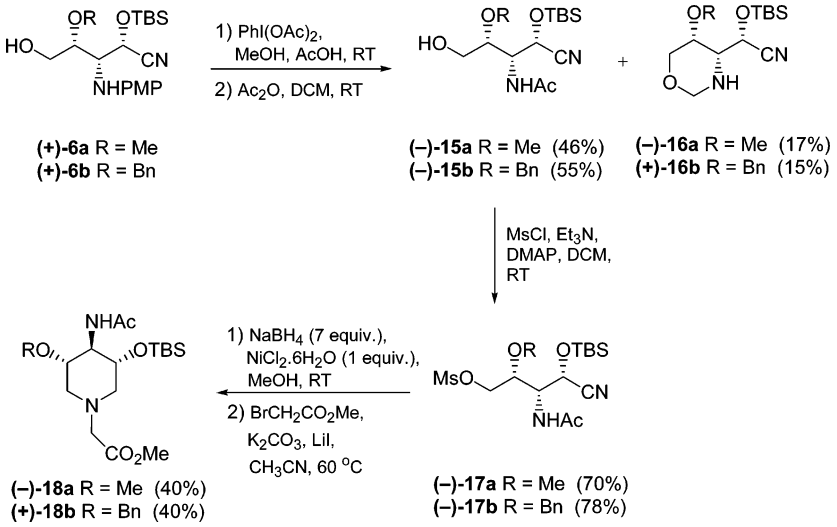


partial debenzylation of the 3-benzyloxy group was observed in compound *syn*-**3c**, with a 4:1 mixture of products, major *syn*-**4b** and minor O-debenzylated *syn*-**4c**, being obtained in this case. Formation of O-debenzylated *syn*-**4c** could not be eliminated completely despite attempting the reaction at shorter times. Starting from *N*-allyl cyanohydrin *syn*-**3e**, the *N*-propyl-β-lactam *syn*-**4e** was isolated in good yield, as a result of the reduction of both the nitrile group and the C=C double bond. Isolation of primary amines **4** under the above experimental conditions is worthy of mention as they could be obtained free of secondary amines and without trapping as protected NH amides by the in situ addition of any acylation agent.[32b,c] Nevertheless, the use of di-*tert*-butyl dicarbonate as trapping agent allowed easy preparation of the corresponding *tert*-butyl carbamates **5a**−**c**, which obviously offer greater synthetic versatility for further transformations due to their facile deprotection (Table 3).

Table 4 summarizes the results of the reduction with $LiBH_4$/Et_2O of cyanohydrins *syn*-**3c**, *syn*-**3d**, and *anti*-**3e**, although in these cases, lower yields were achieved for compounds containing an aliphatic group on the amide nitrogen.

(37) Preparation of aldehydes by reduction of β-lactams is unusual. The formation of intermediate amino aldehydes on route to renieramycin H, ecteinascidin (ET-743), and related natural products has just been described. See, for instance: (a) Vincent, G.; Williams, R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1517. (b) Jin, W.; Metobo, S.; Williams, R. M. *Org. Lett.* **2003**, *5*, 2095. (c) Herberich, B.; Kinugawa, M.; Vázquez, A.; Williams, R. M. *Tetrahedron Lett.* **2001**, *42*, 543.

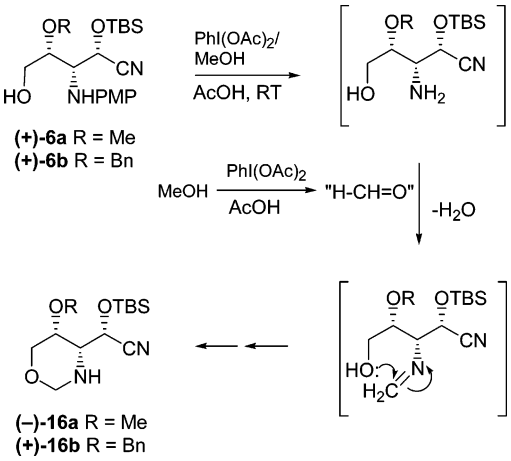
SCHEME 4

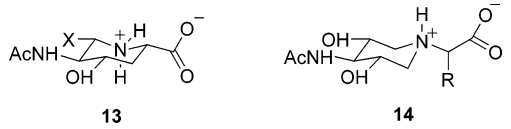


Having demonstrated the facile functional group manipulations of β-lactam cyanohydrins **3** through their chemoselective reduction, we turned our attention to the asymmetric synthesis of fully orthogonally protected *anti*,*anti*-4-amino-3,5-piperidine diols (Scheme 3). Our first task was to develop a direct access to the piperidine ring from diamino alcohol **7a** under Mitsunobu conditions.[38] However, all attempts to transform **7a** in its corresponding 4-aminopiperidine failed using different experimental conditions. Then, we decided to use 3-amino-5-hydroxy nitriles **6a** and **6b** as starting materials. In order to avoid problems associated with the presence of a free amino group, the *p*-anisylamino group in compounds **6** was converted into a *tert*-butyl carbamate by oxidation with (diacetoxyiodo)benzene (DIB) in MeOH/AcOH followed by reaction with di-*tert*-butyl dicarbonate of the resulting primary amino group.[39] In this manner, compounds **10a** and **10b** were prepared in reasonable yield. Interestingly, no protection of the primary hydroxyl group was necessary during oxidation with DIB.[40] Then, alcohols **10** were transformed to mesylates **11** by exposure to methanesulfonyl chloride and triethylamine in the presence of DMAP. Treatment of mesylates **11** with $NaBH_4/NiCl_2$/methanol at room temperature smoothly led to N-unsubstituted piperidines **12** in good yields (Scheme 3).

Next, we decided to apply the above methodology to the synthesis of fully orthogonally protected sialidase inhibitor analogues starting from compounds **6a** and **6b**. *anti*,*anti*-4-Acetamidopiperidines such as **13** and **14** are of interest in studies concerning sialidase (or neuraminidase) transition state analogue inhibitors.[5,41] To the best of our knowledge, only one multistep asymmetric synthesis of compounds **14** has been reported, which starts from 1,2-isopropylidene-α-D-xylofuranose.[5]

SCHEME 5





13 **14**

In order to introduce the 4-acetamido group in a straightforward manner, oxidation of **6a** and **6b** with DIB/MeOH/AcOH was followed by treatment with acetic anhydride giving compounds **15a** and **15b** in good yields, along with compounds **16a** and **16b** as byproducts, respectively. Further treatment of compounds **15a** and **15b** with methanesulfonyl chloride/triethylamine/DMAP in dichloromethane at room temperature gave nitriles **17a** and **17b**. Reductive cyclization with $NaBH_4/NiCl_2$/methanol followed by subsequent treatment with methyl bromoacetate/potassium carbonate/lithium iodide in acetonitrile at 60 °C afforded *N*-methoxycarbonylmethyl piperidines **18a** and **18b**, respectively, in moderate overall yields (Scheme 4). Formation of compounds **16** is unprecedented and could be rationalized as shown in Scheme 5. After oxidative removal of the *p*-anisyl group in **6a** and **6b**, the primary amino group should react with formaldehyde, probably as its methoxyhemiketal, to give the 1,3-oxazine derivatives **16a** and **16b** via nucleophilic cyclization of the intermediate *N*-(3-hydroxy)methanimine.

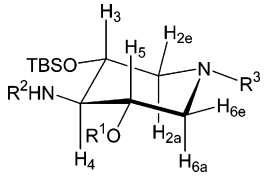
(38) For a related cyclization to piperidines, see: (a) Balasubramanian, Th.; Hassner, A. *Tetrahedron*: *Asymmetry* **1998**, 9, 2201. For a review, see: (b) Mitsunobu, O. *Synthesis* **1981**, 1.

(39) For use of DIB on the oxidative removal of the *o*-anisyl group, see: (a) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734. (b) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 984.

(40) To our surprise, all attemps to oxidize the mesylate derivative of alcohols **6a** and **6b** were unsuccessful.

(41) See, for example: (a) Glanzer, B. I.; Gyorgydeak, Z.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1991**, *74*, 343. (b) Walliman, K.; Vasella, A. *Helv. Chim. Acta* **1990**, *73*, 1359. (c) Czollner, L.; Kuszmann, J.; Vasella, A. *Helv. Chim. Acta* **1990**, *73*, 1338. (d) Bernet, B.; Murty, A. R. C. B.; Vasella, A. *Helv. Chim. Acta* **1990**, *73*, 940.

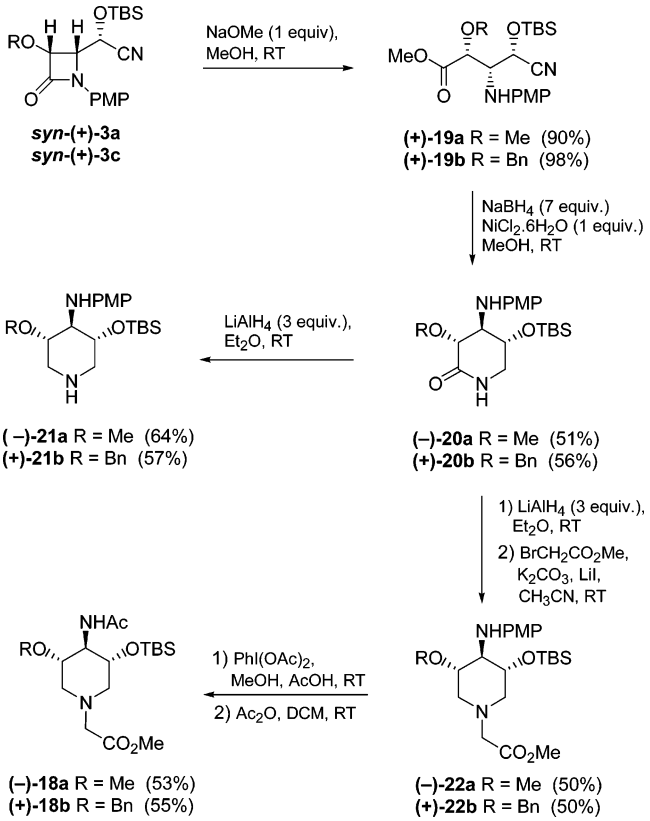
TABLE 5. Selected Coupling Constants for Piperidines 12, 18, 21, and 22[a]



compound	R^1	R^2	R^3	$^2J_{2a,2e}$	$^3J_{2a,3a}$	$^3J_{2e,3}$	$^3J_{3,4}$	$^3J_{4,5}$	$^3J_{5,6a}$	$^3J_{5,6e}$	$^2J_{6a,6e}$
12a	Me	Boc	H	12.4	10.0	5.0	8.9	8.9	11.5	---[b]	11.5
12b	Bn	Boc	H	12.2	10.2	4.8	9.8	9.8	10.0	4.2	12.1
18a[c]	Me	Ac	E[d]	10.7	10.1	5.0	9.6	9.7	10.2	4.7	10.5
18b	Bn	Ac	E[d]	10.8	10.2	4.7	*b*	*b*	10.2	2.1	10.2
21a	Me	PMP	H	12.0	9.7	4.6	9.3	*b*	9.5	2.7	12.1
21b	Bn	PMP	H	11.8	8.5	4.7	8.8	8.6	9.7	4.2	12.0
22a	Me	PMP	E[d]	10.4	10.0	4.8	9.5	9.5	9.9	5.0	10.5
22b[e]	Bn	PMP	E[d]	10.7	10.0	4.7	9.5	9.7	10.2	4.7	10.6

[a] All spectra were recorded at 300 MHz (except for compound **12b**, 500 MHz), at 25 °C, and using $CDCl_3$ as solvent. [b] Measurement of this coupling constant was unsuccessful on the spectra. [c] Additionally, a long-range coupling $^4J_{2e,6e} = 1.8$ Hz and $^3J_{4,NH} = 9.1$ Hz were observed. [d] E = CH_2CO_2Me. [e] Additionally, a long-range coupling $^4J_{2e,6e} = 1.9$ Hz was observed.

SCHEME 6



To improve the overall yield of our synthesis, we explored another route starting from β-lactam cyanohydrins *syn*-**3a** and *syn*-**3c**. Reaction of these compounds with sodium methoxide in methanol at room temperature resulted in the chemoselective opening of the β-lactam ring with formation of the corresponding β-amino esters **19a** and **19b** in very good yields. Reduction of the cyano group in compounds **19a** and **19b** with $NaBH_4$/$NiCl_2$/methanol afforded the corresponding 2-piperidones **20a** and **20b** in good yields.[42] Initial reduction of compound **20a** with LAH in THF[43] both at room temperature and at reflux resulted in partial O-desilylation, and the piperidine **21a** was isolated as the major compound in moderate yield in all cases. Gratifyingly, when compounds **20a** and **20b** were treated with LAH in diethyl ether at room temperature for 30 min, the piperidines **21a** and **21b** were obtained in good yields (Scheme 6). Fully protected sialidase inhibitor analogues **18a** and **18b** were prepared from 2-piperidones **20a** and **20b** via the four-step sequence as shown (Scheme 6). Removal of the PMP group in the final step of the synthesis avoided the formation of byproducts as oxazines **16**, although the yield remained rather similar in both cases. Thus, starting from common synthetic intermediates, β-lactam cyanohydrins *syn*-**3a** and *syn*-**3c**, the overall yield for piperidines **18a** and **18b** was similar for both routes.

The structure and stereochemistry of piperidines **12**, **18**, and **20**−**22** were assigned by NMR studies. The *cis*-stereochemistry of the four-membered ring was set during the cyclization step to form the 2-azetidinone ring, and it was transferred unaltered during the further synthetic steps. The cyclic structures (by DEPT, HETCOR, and COSY) and the stereochemistry (by vicinal proton couplings) of piperidines **12**, **18**, and **20**−**22** were established by NMR one- and two-dimensional techniques. The values collected in Table 5 for vicinal coupling constants show an unequivocally fixed antiperiplanar orientation both for H3−H4 protons (8.8 Hz < $^3J_{3,4}$ < 9.8 Hz) as well as for H4−H5 protons (8.6 Hz < $^3J_{4,5}$ < 9.8 Hz), in agreement with the *anti*,*anti* configuration proposed for the 3,4,5-trisubstituted piperidines.[44] Taking into account that O-silylated cyanohydrins **3** could be obtained and cyclized to piperidines, the stereochemistry at the carbinolic stereogenic center for compounds **3** (and hence **2**) as well as for synthetic intermediates **4**−**11**, **15**−**17**, and **19** was confirmed by comparison with well-established configuration of different prepared 3,4,5-trisubstituted piperidines.

(42) 2-Piperidones **20a** and **20b** were also prepared from amino β-lactams **4a** and **4b** by treatment with sodium methoxide in methanol at reflux, in 57 and 74% yields, respectively. However, partial epimerization was observed for compound **20b**, a 53:47 mixture of epimers at C3 being obtained.

(43) Peyronel, J.-F.; Samuel, O.; Fiaud, J.-C. *J. Org. Chem.* **1987**, *52*, 5320.

(44) Alvarez-Ibarra, C.; Cuervo, R.; Fernández-Monreal, M. C.; Ruiz, M. P. *J. Org. Chem.* **1992**, *57*, 4270 and references cited therein.

Conclusions

In summary, two novel, complementary routes to orthogonally protected enantiopure *anti*,*anti*-4-amino-3,5-piperidine diols were developed in reasonable overall yields starting from optically pure β-lactam cyanohydrin hybrids, utilizing chemoselective reduction protocols of both β-lactam or nitrile moieties as well as oxidative N-dearylation with diacetoxyiodobenzene of a 4-methoxyphenylamino group as key common synthetic steps. In addition, the present strategy allows stereocontrolled construction of all three contiguous stereocenters early in the sequence. A concise asymmetric synthesis of fully orthogonally protected sialidase inhibitors illustrates the utility of the new synthetic protocols.

Experimental Section

General. The same experimental techniques were used as previously reported.[15]

General Procedure for the Reaction between Aldehydes 1 and TBSCN. Preparation of the *O*-[*tert*-Butyl(dimethyl)silyl]-β-lactam Cyanohydrin Derivatives 3. Method A. A solution of TBSCN (0.60 mmol) in anhydrous acetonitrile (1.7 mL) was added dropwise via syringe to a stirred suspension of the appropriate 4-oxoazetidine-2-carbaldehyde **1** (0.50 mmol) and molecular sieves (4 Å, 250 mg) in the same solvent (1.7 mL), at room temperature and under argon atmosphere. The mixture was stirred until disappearance of starting material (TLC). Then, a saturated aqueous NaCl solution (5 mL) was added, and the resulting mixture was extracted with DCM (5 × 10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. After flash chromatography on silica gel of the residue, eluting with hexanes/ethyl acetate mixtures, the two separated *syn*/*anti* isomers of derivatives **3** were obtained. **Method B.** A solution of TBSCN (3.41 mmol) in anhydrous acetonitrile (9.3 mL) was added dropwise via syringe to a stirred suspension of the appropriate 4-oxoazetidine-2-carbaldehyde **1** (2.84 mmol) and Na_2CO_3 (0.71 mmol) in the same solvent (9.3 mL), at room temperature and under argon atmosphere. The mixture was stirred until disappearance of starting material (TLC). Then, a saturated aqueous NaCl solution (30 mL) was added, and the resulting mixture was extracted with DCM (5 × 60 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. After flash chromatography on silica gel of the residue, eluting with hexanes/ethyl acetate mixtures, the two separated *syn*/*anti* isomers of derivatives **3** were obtained.[45]

(+)-(2*S*)-{[*tert*-Butyl(dimethyl)silyl]oxy}[(2*R*,3*R*)-3-methoxy-1-(4-methoxyphenyl)-4-oxoazetidin-2-yl]acetonitrile, *syn*-(+)-3a, and (+)-(2*R*)-{[*tert*-Butyl(dimethyl)silyl]oxy}[(2*R*,3*R*)-3-methoxy-1-(4-methoxyphenyl)-4-oxoazetidin-2-yl]acetonitrile, *anti*-(+)-3a. Method A. From 150 mg (0.64 mmol) of 4-oxoazetidine-2-carbaldehyde (+)-**1a** and after chromatography of the residue eluting with hexanes/ethyl acetate (5:1), both analytically pure less polar isomer *syn*-(+)-**3a** (169 mg, 70%) and the more polar one *anti*-(+)-**3a** (40 mg, 17%) were obtained. **Method B.** From 400 mg (1.70 mmol) of 4-oxoazetidine-2-carbaldehyde (+)-**1a** and after chromatography of the residue eluting with hexanes/ethyl acetate (5:1), both analytically pure less polar isomer *syn*-(+)-**3a** (495 mg, 77%) and the more polar one *anti*-(+)-**3a** (108 mg, 17%) were obtained (94% overall yield). Isomer *syn*-(+)-**3a**: white solid; mp 76−77 °C (hexanes/ethyl acetate); $[\alpha]_D = +70.4$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.138 (s, 3H), 0.121 (s, 3H), 0.804 (s, 9H), 3.672 (s, 3H), 3.785 (s, 3H), 4.588 (dd, 1H, J = 5.1, 7.7 Hz), 4.682 (d, 1H, J = 5.1 Hz), 4.713 (d, 1H, J= 7.7 Hz), 6.841 (**AA′**XX′, 2H), 7.433 (AA′**XX′**, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.6, −5.5, 17.9, 25.3, 55.5, 59.7, 60.4, 62.9, 82.5, 114.0, 118.0, 119.7, 130.3, 156.8, 164.4; IR ($CHCl_3$, cm^{-1}) ν 1759; MS (ES) *m*/*z* 376 ($M^{+\bullet}$, 21), 319 (M − 57, 43), 291 (41), 264 (15), 259 (9), 247 (9), 178 (58), 149 (100). Anal. Calcd for $C_{19}H_{28}N_2O_4Si$: C, 60.61; H, 7.50; N, 7.44. Found: C, 60.71; H, 7.51; N, 7.26. Isomer *anti*-(+)-**3a**: white solid; mp 97−98 °C (hexanes/ethyl acetate); $[\alpha]_D = +79.9$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.110 (s, 3H), 0.204 (s, 3H), 0.923 (s, 9H), 3.681 (s, 3H), 3.798 (s, 3H), 4.389 (dd, 1H, J = 5.2, 2.7 Hz), 4.693 (d, 1H, J = 5.2 Hz), 4.888 (d, 1H, J = 2.7 Hz), 6.866 (**AA′**XX′, 2H), 7.503 (AA′**XX′**, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.6, −5.2, 17.9, 25.4, 55.4, 59.5, 60.4, 61.4, 81.8, 114.2, 117.1, 119.5, 130.0, 156.8, 164.0; IR ($CHCl_3$, cm^{-1}) ν 2054, 1755; MS (ES) *m*/*z* 376 ($M^{+\bullet}$, 17), 319 (M − 57, 48), 291 (11), 264 (17), 259 (5), 247 (4), 178 (56), 149 (100). Anal. Calcd for $C_{19}H_{28}N_2O_4Si$: C, 60.61; H, 7.50; N, 7.44. Found: C, 60.59; H, 7.57; N, 7.34.

General Procedure for Preparation of Amino β-Lactams 4. Sodium borohydride (3.5 mmol) was slowly added to a solution of the appropriate O-silylated cyanohydrin **3** (0.5 mmol) and nickel(II) chloride hexahydrate (0.5 mmol) in methanol (4.2 mL) at 0 °C under argon. The reaction mixture was allowed to warm to room temperature and was stirred until disappearance of starting material (TLC). Methanol was evaporated under vacuum, and the resulting crude was diluted with ethyl acetate (100 mL). Then, an aqueous saturated solution of $NaHCO_3$ was added (50 mL). The resulting mixture was filtered through a pad of Celite, and the solution was extracted with ethyl acetate (4 × 50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to afford the corresponding amino β-lactam **4**.

(+)-(3*R*,4*R*)-4-((1*R*)-2-Amino-1-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-3-methoxy-1-(4-methoxyphenyl)azetidin-2-one, *syn*-(+)-4a. From 100 mg (0.27 mmol) of cyanohydrin *syn*-(+)-**3a** (20 min), 101 mg of analytically pure amine *syn*-(+)-**4a** (100%) was obtained as colorless oil: $[\alpha]_D = +89.5$ (*c* 0.6, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ −0.341 (s, 3H), 0.018 (s, 3H), 0.780 (s, 9H) 1.737 (br s, 2H), 2.920 (m, 2H), 3.632 (s, 3H), 3.784 (s, 3H), 4.123 (m, 1H), 4.547 (d, 1H, J = 5.6 Hz), 4.547 (m, 1H), 6.827 (**AA′**XX′, 2H), 7.438 (AA′**XX′**, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.0, −4.9, 18.0, 25.8, 45.0, 55.5, 58.1, 59.4, 72.7, 82.1, 113.8, 119.6, 131.6, 156.2, 165.8; IR ($CHCl_3$, cm^{-1}) ν 3385, 1744; MS (ES) *m*/*z* 380 ($M^{+\bullet}$, 41), 323 ($M^{+\bullet}$ − 57, 16), 292 (100), 149 (10). Anal. Calcd for $C_{19}H_{32}N_2O_4Si$: C, 59.97; H, 8.48; N, 7.36. Found: C, 60.22; H, 8.73; N, 7.16.

General Procedure for Preparation of β-Lactam Carbamates 5. Sodium borohydride (3.5 mmol) was slowly added over a solution of the appropriate O-silylated cyanohydrin **3** (0.5 mmol), nickel(II) chloride hexahydrate (0.5 mmol), and di-*tert*-butyl dicarbonate (1.0 mmol) in methanol (4.2 mL) at 0 °C under argon. The reaction mixture was allowed to warm to room temperature and was stirred until disappearance of starting material (TLC). Methanol was evaporated under vacuum, and the resulting crude was diluted with ethyl acetate (100 mL). Then, a saturated aqueous solution of $NaHCO_3$ was added (50 mL). The resulting mixture was filtered through a pad of Celite, and the filtrate was extracted with ethyl acetate (4 × 50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography on silica gel of the residue, eluting with hexanes/ethyl acetate mixtures gave β-lactam carbamates **5**.

(+)-*tert*-Butyl (2*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-[(2*R*,3*R*)-3-methoxy-1-(4-methoxyphenyl)-4-oxoazetidin-2-yl]ethylcarbamate, *syn*-(+)-5a. From 137 mg (0.36 mmol) of cyanohydrin *syn*-(+)-**3a** (20 min), carbamate *syn*-(+)-**5a** (160 mg, 92%) was obtained as a pure colorless oil after purification by flash chromatography (hexanes/ethyl acetate 3:1): $[\alpha]_D = +27.3$ (*c* 0.8, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ −0.348 (s, 3H), 0.006 (s, 3H), 0.774 (s, 9H), 1.474 (s, 9H), 3.178 (dt, 1H, J = 14.2, 4.3 Hz), 3.565 (ddd, 1H, J = 14.0, 8.3, 2.8 Hz), 3.672 (s, 3H), 3.786 (s, 3H), 4.167 (m, 1H), 4.286 (dd, 1H, J = 8.6, 5.1 Hz), 4.554 (d, 1H, J = 5.4 Hz), 4.868 (br s, 1H), 6.833 (**AA′**XX′, 2H), 7.415 (AA′**XX′**, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.1, −5.0, 17.9, 25.8, 28.4,

(45) Full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supporting Information.

44.0, 55.5, 58.5, 59.7, 71.1, 79.5, 82.4, 113.9, 119.6, 131.6, 156.1, 156.3, 165.8; IR ($CHCl_3$, cm^{-1}) ν 3462, 1747, 1709; MS (ES) *m/z* 480 ($M^{+\bullet}$, 5), 407 (M − 73, 4), 367 (42), 323 (11), 307 (51), 234 (41), 201 (100), 149 (77), 73 (84), 57 (80). Anal. Calcd for $C_{24}H_{40}N_2O_6Si$: C, 59.97; H, 8.39; N, 5.83. Found: C, 60.13; H, 8.62; N, 5.74.

General Procedure for the Preparation of 3-Amino-5-hydroxypentanenitriles 6. Lithium borohydride (2.25 mmol) was added in portions to a solution of the appropriate O-silylated cyanohydrin **3** (0.75 mmol) in anhydrous diethyl ether (18.6 mL) at 0 °C under argon. The reaction mixture was allowed to warm to room temperature and stirred until disappearance of starting material (TLC). Then, a saturated aqueous solution of $NaHCO_3$ (20 mL) was added, and the resulting mixture was extracted with ethyl acetate (5 × 55 mL). The organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash chromatography on silica gel of the residue, eluting with hexanes/ethyl acetate mixtures, gave compounds **6**.

(+)-(2*S*,3*R*,4*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-hydroxy-4-methoxy-3-[(4-methoxyphenyl)amino]pentanenitrile, (+)-6a. From 280 mg (0.74 mmol) of cyanohydrin *syn*-(+)-**3a**, compound (+)-**6a** (232 mg, 82%) was obtained as a pure colorless oil after purification by flash chromatography (hexanes/ethyl acetate 3:1): $[\alpha]_D = +13.3$ (*c* 0.9, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.119 (s, 3H), 0.203 (s, 3H), 0.914 (s, 9H), 3.575 (s, 3H), 3.756 (s, 3H), 3.842−3.702 (m, 4H), 4.623 (d, 1H, $J = 5.6$ Hz), 6.644 (**AA′**BB′, 2H), 6.791 (AA′**BB′**, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.4, −5.2, 18.0, 25.5, 55.7, 58.3, 59.0, 62.0, 62.0, 77.6, 115.2, 115.3, 118.5, 139.5, 153.2; IR ($CHCl_3$, cm^{-1}) ν 3393; MS (ES) *m/z* 380 ($M^{+\bullet}$, 6), 305 ($M^{+\bullet}$ − 75, 2), 210 ($M^{+\bullet}$ − 170, 100), 178 (24), 160 (53). Anal. Calcd for $C_{19}H_{32}N_2O_4Si$: C, 59.97; H, 8.48; N, 7.36. Found: C, 59.79; H, 8.62; N, 7.02.

General Procedure for Preparation of Carbamates 10 and Amides 15. To a solution of diacetoxy iodobenzene (DIB) (1.70 mmol) in a mixture of methanol (4.7 mL) and acetic acid (0.10 mL) was slowly added a solution of the corresponding 3-amino-5-hydroxypentanenitrile **6** (0.42 mmol) in methanol (1.2 mL) over 20 min. Upon complete addition, the reaction was stirred at rt for 30 min. Then, a 10% aq HCl solution (4.8 mL, wt %) was added. The mixture was stirred for 30 min, at which time a 10% aq $Na_2S_2O_3$ solution (4.8 mL, wt %) was added, and stirring was allowed to continue for an additional 30 min. After that, sodium carbonate was added until the solution was made basic (for carbamates **10**) or neutral (for amides **15**), and a solution of di-*tert*-butyl dicarbonate or acetic anhydride (1.70 mmol) in DCM (2 mL) was added as required. The mixture was stirred overnight at rt. Afterward, methanol was removed under reduced pressure, and the resulting mixture was extracted with DCM (4 × 40 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography on silica gel of the residue eluting with hexanes/ethyl acetate mixtures afforded analytically pure carbamate **10** or amide **15**.

(−)-*tert*-Butyl (1*R*,2*R*)-1-[(*S*)-{[*tert*-Butyl(dimethyl)silyl]oxy}-(cyano)methyl]-3-hydroxy-2-methoxypropylcarbamate, (−)-10a. From 134 mg (0.35 mmol) of (+)-**6a**, compound (−)-**10a** (77 mg, 58%) was obtained after purification by flash chromatography (hexanes/ethyl acetate 3:1) as a pure pale yellow oil: $[\alpha]_D = -6.8$ (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.185 (s, 3H), 0.242 (s, 3H), 0.935 (s, 9H), 1.452 (s, 9H), 2.402 (t, 1H, $J = 6.3$ Hz), 3.525 (s, 3H), 3.530 (m, 1H), 3.751 (m, 2H), 3.982 (dd, 1H, $J =$ 8.2, 6.7 Hz), 4.624 (d, 1H, $J = 6.3$ Hz), 5.053 (d, 1H, $J = 9.3$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.4, −5.3, 18.0, 25.5, 28.2, 53.5, 59.2, 60.9, 62.0, 77.4, 80.6, 118.4, 156.2; IR ($CHCl_3$, cm^{-1}) ν 3447, 1703; MS (ES) *m/z* 347 ($M^{+\bullet}$ − 27, 8), 301 ($M^{+\bullet}$ − 73, 30), 261 ($M^{+\bullet}$ − 57 − 56, 100), 217 ($M^{+\bullet}$ − 57 − 56 − 44, 42), 204 ($M^{+\bullet}$ − 170, 37), 148 ($M^{+\bullet}$ − 170 − 56, 77), 104 ($M^{+\bullet}$ − 170 − 56 − 44, 81), 75 (42), 73 (37), 57 (86). Anal. Calcd for $C_{17}H_{34}N_2O_5Si$: C, 54.51; H, 9.15; N, 7.48. Found: C, 54.61; H, 9.33; N, 7.35.

(−)-*N*-{(1*R*,2*R*)-2-(Benzyloxy)-1-[(*S*)-{[*tert*-butyl(dimethyl)-silyl]oxy}(cyano)methyl]-3-hydroxypropyl}acetamide, (−)-15b. From 196 mg (0.43 mmol) of (+)-**6b** and, after flash chromatography (hexanes/ethyl acetate 1:1), two fractions were obtained. From the more polar one, compound (−)-**15b** (93 mg, 55%) was obtained as a pure pale brown oil: $[\alpha]_D = -27.3$ (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.184 (s, 3H), 0.240 (s, 3H), 0.937 (s, 9H), 2.024 (s, 3H), 3.492 (m, 1H), 3.681 (m, 1H), 4.071 (ddd, 1H, $J =$ 7.3, 5.5, 1.6 Hz), 4.314 (ddd, 1H, $J = 8.5$, 6.6, 1.8 Hz), 4.628 (d, 1H, $J = 11.0$ Hz), 4.686 (d, 1H, $J = 6.3$ Hz), 4.782 (d, 1H, $J =$ 10.8 Hz), 6.116 (d, 1H, $J = 8.8$ Hz), 7.426−7.309 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.4, −5.3, 18.0, 23.1, 25.5, 52.2, 61.2, 61.4, 73.9, 75.0, 118.5, 128.3, 128.6, 128.6, 137.3, 171.2; IR ($CHCl_3$, cm^{-1}) ν 3427, 1661; MS (ES) *m/z* 335 ($M^{+\bullet}$ − 57, 29), 222 ($M^{+\bullet}$ − 170, 16), 91 (100). Anal. Calcd for $C_{20}H_{32}N_2O_4Si$: C, 61.19; H, 8.22; N, 7.14. Found: C, 61.34; H, 8.02; N, 6.99. From the less polar fraction, **(+)-(2*S*)-[(4R,5*R*)-5-(benzyloxy)-1,3-oxazinan-4-yl]{[*tert*-butyl(dimethyl)silyl]oxy}acetonitrile, (+)-16b** (24 mg, 15%) was isolated as a pure pale brown oil: $[\alpha]_D = +5.4$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.154 (s, 3H), 0.211 (s, 3H), 0.924 (s, 9H), 3.133 (dd, 1H, $J = 7.4$, 2.1 Hz), 3.598 (br s, 1H), 3.598 (d, 1H, $J = 11.7$ Hz), 4.241 (d, 1H, $J = 11.7$ Hz), 4.265 (d, 1H, $J = 10.4$ Hz), 4.561 (d, 1H, $J = 7.4$ Hz), 4.626 (d, 1H, $J = 11.4$ Hz), 4.662 (d, 1H, $J = 10.2$ Hz), 4.720 (1H, d, $J =$ 11.5 Hz), 7.445−7.307 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, −5.2, 18.1, 25.5, 60.6, 63.0, 67.4, 70.0, 71.5, 79.3, 118.3, 127.9, 128.2, 128.4, 137.5; IR ($CHCl_3$, cm^{-1}) ν 3310; MS (ES) *m/z* 361 ($M^{+\bullet}$ − 1, 1), 305($M^{+\bullet}$ − 57, 20), 192 ($M^{+\bullet}$ − 170, 69), 91 (100). Anal. Calcd for $C_{19}H_{30}N_2O_3Si$: C, 62.95; H, 8.34; N, 7.73. Found: C, 63.03; H, 8.37; N, 7.54.

General Procedure for Preparation of Mesylates 11 and 17. Triethylamine (1.12 mmol), DMAP (cat.), and methanesulfonyl chloride (0.56 mmol) were sequentially added dropwise via syringe to a solution of the corresponding alcohol, **10** or **15** (0.28 mmol), in anhydrous DCM (4.4 mL) at rt under argon atmosphere. The resulting mixture was stirred until disappearance of starting material (TLC). The crude mixture was diluted with DCM (60 mL) and washed successively with an aq saturated solution of NH_4Cl (1 × 15 mL) and brine (1 × 15 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure mesylates **11** or **17**, respectively.

(−)-(2*R*,3*R*,4*S*)-3-[(*tert*-Butoxycarbonyl)amino]-4-{[*tert*-butyl-(dimethyl)silyl]oxy}-4-cyano-2-methoxybutyl Methanesulfonate, (−)-11a. From 75 mg (0.20 mmol) of (−)-**10a**, compound (−)-**11a** (76 mg, 84%) was obtained as a pure pale brown oil after purification by flash chromatography (hexanes/ethyl acetate 4:1): $[\alpha]_D = -3.7$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.188 (s, 3H), 0.242 (s, 3H), 0.934 (s, 9H), 1.449 (s, 9H), 3.047 (s, 3H), 3.569 (s, 3H), 3.910 (1H, dd, $J = 8.3$, 6.1 Hz), 4.018 (t, 1H, $J =$ 6.0 Hz), 4.146 (dd, 1H, $J = 10.4$, 6.2 Hz), 4.277 (dd, 1H, $J =$ 10.4, 5.9 Hz), 4.618 (d, 1H, $J = 5.9$ Hz), 5.133 (d, 1H, $J = 9.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.4, −5.3, 17.9, 25.4, 28.2, 37.5, 53.2, 59.7, 61.6, 67.2, 74.5, 80.71, 118.2, 155.2; IR ($CHCl_3$, cm^{-1}) ν 1712; MS (ES) *m/z* 379 ($M^{+\bullet}$ − 73, 32), 339 ($M^{+\bullet}$ − 57 − 56, 100), 295 ($M^{+\bullet}$ − 57 − 56 − 44, 14), 282 ($M^{+\bullet}$ − 170, 22), 243 ($M^{+\bullet}$ − 153 − 56, 50), 226 ($M^{+\bullet}$ − 170 − 56, 22), 182 ($M^{+\bullet}$ − 170 − 56 − 44, 81), 153 (42), 86 ($M^{+\bullet}$ − 170 − 56 − 44 − 96, 62), 75 (19), 73 (29), 57 (57). Anal. Calcd for $C_{18}H_{36}N_2O_7SSi$: C, 47.76; H, 8.02; N, 6.19. Found: C, 47.87; H, 8.19; N, 5.99.

General Procedure for Preparation of Piperidines 12. Starting from methane sulfonates **11**, piperidines **12** were obtained adopting the same protocol indicated above for the synthesis of amino β-lactams **4**.

(−)-*tert*-Butyl (3*R*,4*R*,5*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-methoxypiperidin-4-yl-carbamate, (−)-12a. From 60 mg (0.13 mmol) of mesylate (−)-**11a**, and after purification by flash chromatography on silica gel, eluting first with ethyl acetate and finally with methanol, compound (−)-**12a** (28 mg, 59%) was

obtained as a pure white solid: mp 130−132 °C (methanol/ethyl acetate); $[\alpha]_D = -8.5$ (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.052 (s, 3H), 0.070 (s, 3H), 0.872 (s, 9H), 1.447 (9H, s), 2.408 (1H, t, $J = 11.5$ Hz), 2.450 (t, 1H, $J = 11.2$ Hz), 3.085 (dd, 1H, $J = 12.4$, 5.0 Hz), 3.178 (t, 1H, $J = 8.9$ Hz), 3.289 (m, 2H), 3.412 (s, 3H), 3.612 (m, 1H), 4.538 (br d, 1H, $J = 7.8$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ −4.8, −4.6, 17.9, 25.7, 28.4, 49.0, 52.7, 57.9, 61.2, 70.8, 79.1, 155.6; IR ($CHCl_3$, cm^{-1}) ν 1695; MS (ES) *m/z* 287 ($M^{+\bullet}$ − 73, 7), 247 ($M^{+\bullet}$ − 57 − 56, 100), 201 (36), 186 (28) 116 (7), 101 (6), 73 (15), 57 (18). Anal. Calcd for $C_{17}H_{36}N_2O_4Si$: C, 56.63; H, 10.06; N, 7.77. Found: C, 56.79; H, 9.91; N, 7.59.

General Procedure for Preparation of Methyl Esters 19. A solution of the appropriate O-silylated cyanohydrin **3** (0.31 mmol) in methanol (7.5 mL) was added to sodium methoxide (0.31 mmol) at rt under argon atmosphere. The mixture was stirred at the same temperature for 75 min. Brine (15 mL) was added to the crude, and methanol was evaporated under reduced pressure. The resulting mixture was extracted with ethyl acetate (5 × 30 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to afford compound **19**, which could be used in the next step without ulterior purification.

(+)-Methyl (2*R*,3*R*,4*S*)-2-(Benzyloxy)-4-{[*tert*-butyl(dimethyl)-silyl]oxy}-4-cyano-3-[(4-methoxyphenyl)amino]butanoate, (+)-19b. From 142 mg (0.31 mmol) of the O-silylated cyanohydrin s*yn*-(+)-**3c**, pure compound (+)-**19b** (148 mg, 98%) was obtained as a pale brown oil: $[\alpha]_D = +2.2$ (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 0.095 (s, 3H), 0.179 (s, 3H), 0.883 (s, 9H), 3.618 (s, 3H), 3.740 (s, 3H), 4.044 (dd, 1H, $J = 6.3$, 2.2 Hz), 4.538 (d, 1H, $J = 2.2$ Hz), 4.606 (d, 1H, $J = 11.0$ Hz), 4.661 (d, 1H, $J = 6.4$ Hz), 4.853 (d, 1H, $J = 10.7$ Hz), 6.609 (**AA′**BB′, 2H), 6.750 (AA′**BB′**, 2H), 7.505−7.336 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.4, −5.3, 18.0, 25.5, 52.2, 55.7, 59.9, 62.3, 73.6, 74.9, 114.8, 115.5, 118.3, 128.2, 128.4, 128.9, 136.5, 139.7, 153.0, 170.9; IR ($CHCl_3$, cm^{-1}) ν 3369, 1751; MS (ES) *m/z* 484 ($M^{+\bullet}$, 3), 314 ($M^{+\bullet}$ − 170, 60), 91 (100). Anal. Calcd for $C_{26}H_{36}N_2O_5Si$: C, 64.43; H, 7.49; N, 5.78. Found: C, 64.15; H, 7.57; N, 5.69.

General Procedure for Preparation of Piperidin-2-ones 20. Method A. A solution of the appropriate amino β-lactam **4** (0.68 mmol) in methanol (16.2 mL) was added to sodium methoxide (0.82 mmol) at rt under argon atmosphere. The mixture was stirred at reflux for 8 h. Brine (30 mL) was added to the crude, and methanol was evaporated under reduced pressure. The resulting mixture was extracted with ethyl acetate (5 × 60 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue on silica gel using hexanes/ethyl acetate mixtures afforded the corresponding compound **20**. **Method B.** Starting from the appropriate methyl ester **19**, piperidine-2-ones **20** were obtained adopting the same protocol indicated above for the synthesis of amino β-lactams **4**.

(+)-(3*R*,4*R*,5*R*)-3-(Benzyloxy)-5-{[*tert*-butyl(dimethyl)silyl]-oxy}-4-[(4-methoxyphenyl)amino]piperidin-2-one, (+)-20b. Method B. From 65 mg (0.13 mmol) of the methyl ester (+)-**19b** and after flash chromatography (hexanes/ethyl acetate 1:1), pure compound (+)-**20b** (34 mg, 56%) was obtained as a pale brown oil: $[\alpha]_D = +5.0$ (*c* 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ −0.020 (s, 3H), 0.053 (s, 3H), 0.845 (s, 9H), 3.225−3.363 (m, 2H), 3.542 (t, 1H, $J = 7.6$ Hz), 3.740 (d, 1H, $J = 7.6$ Hz), 3.760 (s, 3H), 3.750−3.840 (m, 1H), 4.705 (d, 1H, $J = 11.7$ Hz), 4.938 (d, 1H, $J = 11.7$ Hz), 5.984 (br s, 1H), 6.628 (**AA′**BB′, 2H), 6.744 (AA′**BB′**, 2H), 7.342 (br s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −4.8, −4.7, 17.9, 25.7, 45.7, 55.7, 62.1, 71.0, 73.0, 77.6, 114.6, 115.4, 128.0, 128.4, 128.6, 137.6, 141.7, 152.6, 171.5; IR ($CHCl_3$, cm^{-1}) ν 3402, 1684; MS (ES) *m/z* 456 ($M^{+\bullet}$, 22), 399 ($M^{+\bullet}$ − 57, 6), 365 ($M^{+\bullet}$ − 91, 33), 308 (6), 292 (100), 91 (48). Anal. Calcd for $C_{25}H_{36}N_2O_4Si$: C, 65.75; H, 7.95; N, 6.13. Found: C, 65.89; H, 7.67; N, 5.98.

General Procedure for Synthesis of Piperidines 22. A solution of the appropriate piperidine-2-one **20** (0.26 mmol) in anhydrous diethyl ether (1.25 mL) was slowly added via syringe to a suspension of LAH (0.78 mmol) in anhydrous diethyl ether at 0 °C under argon atmosphere. The reaction mixture was allowed to warm at room temperature and stirred at rt for 30 min. The crude was cooled at 0 °C, and a saturated aqueous solution of $NaHCO_3$ was added (5 mL). The resulting mixture was extracted with ethyl acetate (5 × 17 mL). The organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was diluted with anhydrous acetonitrile (2.2 mL), and then methyl bromoacetate (0.39 mmol), potassium carbonate (0.78 mmol), and a catalytic amount of lithium iodide were sequentially added at rt under argon atmosphere. The reaction mixture was stirred at rt for 3 h. Then, water was added (1.4 mL), and the resulting mixture was extracted with DCM (5 × 7 mL). The organic layer was dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. Flash chromatography on silica gel of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds **22**.

(+)-Methyl {(3*S*,4*R*,5*R*)-3-(Benzyloxy)-5-{[*tert*-butyl(dimeth-yl)silyl]oxy}-4-[(4-methoxyphenyl)amino]piperidin-1-yl}-acetate, (+)-22b. From 118 mg (0.26 mmol) of the piperidine-2-one (+)-**20b** and, after flash chromatography (hexanes/ethyl acetate 3:1), pure piperidine (+)-**22b** (67 mg, 50%) was obtained as a pale brown oil: $[\alpha]_D = +25.5$ (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ −0.070 (s, 3H), 0.032 (s, 3H), 0.803 (s, 9H), 2.291 (t, 1H, $J = 10.4$ Hz), 2.291 (t, 1H, $J = 10.4$ Hz), 2.969 (ddd, 1H, $J = 10.7$, 4.8, 1.8 Hz), 3.068 (t, 1H, $J = 9.4$ Hz), 3.177 (ddd, 1H, $J = 10.6$, 4.7, 1.7 Hz), 3.313 (br s, 2H), 3.417 (td, 1H, $J = 9.9$, 4.7 Hz), 3.598 (td, 1H, $J = 9.5$, 4.6 Hz), 3.744 (s, 6H), 4.549 (AB, 2H, $J = 11.8$ Hz), 6.716 (br s, 4H), 7.332−7.178 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −4.8, −4.6, 17.9, 25.7, 51.7, 55.8, 56.4, 58.5, 59.6, 65.1, 72.2, 72.4, 78.2, 114.4, 115.0, 127.6, 127.9, 128.3, 138.3, 143.7, 151.9, 170.6; IR ($CHCl_3$, cm^{-1}) ν 1746; MS (ES) *m/z* 514 (M^{+}, 80), 499 ($M^{+\bullet}$ − 15, 2), 457 ($M^{+\bullet}$ − 57, 10), 455 ($M^{+\bullet}$ − 59, 10), 279 ($M^{+\bullet}$ − 235, 100), 255 ($M^{+\bullet}$ − 259, 100), 222 ($M^{+\bullet}$ − 235 − 57, 10), 164 ($M^{+\bullet}$ − 259 − 91, 68), 91 (52), 73 (22). Anal. Calcd for $C_{28}H_{42}N_2O_5Si$: C, 65.34; H, 8.22; N, 5.44. Found: C, 65.24; H, 8.38; N, 5.60.

General Procedure for Synthesis of Piperidines 18. Method A. Sodium borohydride (1.54 mmol) was added in portions to a solution of the appropriate mesylate **17** (0.22 mmol) and nickel(II) chloride hexahydrate (0.22 mmol) in methanol (1.7 mL) at 0 °C under argon. The reaction mixture was allowed to warm to room temperature, stirred at rt for 45 min, and then methanol was evaporated under vacuum. The residue was diluted with ethyl acetate (50 mL), and an aq saturated solution of $NaHCO_3$ was added (25 mL). The resulting mixture was filtered, and the solution was extracted with ethyl acetate (4 × 25 mL). The organic layer was dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. The residue was diluted with anhydrous acetonitrile (2.4 mL), and methyl bromoacetate (0.33 mmol), potassium carbonate (0.66 mmol), and a catalytic amount of lithium iodide were sequentially added at rt under argon atmosphere. The reaction mixture was stirred at 60 °C for 2 h, and it was allowed to cool to rt. Water was then added (1.5 mL), and the resulting crude was extracted with DCM (5 × 10 mL). The organic layer was dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the corresponding analytically pure piperidine **18**. **Method B.** Starting from the appropriate piperidine **22**, piperidines **18** were obtained adopting the same protocol indicated above for amides **15**.

(+)-Methyl ((3*S*,4*R*,5*R*)-4-(Acetylamino)-3-(benzyloxy)-5-{[*tert*-butyl(dimethyl)silyl]oxy}piperidin-1-yl)acetate, (+)-18b. Method A. From 88 mg (0.19 mmol) of mesylate (−)-**17b** and, after flash chromatography (hexanes/ethyl acetate 1:1), pure piperidine (+)-**18b** (34 mg, 40%) was obtained. **Method B.** From 52 mg (0.10 mmol) of piperidine (+)-**22b** and, after flash chromatography (hexanes/ethyl acetate 1:1), pure piperidine (+)-**18b** (25 mg, 55%) was obtained as a pale brown oil: $[\alpha]_D = +6.9$ (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.013 (s, 3H), 0.024 (s,

3H), 0.846 (s, 9H), 1.937 (s, 3H), 2.267 (t, 1H, $J = 10.2$ Hz), 2.267 (t, 1H, $J = 10.2$ Hz), 2.931 (dd, 1H, $J = 10.8$, 4.7 Hz), 3.162 (br dd, 1H, $J = 8.4$, 2.1 Hz), 3.297 (br s, 2H), 3.597 (m, 2H), 3.732 (s, 3H), 3.732 (m, 1H), 4.438 (d, 1H, $J = 12.1$ Hz), 4.652 (d, 1H, $J = 12.1$ Hz), 5.020 (br d, 1H, $J = 7.5$ Hz), 7.344−7.282 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −4.8, −4.5, 17.8, 23.8, 25.6, 51.6, 56.1, 58.4, 59.4, 69.6, 71.6, 75.1, 127.7, 127.9, 128.3, 138.4, 169.9, 170.6; IR ($CHCl_3$, cm^{-1}) ν 1743, 1660; MS (ES) *m/z* 435 ($M^{+\bullet}$ − 15, 7), 393 ($M^{+\bullet}$ − 57, 86), 391 ($M^{+\bullet}$ − 59, 52), 359 ($M^{+\bullet}$ − 91, 14), 285 ($M^{+\bullet}$ − 57 − 108, 20), 283 ($M^{+\bullet}$ − 59 − 108, 17), 258 (15), 209 (76), 116 (35), 91(100). Anal. Calcd for $C_{23}H_{36}N_2O_5Si$: C, 61.30; H, 8.50; N, 6.22. Found: C, 61.49; H, 8.33; N, 5.98.

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Supporting Information Available: Compound characterization data and experimental procedures for compounds **2a**,**b**, **3b**−**e**, *anti*-(+)-**4a**, **4b**−**e**, *anti*-(+)-**5a**, **5b**,**c**, **6b**−**d**, (+)-**7a**, (−)-**7b**, (+)-**8**, (+)-**9**, (−)-**10b**, (−)-**11b**, (−)-**12b**, (−)-**15a**, (−)-**16a**, **17**, (−)-**18a**, (+)-**19a**, (−)-**20a**, **21**, and (−)-**22a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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