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Tandem Nucleophilic Addition/Cyclization Reaction in the Synthesis of Ketimine-Type Iminosugars

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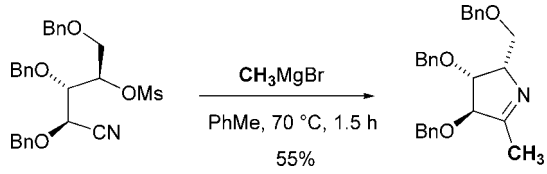

The biological activity of unsaturated iminosugars has not yet been extensively studied because of a lack of general synthetic methods. A practical synthesis of these cyclic ketimine sugars was developed, which was based on a tandem addition−cyclization reaction of a Grignard reagent to a ω-methanesulfonylglyconitrile.

Iminosugars are naturally occurring sugar mimics displaying well-documented glycosidase[1] or glycosyltransferase[2] inhibition potencies. Recent years have seen an increasing interest in natural or synthetic iminosugars as biological tools or potential therapeutics in the treatment of various infections,[3] cancer,[4] and certain genetic disorders.[5] Iminosugars are usually classified into five structural classes: the polyhydroxylated pyrrolidines, pyrrolizidines, piperidines, indolizidines, and nortropanes. Recently, two polyhydroxylated alkaloids featuring an unprecedented ketimine moiety have been isolated from the branches of *Broussonetia kazinoki*.[6] Broussonetines U and U1 (Figure 1) might belong to the sixth class of iminosugars, i.e., the polyhydroxypyrrolines.[7] Broussonetines are 18-carbon chain alkaloids featuring a 13-carbon substituent at the 2-alkyl position of the 5-membered ring. Because broussonetines appear to be biosynthesized through intermediates related to sphingosines, which play important roles in biological processes, the synthesis and biological evaluation of these alkaloids and related analogues is of great interest.[8] There has been enormous effort expended in the search for synthetic methods toward the standard iminosugars. Nevertheless, the development of a general approach to polyhydroxyketimines remains challenging. A first example of such an approach has been described recently,[9] which involved an *exo*-imino- to *endo*-iminocyclitol rearrangement as the key step, occurring in 25–42% yield. However, the introduction of the C-2 substituent appeared at an early stage of the synthetic sequence, limiting the versatility required for the synthesis of a library of analogues. Herein, we describe a new synthesis of novel cyclic ketimines sugars **1a**−**h**

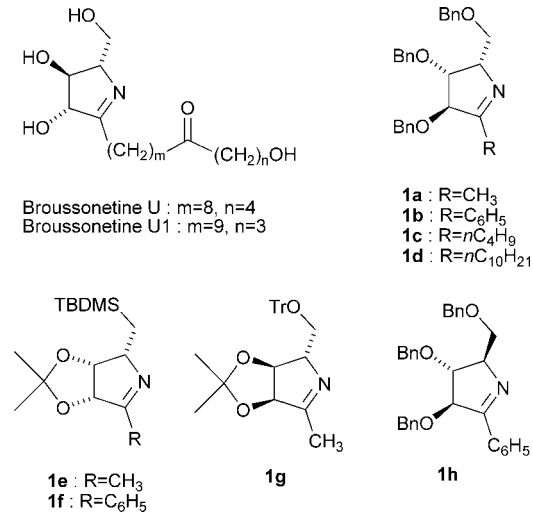

FIGURE 1. Structures of unsaturated iminosugars.

(1) *Iminosugars as glycosidase inhibitors: Nojirimycin and beyond*; Stütz, A. E., Ed.; Wiley-VCH: Weinheim, Germany, 1999.

(2) (a) Gautier-Lefebvre, I.; Behr, J.-B.; Guillerm, G.; Muzard, M. *Eur. J. Med. Chem.* **2005**, *40*, 1255. (b) Djebaili, M.; Behr, J.-B. J. *Enzyme Inhib. Med. Chem.* **2005**, *20*, 123. (c) Compain, P.; Martin, O. R. *Curr. Top. Med. Chem.* **2003**, *3*, 525. (d) Compain, P.; Martin, O. R. *Bioorg. Med. Chem.* **2001**, *9*, 3077.

(3) (a) Bosco, M.; Bisseret, P.; Constant, P.; Eustache, J. *Tetrahedron Lett.* **2007**, *48*, 153. (b) Steet, R.; Chung, S.; Lee, W.-S.; Pine, C. W.; Do, H.; Kornfeld, S. *Biochem. Pharmacol.* **2007**, *73*, 1376. (c) Liautard, V.; Christina, A. E.; Desvergnes, V.; Martin, O. R. *J. Org. Chem.* **2006**, *71*, 7337. (d) Behr, J.-B.; Gainvors-Claisse, A.; Belarbi, A. *Nat. Prod. Res.* **2006**, *20*, 1308. (e) Robina, I.; Moreno-Vargas, A. J.; Carmona, A. T.; Vogel, P. *Curr. Drug Metab.* **2004**, *5*, 329. (f) Behr, J.-B. *Curr. Med. Chem. (Anti Infective Agents)* **2003**, *2*, 173.

(4) (a) Moreno-Vargas, A. J.; Carmona, A. T.; Mora, F.; Vogel, P.; Robina, I. *Chem. Commun.* **2005**, 4949. (b) Fiaux, H.; Popowycz, F.; Favre, S.; Schütz, C.; Vogel, P.; Gerber-Lemaire, S.; Juillerat-Jeanneret, L. *J. Med. Chem.* **2005**, *48*, 4237. (c) Nishimura, Y. *Curr. Top. Med. Chem.* **2003**, *3*, 575. (d) Barchi, J. J. *Curr. Pharm. Des.* **2000**, *6*, 485.

(5) (a) Yu, Z.; Sawkar, A. R.; Whalen, L. J.; Wong, C.-H.; Kelly, J. W. *J. Med. Chem.* **2007**, *50*, 94. (b) Wennekes, T.; van den Berg, R. J.; Donker, W.; van der Marel, G. A.; Strijland, A.; Aerts, J. M.; Overkleeft, H. S. *J. Org. Chem.* **2007**, *72*, 1088. (c) Faugeroux, V.; Génisson, Y.; Andrieu-Abadie, N.; Colié, S.; Levade, T.; Baltas, M. *Org. Biomol. Chem.* **2006**, *4*, 4437.

(6) (a) Tsukamoto, D.; Shibano, M.; Okamoto, R.; Kusano, G. *Chem. Pharm. Bull.* **2001**, *49*, 492. (b) Tsukamoto, D.; Shibano, M.; Kusano, G. *Chem. Pharm. Bull.* **2001**, *49*, 1487.

(7) Nectrisine, the cyclic imine nominally derived from dehydration of 4-amino-4-deoxy-D-arabinose, is an example of naturally occurring aldimine-type 5-membered iminosugar and might be classified into the pyrroline-derived iminosugars as well. In opposition to ketimines, numerous syntheses of nectrisine and other cyclic sugar aldimines have appeared in the literature, which use, for instance, a chlorination/elimination strategy from the corresponding pyrrolidine. For an example, see: Chapman, T. M.; Courtney, S.; Hay, P.; Davis, B. G. *Chem. Eur. J.* **2003**, *9*, 3397.

(8) Shibano, M.; Tsukamoto, D.; Kusano, G. *Heterocycles* **2002**, *57*, 1539.

(9) Only one example of a general synthesis of ketimine-type iminosugars has been reported so far; see: Moriarty, R. M.; Mitan, C. I.; Branza-Nichita, N.; Phares, K. R.; Parrish, D. *Org. Lett.* **2006**, *8*, 3465. Some other unsaturated iminosugars have been obtained by specific transformations; see: (a) Izquierdo, I.; Plaza, M. T.; Rodríguez, M.; Franco, F.; Martos, A. *Tetrahedron* **2005**, *61*, 11697. (b) Davis, B. G.; Maughan, M. A.; Chapman, T. M.; Villard, R.; Courtney, S. *Org. Lett.* **2002**, *4*, 103. (c) Yokoyama, M.; Ikenogami, T.; Togo, H. J. *Chem. Soc., Perkin Trans. 1* **2000**, 2067. (d) Schuster, M.; Blechert, S. *Tetrahedron: Asymmetry* **1999**, *10*, 3139. (e) Bouix, C.; Bisseret, P.; Eustache, J. *Tetrahedron Lett.* **1998**, *39*, 825. (f) Takayama, S.; Martin, R.; Wu, J.; Laslo, K.; Siuzdak, G.; Wong, C.-H. J. *Am. Chem. Soc.* **1997**, *119*, 8146.

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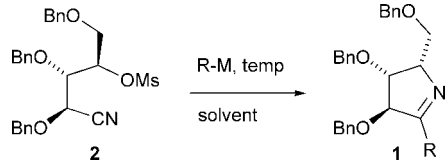
TABLE 1. Screening of Various Conditions for the Addition of Organometallics to Nitrile Mesyl Ester 2



entry	[R−M][a]	*T* (°C)	solvent	additive	time (h)	conversion[b] (%)	yield[c] (%)
1	CH_3−MgBr	20	THF		24	<5	
2	CH_3−MgBr	20	THF	CuI[d]	24	<5	
3	CH_3−MgBr	20	Et_2O		24	<5	
4	CH_3−MgBr	20	Et_2O	$LiClO_4$[a]	24	<5	
5	CH_3−MgBr	20	PhMe		24	30	
6	CH_3−MgBr	20	PhMe	$LiClO_4$[a]	24	60	**1a** (10)
7	CH_3−MgBr	70	PhMe		1.5	100	**1a** (55)
8	CH_3−MgBr	70	PhMe	THF[e]	1.5	35	
9	CH_3−Li	70	PhMe		1.5	100	**1a** (26)
10	C_6H_5−MgBr	70	PhMe		1.5	100	**1b** (61)
11	nC_4H_9−MgBr	70	PhMe		1.5	100	**1c** (56)
12	$nC_{10}H_{21}$−MgBr	70	PhMe		1.5	100	**1d** (38)

[a] 1.5 equiv was added. [b] The amount of remaining starting material was determined by ^{1}H NMR analysis of the crude reaction mixtures. [c] Yields refer to isolated, purified (SiO_2) product. [d] 10 mol % of catalyst was used. [e] A 3 M solution of CH_3MgBr in THF was used as the reagent, giving rise to a reaction mixture that contained 5% THF in toluene as the solvent.

which is based on the tandem addition/cyclization reaction of Grignard reagents to easily available ω-methanesulfonylglyconononitriles.

Among the various syntheses of cyclic ketimines,[10] the reaction of ω-halonitriles with organometallic reagents allows a rapid access to simple C-2-substituted pyrrolines and tetrahydropyridines.[11] Nevertheless, this transformation has not found widespread applications since unwanted α-deprotonation competes with nucleophilic addition to the nitrile functionality,[12] leading to non-negligible amounts of side products. Nevertheless, we wished to explore the application of this reaction to polyhydroxycyano compounds, such as glyconononitriles, in an attempt to prepare the target unsaturated iminosugars.

The 5- or 6-*O*-methanesulfonylglyconononitriles are readily available building blocks, which are obtained from suitably protected carbohydrates by a two-step sequence involving the reaction of the free hemiacetal function with hydroxylamine followed by a dehydration/mesylation procedure with an excess of methanesulfonyl chloride. A series of such activated glyconononitriles has been recently exploited for the synthesis of spirocyclopropyliminosugars.[13] In this work, we used 4-*O*-methanesulfonyl-2,3,5-tri-*O*-benzyl-D-arabinononitrile **2**[14] as the model substrate to experiment the feasibility of the method and to establish the most adequate reaction conditions.

In a first set of experiments, **2** was reacted with CH_3MgBr (1.5 equiv from a 3 M ethereal solution) at room temperature in diethyl ether or THF for 24 h (Table 1, entries 1 and 3). No evolution of the reaction could be detected (TLC monitoring) under these conditions, and the starting material was entirely recovered. Efforts to overcome the lack of reactivity observed in these coordinating solvents by increasing the reaction temperature failed. Alternatively, the addition of copper iodide, known to accelerate drastically the addition of Grignard reagents to nitriles,[15] was unsuccessful (entry 2). In a same manner, the use of lithium perchlorate as an activating agent failed (entry 4).[16]

In some cases, nonpolar solvents have been reported to increase the reactivity of organometallics toward nitriles by modulating the solvation of the nucleophile.[17] When the reaction of **2** with methylmagnesium bromide was conducted in toluene at room temperature, TLC monitoring revealed the formation of a more polar product. NMR analysis of the crude mixture after workup (addition of a saturated ammonium chloride solution and extraction with Et_2O) revealed a 30% conversion after 24 h (Table 1, entry 5), and unreacted **2** could be separated after chromatography. As expected, the newly formed compound was the imine **1a**, resulting from a tandem addition/cyclization process (Scheme 1). Basically, the structure of **1a** was assessed by ^{1}H NMR (δ, 2.13, CH_3), ^{13}C NMR (δ, 175.8, C-2; δ, 18.4, CH_3), IR (1646 cm^{-1}, C═N), and HRMS. The configuration at C-5 in **1a** might be the opposite of that in the starting material, since analogous intramolecular displacements have proven of the S_N2 type.[18] This was firmly established by NOE experiments: the cis relationship between H-3 and the exocyclic H-$6_{a,b}$ in the proposed structure **1a** was assessed by a 5.1% nuclear Overhauser effect (Scheme 1). Compound **1a** was stable at −20 °C for weeks and turned brown with little decomposition by standing several days in air at room temperature.

Having established the feasibility of the expected transformation, we sought to improve the reaction efficiency. In toluene, the addition of 1 equiv of $LiClO_4$ clearly accelerates the addition of CH_3MgBr to the nitrile **2** (entry 6). However, in this case, a

(10) (a) Liang, Y.; Dong, D.; Liu, Y.; Wang, Y.; Pan, W.; Choi, Y.; Liu, Q. *Synthesis* **2006**, 3301. (b) Savoia, D.; Alvaro, G.; Di Fabio, R.; Gualandi, A.; Fiorelli, C. *J. Org. Chem.* **2006**, *71*, 9373. (c) Lee, M. J.; Lee, K. Y.; Park, D. Y.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1281. (d) Kondo, T.; Okada, T.; Titsudo, T.-A. *J. Am. Chem. Soc.* **2002**, *124*, 186. (e) Giovannini, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1989**, *54*, 228.

(11) (a) Fry, D. F.; Brown, M.; McDonald, J. C.; Dieter, R. K. *Tetrahedron Lett.* **1996**, *37*, 6227. (b) Gallulo, V.; Diams, L.; Zezza, C. A.; Smith, M. B. *Org. Prep. Proc. Int.* **1989**, *21*, 297. (c) Larchevêque, M.; Debal, A.; Cuvigny, T. *Bull. Soc. Chim. Fr.* **1974**, *n/a*, 1710.

(12) Fleming, F. F.; Wei, Y.; Liu, W.; Zhang, Z. *Org. Lett.* **2007**, *9*, 2733.

(13) Laroche, C.; Behr, J.-B.; Szymoniak, J.; Bertus, P.; Schütz, C.; Vogel, P.; Plantier-Royon, R. *Bioorg. Med. Chem.* **2006**, *14*, 4047.

(14) Buchanan, G. J.; Lumbard, K. W.; Sturgeon, R. J.; Thompson, D. K.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1990**, *n/a*, 699.

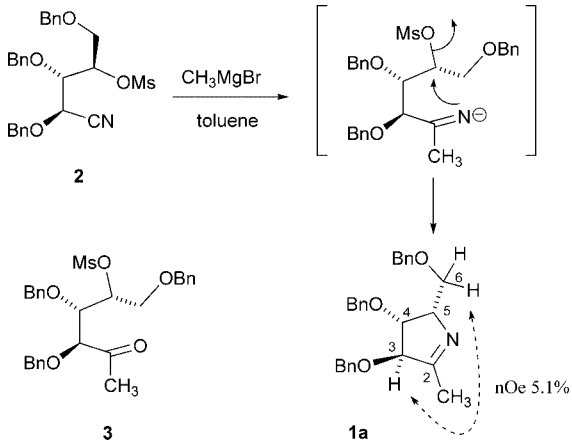
(15) Taber, D. F.; Yu, H. *J. Org. Chem.* **1997**, *62*, 1687.

(16) Chastrette, M.; Amouroux, R.; Subit, M. J. *Organomet. Chem.* **1975**, *99*, C41.

(17) (a) Fry, D. F.; Fowler, C. B.; Dieter, R. K. *Synlett* **1994**, *n/a*, 836. (b) Cannone, P.; Foscolos, G. B.; Lemay, G. *Tetrahedron Lett.* **1980**, *21*, 155.

(18) Laroche, C.; Plantier-Royon, R.; Szymoniak, J.; Bertus, P.; Behr, J.-B. *Synlett* **2006**, *n/a*, 233.

SCHEME 1. Tandem Addition/Cyclization Reaction Strategy for the Synthesis of 1a

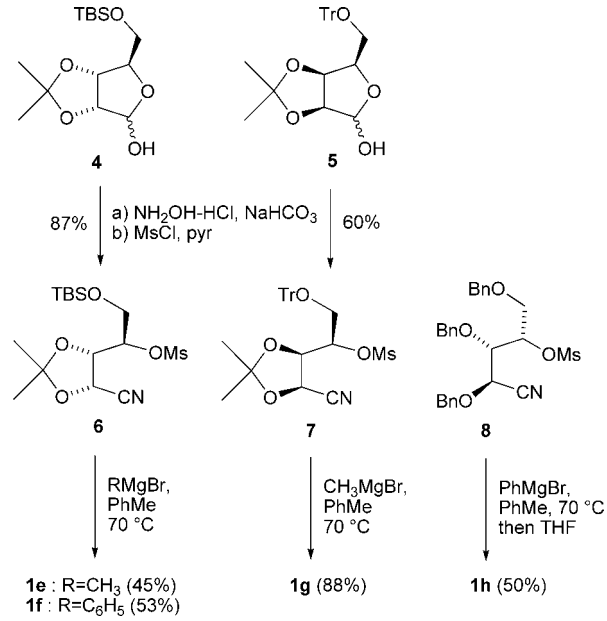


mixture of products was obtained, and **1a** was isolated in only 10% yield. The major product of the reaction was the methanesulfonyl ketone **3**, resulting from hydrolysis of the intermediate ketimine salt during the workup (Scheme 1). We assumed that strong chelation of the ketimine salt with lithium certainly hampers an efficient ring closure. Nevertheless, when the reaction of **2** with CH_3MgBr was performed in toluene at 70 °C without any additive, a complete transformation of the starting material occurred after 1.5 h and imine **1a** could be isolated in 55% yield after silica gel chromatography (entry 7). Interestingly, when a 3 M solution of CH_3MgBr *in THF* was used instead of the ethereal solution (150 μL of the reagent in 3 mL of toluene), only 35% conversion was reached after 1.5 h at 70 °C (entry 8), which underlines the strong solvent sensitivity of this reaction, as outlined above. It was previously reported that organolithium reagents are significantly more reactive toward nitriles than the corresponding Grignard reagents.[11b,19] However, reaction of **2** with CH_3Li (entry 9) in the conditions described by Zezza et al. led to a sluggish reaction mixture and a marked reduction in the yield of target imine **1a**.

The scope of this transformation was investigated next by reacting **2** with PhMgBr, *n*-BuMgBr, and $CH_3(CH_2)_9MgBr$ under the conditions stated above (1.5 equiv of the organometallic species, toluene as the solvent, 1.5 h, 70 °C). The 2-phenyl- or 2-butyl-Δ-pyrrolines **1b** and **1c** were isolated in 61% and 56% yield, respectively (Table 1). A lower yield (38%) was obtained for the decyl-substituted ketimine **1d** as the result of a tedious separation from Würtz-type compound present in the freshly prepared Grignard reagent. In each case, TLC monitoring of the reaction as well as NMR analysis of the crude reaction mixture showed no remaining starting material (100% conversion). However, the presence of byproduct could be observed in most of the cases, and some of the ketimine sugars proved to be moderately stable over silica gel, which account for the 50–60% isolated yields.

To investigate the method further, we expanded the array of sugar substrates (D-*ribo* **6**, D-*lyxo* **7**, and L-*xylo* **8**) focusing on the protecting groups tolerance (*O*-TBS, *O*-Tr, *O*-isopropylidene). Glyconitriles **6** and **7** were prepared from the known precursors **4**[20] and **5**[21] by the standard procedure (formation of

SCHEME 2. Synthesis of Unsaturated Iminosugars 1e−h



the corresponding oxime and dehydration/mesylation with methanesulfonylchloride, Scheme 2), whereas compound **8** was prepared as described in a previous paper.[13] Thus, the protected ribononitrile **6** was successfully reacted with methyl- or phenylmagnesium bromide under the conditions developed above (Scheme 2) to give rise to the desired compounds **1e** and **1f** in 45% and 53% yield, respectively. Interestingly, the trityl lyxose **7** underwent the addition/cyclization procedure with CH_3MgBr with the greatest efficiency to afford **1g** in a very good yield (88%). In stark contrast to the reaction with other substrates, initial experiments with L-xylono-derived nitrile **8** showed that the conditions stated above failed to give the desired ketimine. In this case, it appeared that the cyclization was not spontaneous, giving rise to secondary products during the workup. The addition of $BF_3 \cdot OEt_2$ in the reaction mixture was not sufficient to induce the expected ring formation since only 8% imine could be isolated. These results prompted us to choose another protocol. On the basis of a successful procedure utilizing THF to promote analogous cyclization,[17a] compound **8** was reacted first with PhMgBr in toluene at 70 °C for 1.5 h, THF was then added, and the reaction mixture was allowed to stir overnight at room temperature. This procedure afforded imine **1h** in greatly improved yield (50%).

One of our longer term goals is to develop a series of deprotected unsaturated iminosugars to screen their therapeutic potential. Thus, it is important to explore the viability of the subsequent deprotection step, in particular when *O*-Bn groups were used.

In this study, we experimented with boron trichloride as the debenzylating agent to prevent hydrogenation of the ketimine (Scheme 3). Gratifyingly, the reaction of **1a** with BCl_3 for 6 h at −60 °C afforded the deprotected cyclic imine **9** cleanly,[22] without the imino group being affected. Compound **9** was isolated in its iminium chloride form as a consequence of in

(19) Zezza, C. A.; Smith, M. B.; Ross, B. A.; Arhin, A.; Cronin, P. L. *J. Org. Chem.* **1984**, *49*, 4397.

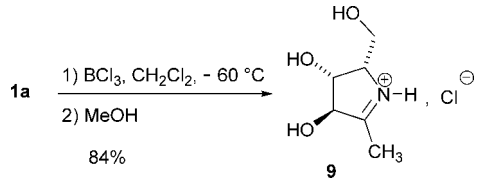
(20) Choi, W. J.; Moon, H. R.; Kim, H. O.; Yoo, B. N.; Lee, J. A.; Shin, D. H.; Jeong, L. S. *J. Org. Chem.* **2004**, *69*, 2634.

(21) Fan, G.-T.; Pan, Y.-S.; Lu, K.-C.; Cheng, Y.-P.; Lin, W.-C.; Lin, S.; Lin, C.-H.; Wong, C.-H.; Fang, J.-M.; Lin, C.-C. *Tetrahedron* **2005**, *61*, 1855.

(22) As determined by the ^1H and ^{13}C NMR spectra of the crude material.

(23) Movassaghi, M.; Chen, B. Despite their low basicity, ketimines are known to form stable iminium salts by reaction with strong acids. *Angew. Chem., Int. Ed.* **2007**, *46*, 565.

SCHEME 3. Debenzylation of Compound 1a



situ reaction with HCl generated during the procedure.[23] The ^{13}C NMR spectrum of **9** showed δ 197.9 ppm for C-2, which is consistent with protonation at nitrogen as observed for 2-methyl-Δ-pyrroline hydrochloride (δ 196.4).[24] Purification of **9** was performed by chromatography on a hydrophobic HP20 support by elution with 1 mM HCl.

In summary, we have successfully developed a simple reaction for the direct formation of unsaturated iminosugars, starting from readily accessible ω-methanesulfonylglyconononitriles. Since only a few preparative methods are available for such compounds, the reaction described herein would provide a new convenient route. Furthermore, variation of the Grignard reagent in the tandem nucleophilic addition/cyclization reaction allows for a range of different side chains to be introduced easily, with the goal of generating libraries of broussonetine analogues.

Experimental Section

General Procedure for the Synthesis of Cyclic Ketimine Sugars. A solution of glyconononitrile (0.40 mmol) in toluene (7 mL) under argon was heated at 70 °C, and the Grignard reagent (1.5 equiv) was added dropwise. The solution was stirred at 70 °C for 1.5 h and cooled to rt. Diethyl ether (20 mL) and a saturated solution of NH_4Cl (20 mL) were successively added, and the resulting solution was extracted. The aqueous phase was extracted with Et_2O (2 × 20 mL), and the organic layers were washed with brine, dried ($MgSO_4$), and evaporated. The crude sample of **1** was purified by silica gel chromatography to yield the pure compound. Data of selected example (3*R*,4*R*,5*S*)-3,4-dibenzyloxy-5-benzyloxymethyl-2-methyl-1-pyrroline **1a**: colorless oil (55%); R_f = 0.50 (PE/EtOAc 6:4); $[\alpha]^{20}_D = -67.1$ (*c* 1.1, $CHCl_3$); IR (film) 3063, 3030, 2920, 2861, 1646, 1496, 1454, 1363 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ 2.13 (3 H, s), 3.80 (2 H, d, J = 4.2 Hz), 4.22–4.35 (2 H, m), 4.59 (1 H, m), 4.55–4.72 (6 H, m), 7.25–7.45 (15 H, m, Ar-*H*); ^{13}C NMR (62.5 MHz; $CDCl_3$) δ 18.4 (CH_3), 68.8 (CH_2), 70.8 (CH), 73.0 (CH_2), 73.1 (CH_2), 73.8 (CH_2), 84.4 (CH), 89.4 (CH), 127.8–128.9 (Ar-CH), 138.3 (Ar-C), 138.4 (Ar-C), 138.9 (Ar-C), 175.8 (C); ESI-HRMS calcd for $C_{27}H_{30}NO_3$ $[M + H]^+$ 416.2226, found 416.2219.

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Supporting Information Available: General details as well as experimental procedures for the preparation of new nitriles **6** and **7** and for the deprotection of **1a**. Characterization data and copies of NMR spectra (^1H, ^{13}C) for compounds **1a**−**h**, **6**, **7**, **9**, 2-methylpyrroline hydrochloride, and 2-methylpyrroline. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) 2-Methyl-Δ-pyrroline hydrochloride was prepared from commercial 2-methyl-Δ-pyrroline (δ 181.0 for C-2) by stirring in 1 M HCl for 0.5 h and evaporation of the solvents. The NMR spectra of both compounds can be found in the Supporting Information.