Stereoselective Nucleophilic Formylation and Cyanation of α-Alkoxy- and α-Aminoaldehydes

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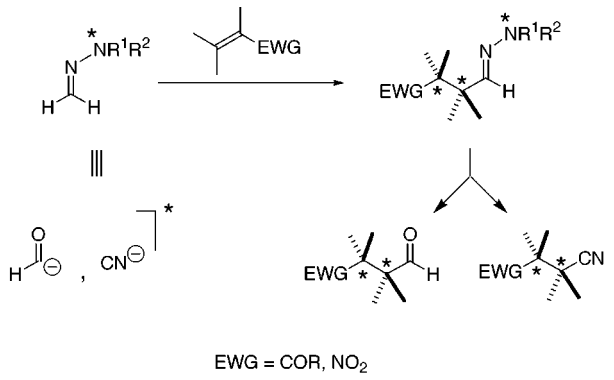
The spontaneous 1,2-addition of formaldehyde *N*,*N*-dialkylhydrazones to carbohydrate-derived α-alkoxyaldehydes takes place under neutral conditions and in the absence of catalysts or promoters to afford the corresponding α-hydroxyhydrazones in good to excellent yields and with highly *anti* diastereoselectivities. Subsequent transformations of the hydrazono group into aldehydes and nitriles following known procedures provide a new entry into the homologation of carbohydrates and the synthesis of cyanohydrins, respectively. Additionally, reaction of methyleneaminopyrrolidine with *N*-Boc-protected α-aminoaldehydes from natural amino acids efficiently affords the corresponding adducts under the same conditions. From these adducts, a variety of biologically interesting α-hydroxy-*β*-aminocarbonyl compounds can be accessed upon manipulation of the hydrazone moiety.

Introduction

The aza-enamine character of *N*,*N*-dialkylhydrazones was experimentally established by Brehme and coworkers from their reactions with strong electrophiles such as unhindered iminium salts,[1] sulfonyl isocyanates,[2] and the Vilsmeier reagent,[3] and was later confirmed in trifluoroacetylation reactions.[4] On the basis of these precedents, we found that the enhanced nucleophilicity of *formaldehyde N*,*N*-diakylhydrazones allows it to perform addition reactions unto weaker electrophiles such as conjugated nitroalkenes[5] and enones.[6] After efficient deprotections into aldehydes and nitriles, the overall process appears to be a short approach to the formylation and cyanation of these substrates (Scheme 1).

In 1993, Katayama et al.[7] reported the intramolecular, Lewis acid-promoted 1,2-addition of the azomethine carbon of *N*-aminoindoline-derived hydrazones to a neighboring carbonyl group in carbocyclization reactions. Unfortunately, it was not possible to develop an intermolecular version of this interesting reaction, presumably due to the poor nucleophilicity of this type of hydrazone. Trusting again in the higher reactivity exhibited by formaldehyde *N*,*N*-dialkylhydrazones, we started studies on the intermolecular 1,2-addition of these reagents to carbonyl compounds.

Scheme 1. Conjugate Addition of Formaldehyde *N*,*N*-Dialkylhydrazones to Michael-Type Electrophiles



EWG = COR, NO_2

During our preliminary investigations that were carried out using simple aldehydes, we found that the desired adducts could be obtained in moderate yields by using $ZnCl_2$ or Et_2AlCl as a promoter.[8] However, it was later discovered that the inductive effect of the α-fluorine atoms in trifluoromethylketones increases the reactivity of the carbonyl group up to the level needed for the spontaneous 1,2-addition of formaldehyde *N*,*N*-dialkylhydrazones[9] (Scheme 2).

Taking into account the interest for the expected products and the availability of the starting materials,

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(1) Brehme, R.; Nikolajewski, H. E. *Tetrahedron* **1976**, *32*, 731.
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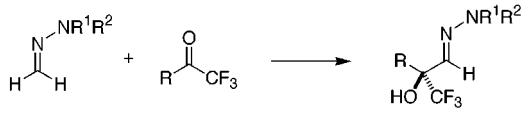
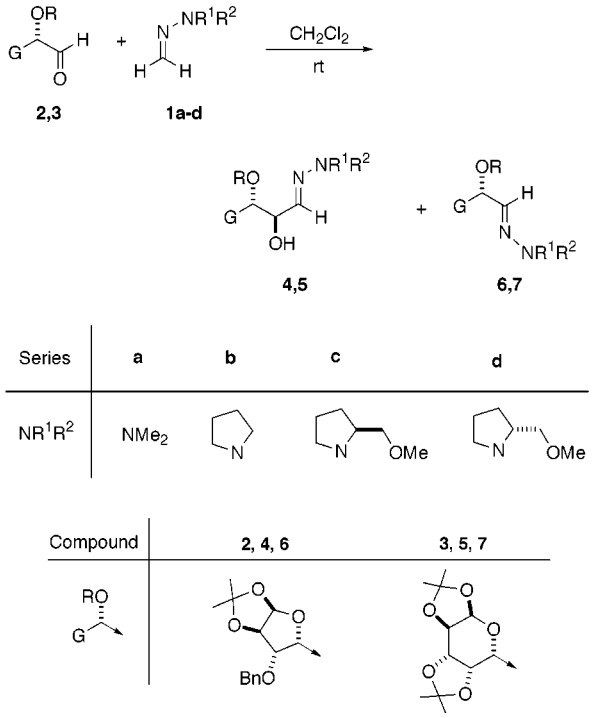
Scheme 2. 1,2-Addition of Formaldehyde *N*,*N*-Dialkylhydrazones to Trifluoromethylketones



Scheme 3. 1,2-Addition of Formaldehyde *N*,*N*-Dialkylhydrazones to Dialdoses 2 and 3



we also decided to investigate the behavior of other α-heterosubstituted aldehydes, such as carbohydrate-derived α-alkoxyaldehydes[10] and *N*-protected α-aminoaldehydes from natural amino acids, in this context. Although the intrinsic enhancement of the carbonyl reactivity by inductive effect in this case is clearly lower than that for the three fluorine atoms, it was expected a priori that these compounds, being more reactive than simple aldehydes on one side and presenting lower steric hindrance than trifluoromethylketones on the other, could also behave as suitable substrates for the *uncatalyzed* addition reaction, which is particularly attractive for the very mild and experimentally simple conditions required. In this paper we report the results that were collected on the basis of this hypothesis.

Results and Discussion

We started by studying the addition of the simplest formaldehyde *N*,*N*-dimethylhydrazone **1a** to readily available α-D-xylodialdofuranose and α-D-galactodialdopyranose derivatives **2** and **3**. Although the expected adducts **4a** and **5a** were obtained under uncatalyzed conditions, the results using this reagent were disappointing due to the competition of a hydrazono transfer reaction, which afforded substantial amounts of hydrazones **6a** and **7a** as undesired byproducts (Scheme 3, Table 1, entries 1 and 5).

Considering the better performance usually observed for pyrrolidine-derived enamines,[11] we also investigated the use of readily available **1b**[9b] as the reagent. Fortunately, the higher nucleophilicity of this reagent was found to furnish faster 1,2-addition reactions, thereby minimizing or suppressing the formation of the undesired hydrazones **6** and **7**. Consequently, this improvement enabled the isolation of the corresponding 1,2-adducts **4b** and **5b** in acceptable yields (Table 1, entries 2 and 6). Interestingly, these compounds were obtained as single diastereomers (de >98%), as determined by ^{1}H and ^{13}C NMR analyses of the reaction crudes. A lower asymmetric induction was observed for the addition of **1b** to 2,3-*O*-isopropylidene-D-glyceraldehyde (**8**). The corresponding adducts **9** were obtained in 70% yield as a 79:21 mixture of (2*S*,3*R*) and (2*R*,3*R*) diastereomers, which could be easily separated by flash chromatography (Scheme 4, Table 1, entry 9).

Double-induction experiments using compounds **2** and **3** and chiral formaldehyde (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP)-derived hydrazone **1c**[5d] and its (*R*) enantiomer **1d**[5e] were also undertaken. The reactions between the mismatched pairs **2**/**1d** and **3**/**1d** afforded products (2*R*)-**4d** and (2*R*)-**5d**, respectively, in lower yields and diastereomeric excesses than those observed for **1b** (entries 4 and 8). Therefore, the extent of the induction effected by these substrates proved to be clearly higher than that effected by the chiral reagent **1d**, and consequently, the (2*S*)-**4d** and (2*S*)-**5d** diastereomers are formed in small percentages only (3 and 11%, respectively). On the other hand, the reactions between the matched pairs **2**/**1c** and **3**/**1c** afforded adducts (2*R*)-**4c** and (2*R*)-**5c** as single diastereomers (entries 3 and 7). These double-induction experiments appear to lack practical interest because the "mismatched" reaction is inefficient for the synthesis of *syn* adducts while the "matched" reaction does not provide any significant improvement of the results obtained using the achiral reagent **1b**. It should be pointed out, however, that adducts **4c**,**d** and **5c**,**d** are interesting intermediates in which the chiral information contained in the original reagent can be used in further stereoselective C−C bond-forming processes as in the addition of organometallic reagents[12] and nucleophilic free radicals[13] to the C=N bond of chiral hydrazones.

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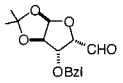
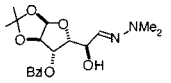
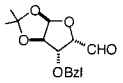
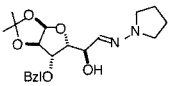
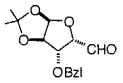
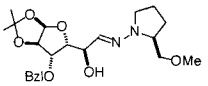
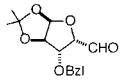
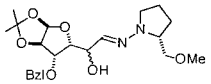
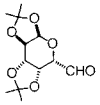
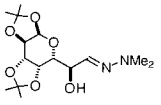
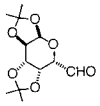
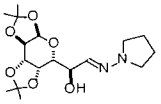
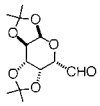
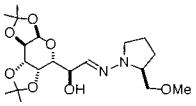
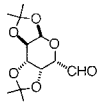
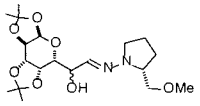
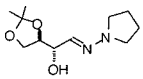
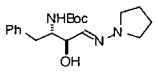
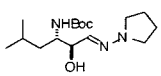
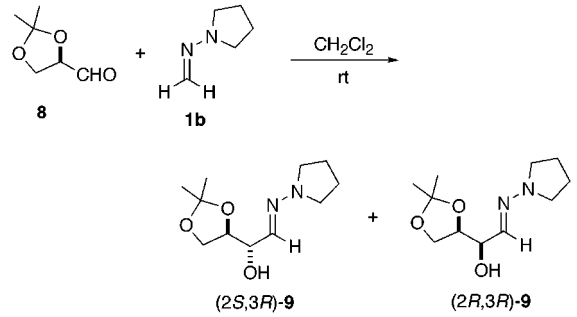
Table 1. Synthesis of α-Hydroxyhydrazones 4, 5, 9, 12, and 13

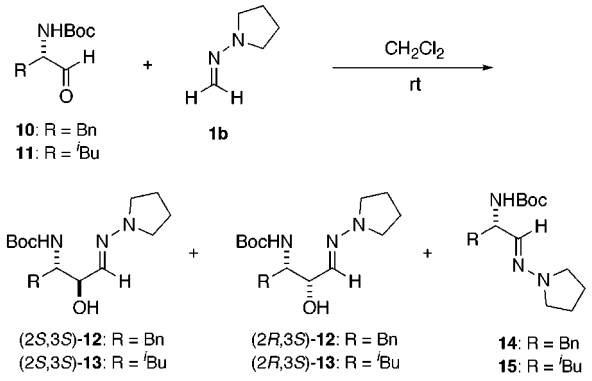
entry	aldehyde	reagent	product[a]	yield (%)[b]	d.r.[c]	by-product (%)
1	 **2**	**1a**	 **4a**	38	>98:2	**6a**, 51
2	 **2**	**1b**	 **4b**	73	>98:2	-
3	 **2**	**1c**	 **4c**	80	>98:2	-
4	 **2**	**1d**	 **4d**	65[d]	97:3	-
5	 **3**	**1a**	 **5a**	45	>98:2	**7a**, 38
6	 **3**	**1b**	 **5b**	68	>98:2	**7b**, 20
7	 **3**	**1c**	 **5c**	60	>98:2	**7c**, 11
8	 **3**	**1d**	 **5d**	42[d]	89:11	-
9	 **8**	**1b**	 (2*S*,3*R*)-**9**	70	79:21	-
10	 **10**	**1b**	 (2*S*,3*S*)-**12**	82	85:15	**14**, 8
11	 **11**	**1b**	 (2*S*,3*S*)-**13**	75	78:22	**15**, 6

[a] Spontaneously formed in dry CH_2Cl_2 at room temperature. [b] Isolated yield. [c] Determined in the reaction crude by ^1H NMR and/or ^{13}C NMR. [d] Inseparable mixture of diastereomers.

Scheme 4. 1,2-Addition of Formaldehyde *N*,*N*-Dialkylhydrazones to Isopropylidene Glyceraldehyde 8



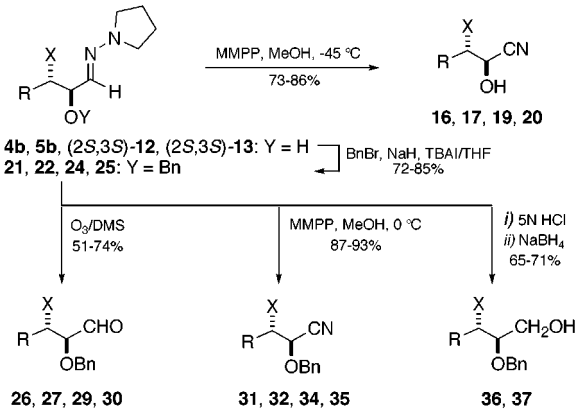
Scheme 5. 1,2-Addition of Formaldehyde *N*,*N*-Dialkylhydrazones to α-Aminoaldehydes



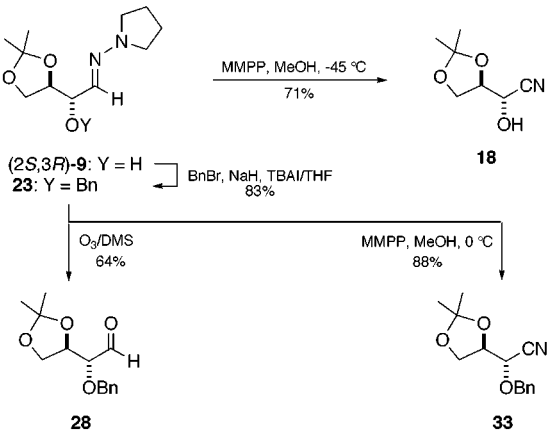
To explore the desirable extension of this methodology to α-aminoaldehydes, the addition of **1b** to *N*-Boc-L-phenylalaninal **10** and *N*-Boc-L-leucinal **11** was also investigated. Considering the lower electronegativity of nitrogen, we chose the *N*-Boc protecting group as the first option in order to procure a reasonable inductive effect by the nitrogenated moiety (higher aldehyde reactivity) while maintaining a relatively low steric hindrance with respect to other common derivatives such as α-dibenzylaminoaldehydes. The 1,2-addition of **1b** to **10** and **11** proceeded smoothly to afford the expected adducts **12** and **13** in good yields and moderate-to-good *anti* selectivities, along with small amounts (8 and 6%, respectively) of hydrazono transfer byproducts **14** and **15** (Scheme 5, Table 1, entries 10 and 11). Both the major (2*S*,3*S*) and minor (2*R*,3*S*) diastereomers of **12** and **13** could be easily separated by flash chromatography to get optically pure compounds. It should be stressed here that *erythro*-*β*-amino-α-hydroxyacids are important components of several biologically active compounds. For instance, (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid (allophenylnorstatine, AHPA, see transformations from **12** below) is a key component of HIV-protease inhibitors KNI-227 and KNI-272,[14] and several of its derivatives are potent and specific inhibitors of leukotriene A_4 hydrolase.[15]

Synthesis of α,*β*-Dihydroxy- and *β*-Amino-α-hydroxycarbonyl Derivatives. A variety of densely functionalized compounds can be synthesized from adducts

Scheme 6. Transformations from Hydrazones 4b, 5b, (2*S*,3*S*)-12, and (2*S*,3*S*)-13



Scheme 7. Transformations from Hydrazone (2*S*,3*R*)-9



4, **5**, **9**, **12**, and **13** upon manipulation of their hydrazono terminus. According to the procedure we previously reported,[16] magnesium monoperoxyphthalate (MMPP) was successfully used as the reagent for the racemization-free oxidative cleavage of the hydrazone moiety of the new α-hydroxyhydrazones to give the corresponding cyanohydrins in high yields (Schemes 6 and 7, Table 2) and in optically pure form. Thus, the *β*-alkoxy-α-hydroxyhydrazones **4b**, **5b**, and (2*S*,3*R*)-**9** were directly transformed into the *β*-alkoxycyanohydrins **16**−**18**, while *β*-amino-α-hydroxyhydrazones (2*S*,3*S*)-**12** and (2*S*,3*S*)-**13** afforded the corresponding *β*-aminocyanohydrins **19** and **20** in a similar way (Schemes 6 and 7, Table 2). In addition to the advantages mentioned above for the choice of *N*-Boc protecting groups in the original aminoaldehydes **10** and **11**, a supplementary benefit for this kind of protection now comes into view: the low-nucleophilic carbamate nitrogen in derivatives **12** and **13** easily survives the oxidative conditions needed for the synthesis of these cyanohydrins.

Taking into account the limited stability of α-hydroxyaldehydes, we recognized that the free 2-hydroxy groups had to be protected before the regeneration of the carbonyl group from the parent of α-hydroxyhydrazones. Hence, compounds **4b**, **5b**, (2*S*,3*R*)-**9**, **12**, and **13** were transformed into their corresponding benzyl ethers **21**−**25** under standard conditions (NaH, BnBr, and TBAI). Subsequent cleavage of these materials by ozonolysis

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Table 2. Synthesis of Free Cyanohydrins 16−20, Benzyloxyhydrazones 21−25, Benzyloxyaldehydes 26−30, and Benzylcyanohydrins 31−35

starting material	cyanohydrins **16−20**	yield (%)	hydrazones **21−25**	yield (%)	aldehydes **26−30**	yield (%)	cyanohydrins **31−35**	yield (%)
4b	**16**	86	**21**	85	**26**	74	**31**	89
5b	**17**	73	**22**	84	**27**	61	**32**	93
(2*S*,3*R*)-**9**	**18**	71	**23**	83	**28**	64	**33**	88
(2*S*,3*S*)-**12**	**19**	82	**24**	72	**29**	51	**34**	93
(2*S*,3*S*)-**13**	**20**	85	**25**	73	**30**	62	**35**	87

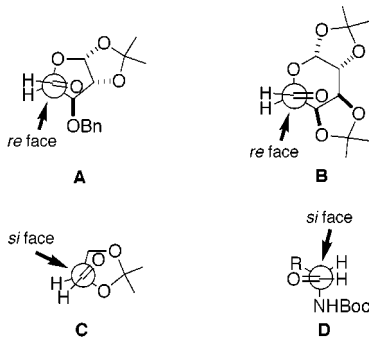

Figure 1. Model for nucleophilic addition to compounds **2**, **3**, **8**, **10**, and **11**.

Scheme 8

afforded α-benzyloxyaldehydes **26**−**30** in moderate-to-good yields. Alternatively, compounds **21**−**25** could also be transformed into the corresponding benzyl-protected cyanohydrins **31**−**35** using again MMPP for the oxidative cleavage of the hydrazone moiety. Finally, dialdose derivatives **21** and **22** were hydrolyzed (5 M HCl/Et_2O) and reduced in situ to afford aldoses **36** and **37** in 71 and 65% yields, respectively (Scheme 6).

Stereochemical Aspects. The absolute configurations of the newly created stereogenic centers of **4b**, **5b**, and (2*S*,3*R*)-**9** and their derivatives were inferred from those of their corresponding α-benzyloxyaldehydes **26**−**28**, respectively. The latter were determined after comparison of their physical and spectroscopical data with those reported in the literature.[17] The (2*S*) configuration of *β*-aminocyanohydrin **19** was deduced after comparison of its physical and spectroscopic characteristics with those of the known (2*R*,3*S*) isomer;[18] those of parent (2*S*,3*S*)-**12** and its derivatives were deduced thereafter, and those of (2*S*,3*S*)-**13** and its derivatives were assigned by analogy. In all cases, *erythro*-configured compounds were isolated as major or sole products; the *anti* selectivities observed for the 1,2-addition to the aldehyde are in agreement with the nonchelated Felkin−Ahn model for nucleophilic addition to chiral carbonyl compounds[19] (Figure 1, structures **A**−**D**). The (2*R*) configuration established for **4b** was also assigned to compounds **4a**, **4c**, and **4d** after transformation of these adducts into the same known compound **38** (Scheme 8).

Conclusions

The moderate enhancement of aldehyde carbonyl reactivity that is effected by an oxygen or nitrogen atom at the α-position suffices for the spontaneous 1,2-addition of formaldehyde *N*,*N*-dialkylhydrazones, behaving as soft and neutral carbon nucleophiles. Using this reaction as the key step, adequate substrates available from natural sources can be transformed into useful compounds in a very simple way. Thus, after regeneration of the carbonyl group, the process starting from carbohydrate-derived α-alkoxyaldehydes represents an alternative to the few existing methods for their stereoselective homologation.[20] Starting from aminoaldehydes, the *β*-amino-α-hydroxycarbonyl compounds that are synthesized constitute valuable, densely functionalized intermediates.

Finally, the high-yielding, racemization-free hydrazone-to-nitrile transformation proved to be useful for the synthesis of diverse, optically pure carbohydrate-derived cyanohydrins and α-hydroxy-*β*-aminonitriles, which complement the synthetic potential of the methodology.

Experimental Section

Melting points were determined using a metal block and are uncorrected. Optical rotations were measured at room temperature. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ with either TMS (^1H, 0.00 ppm; ^{13}C, 0.00 ppm) or $CDCl_3$ (^1H, 7.26 ppm; ^{13}C, 77.00 ppm) as an internal reference. FT-IR spectra were recorded for KBr pellets or films. EI-mass spectra were recorded at 70 eV using an ionizing current of 100 μA, an accelerating voltage of 4 kV, and a resolution of 1000 or 10 000 (10% valley definition). The reactions were monitored by TLC. Purification of the products was carried out by flash chromatography (silica gel, 0.063−0.200 nm). The light petroleum ether (PE) used had a boiling range of 40−65 °C. Tetrahydrofuran (THF) was distilled from sodium benzophenoneketyl immediately prior to use.

Synthesis of Adducts 4, 5, 9, 12, and 13: General Procedure. To a solution of aldehyde **2**, **3**, **8**, **10**, or **11** (1 mmol) in dry CH_2Cl_2 (4 mL) was added the hydrazone **1a**−**d** (2 mmol) under an argon atmosphere. The mixture was stirred at room temperature until TLC or ^1H NMR indicated total consumption of the starting material had occurred. The crude was evaporated, and the residue was purified by flash chromatography. Representative spectral and analytical data for compounds **4b** and **12** follow.

3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-glucohexodialdo-1,4-furanose *N*,*N*-Butylenehydrazone (4b). Flash chromatography (1:1 Et_2O/PE) gave 275 mg (73%) of crystalline **4b**: mp 70−72 °C; $[\alpha]^{25}_D$ −27.6 (*c* 1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.33 (s, 3H), 1.49 (s, 3H), 1.90 (m, 4H), 3.18 (m, 4H), 3.75 (d, 1H, J = 2.9 Hz), 4.05 (dd, 1H, J = 2.9, 8.2 Hz), 4.19

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(d, 1H, J = 2.9 Hz), 4.59−4.61 (m, 1H), 4.62 (d, 1H, J = 3.7 Hz), 4.70 (m, 2H), 5.98 (d, 1H, J = 3.7 Hz), 6.73 (d, 1H, J = 2.9 Hz), 7.28−7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.1, 26.1, 26.7, 51.2, 67.9, 72.4, 82.0, 82.2, 105.2, 111.6, 127.7, 128.3, 133.9, 137.5; IR (film, cm^{-1}) 3647−3088, 1597, 1495; MS (EI) 376 (M^+, 21), 361 (19), 358 (100). Anal. Calcd for $C_{20}H_{28}N_2O_5$: C, 63.80; H, 7.50; N, 7.44. Found: C, 64.02; H, 7.44; N, 7.46.

(2*S*,3*S*)- and (2*R*,3*S*)-3-(*tert*-Butoxycarbonylamino)-2-hydroxy-4-phenylbutyraldehyde *N*,*N*-Butylenehydrazone [(2*S*,3*S*)- and (2*R*,3*S*)-12]. Flash chromatography (1:2 Et_2O/hexane) gave 240 mg (69%) of (2*S*,3*S*)-**12** and 41 mg (12%) of (2*R*,3*S*)-**12** as oils. (2*S*,3*S*)-**12**: $[\alpha]^{29}_D$ −20.3 (*c* 1, CH_2Cl_2); ^{1}H NMR (DMSO-d_6, 70 °C, 300 MHz) δ 1.30 (s, 9H), 1.75−1.84 (m, 4H), 2.66 (dd, 1H, J = 8.6, 13.7 Hz), 2.86 (dd, 1H, J = 5.8, 13.7 Hz), 3.02−3.06 (m, 4H), 3.71−3.80 (m, 1H), 3.96−4.00 (m, 1H), 4.69 (bs, 1H), 6.08 (bs, 1H), 6.40 (d, 1H, J = 5.6 Hz), 7.13−7.25 (m, 5H); ^{13}C NMR ($CDCl_3$, 70 °C, 75 MHz) δ 23.1, 28.2, 38.3, 51.2, 54.4, 70.2, 79.0, 126.2, 128.3, 129.4, 134.0, 138.3, 155.7; IR (film, cm^{-1}) br 3360, 1707, 1499; MS (EI) 347 (M^+, 1), 127 (85), 71 (100); HRMS *m*/*z* calcd for $C_{19}H_{29}N_3O_3$ 347.2209, found 347.2215. (2*R*,3*S*)-**12**: $[\alpha]^{29}_D$ +1.0 (*c* 1, CH_2Cl_2); ^{1}H NMR (DMSO-d_6, 70 °C, 500 MHz) δ 1.26 (s, 9H), 1.75−1.84 (m, 4H), 2.58 (dd, 1H, J = 10.0, 14.0 Hz), 2.99 (dd, 1H, J = 3.9, 13.9 Hz), 3.02−3.06 (m, 4H), 3.67−3.77 (m, 1H), 3.89−3.94 (m, 1H), 4.83 (bs, 1H), 6.25 (bs, 1H), 6.40 (d, 1H, J = 6.1 Hz), 7.13−7.25 (m, 5H); ^{13}C NMR ($CDCl_3$, 70 °C, 75 MHz) δ 22.5, 27.9, 38.7, 50.2, 54.7, 69.2, 77.3, 80.3, 126.5, 128.8, 129.9, 130.3, 137.2, 140.5, 154.9; IR (film, cm^{-1}) br 3370, 1705, 1498; MS (EI) 347 (M^+, 3), 127 (95), 71 (100). Anal. Calcd for $C_{19}H_{29}N_3O_3$: C, 65.68; H, 5.51; N, 12.10. Found: C, 66.01; H, 5.82; N, 12.37.

Synthesis of Cyanohydrins 16−20: General Procedure. To a stirred, cooled (−45 °C) solution of α-hydroxyhydrazone **4b**, **5b**, (2*S*,3*R*)-**9**, (2*S*,3*S*)-**12**, or (2*S*,3*S*)-**13** (1 mmol) in MeOH (3 mL) was added dropwise a precooled (−45 °C) solution of magnesium monoperoxyphthalate hexahydrate (2.5 mmol) in MeOH (10 mL). After completion (10−15 min), CH_2Cl_2 and H_2O were added, and the organic layer was washed with brine (2 × 10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography. Representative spectral and analytical data for compounds **16** and **19** are as follows.

3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*gluco*-hexofuranurononitrile (16). Flash chromatography (1:2 Et_2O/PE) gave 275 mg (90%) of crystalline **16**: mp 78−80 °C; $[\alpha]^{25}_D$ −63.9 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.34 (s, 3H), 1.48 (s, 3H), 3.86 (bs, 1H), 4.32 (d, 1H, J = 3.7 Hz), 4.39 (dd, 1H, J = 3.7, 5.3 Hz), 4.62 (d, 1H, J = 11.3 Hz), 4.65 (d, 1H, J = 3.6 Hz), 4.74 (d, 1H, J = 11.3 Hz), 4.74−4.76 (m, 1H), 6.03 (d, 1H, J = 3.6 Hz), 7.26−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.1, 26.8, 60.3, 72.9, 79.0, 81.7, 82.9, 105.5, 112.5, 118.0, 128.1, 128.5, 128.7, 135.9; IR (film, cm^{-1}) br 3423, 1454; MS (EI) 263 (2), 91 (100). Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.89; H, 6.50; N, 4.51.

(2*S*,3*S*)-3-(*tert*-Butoxycarbonylamino)-2-hydroxy-4-phenylbutyronitrile (19). Flash chromatography (1:2 Et_2O/PE) gave 226 mg (82%) of crystalline **19**: mp 93−94 °C; $[\alpha]^{25}_D$ −30.3 (*c* 1, CH_2Cl_2); ^{1}H NMR (DMSO-d_6, 70 °C, 300 MHz) δ 1.30 (s, 9H), 2.72 (dd, 1H, J = 10.4, 14.0 Hz), 2.94 (dd, 1H, J = 4.0, 14.0 Hz), 3.82−3.91 (m, 1H), 4.54 (dd, 1H, J = 4.3, 6.2 Hz), 6.50 (d, 1H, J = 6.2 Hz), 6.76 (bs, 1H), 7.14−7.34 (m, 5H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 28.1, 35.5, 55.8, 63.8, 81.2, 118.5, 127.0, 128.8, 129.1, 136.4, 156.6; IR (film, cm^{-1}) br 3385, 1696, 1516; MS (CI) 277 (M^+ + 1, 5), 194 (100). Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14. Found: C, 65.04; H, 7.53; N, 9.82.

Synthesis of α-Benzyloxyhydrazones 21−25: General Procedure. To a stirred solution of α-hydroxyhydrazone **4**, **5**, (*S*)-**9**, (*S*)-**12**, or (*S*)-**13** (0.6 mmol) in dry THF (3 mL) were added Bu_4NI (0.06 mmol), BnBr (0.9 mmol), and NaH (0.9 mmol) under an argon atmosphere. The reaction mixture was stirred at room temperature until completion (TLC monitoring) and treated with NaOMe (1 M in MeOH, 0.5 mL) for 15 min. Et_2O (10 mL) and H_2O (10 mL) were added, the aqueous phase was extracted with more Et_2O (5 mL), and the combined organic layer was washed with saturated NH_4Cl (3 × 10 mL) and H_2O (20 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography. Representative spectral and analytical data for compounds **21** and **24** are as follows.

3,5-Di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*gluco*-hexodialdo-1,4-furanose *N*,*N*-Butylenehydrazone (21). Flash chromatography (1:2 Et_2O/hexane) gave 238 mg (85%) of **21** as an oil: $[\alpha]^{25}_D$ −36.5 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.30 (s, 3H), 1.49 (s, 3H), 1.87−1.89 (m, 4H), 3.18−3.27 (m, 4H), 4.12 (d, 1H, J = 2.9 Hz), 4.33 (dd, 1H, J = 2.9, 9.2 Hz), 4.37 (dd, 1H, J = 7.2, 9.2 Hz), 4.40 (d, 1H, J = 11.5 Hz), 4.52 (d, 1H, J = 11.8 Hz), 4.60 (d, 1H, J = 3.8 Hz), 4.63 (d, 1H, J = 11.8 Hz), 4.64 (d, 1H, J = 11.5 Hz), 5.93 (d, 1H, J = 3.8 Hz), 6.38 (d, 1H, J = 3.8 Hz), 7.26−7.28 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.3, 26.1, 26.6, 50.6, 70.0, 72.0, 76.7, 80.6, 81.5, 82.1, 105.0, 111.4, 127.3, 127.3, 127.5, 127.6, 128.1, 128.2, 131.8; IR (film, cm^{-1}) 2874, 1497; MS (EI) 466 (M^+, 2), 108 (100). Anal. Calcd for $C_{27}H_{34}N_2O_5$: C, 69.50; H, 7.34; N, 6.00. Found: C, 69.91; H, 7.84; N, 5.57.

(2*S*,3*S*)-2-Benzyloxy-3-(*tert*-butoxycarbonylamino)-4-phenylbutyraldehyde *N*,*N*-Butylenehydrazone (24). Flash chromatography (1:2 Et_2O/hexane) gave 189 mg (72%) of **24** as an oil: $[\alpha]^{25}_D$ −3.8 (*c* 1.42, CH_2Cl_2); ^{1}H NMR (DMSO-d_6, 75 °C, 300 MHz) δ 1.30 (s, 9H), 1.78−1.85 (m, 4H), 2.69 (dd, 1H, J = 8.7, 13.7 Hz), 2.86 (dd, 1H, J = 5.2, 13.7 Hz), 3.5−3.09 (m, 4H), 3.80−3.91 (m, 2H), 4.37 (d, 1H, J = 12.2 Hz), 4.54 (d, 1H, J = 12.2 Hz), 6.31 (d, 1H, J = 6.9 Hz), 6.32 (bs, 1H), 7.14−7.34 (m, 10H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 22.8, 28.2, 36.5, 50.4, 54.9, 69.3, 77.5, 80.2, 125.8, 127.2, 127.4, 128.0, 130.0, 132.3, 138.8, 139.1, 155.3; IR (film, cm^{-1}) 1696, 1593; MS (EI) 437 (M^+, 1), 217 (65), 91 (100); HRMS *m*/*z* calcd for $C_{26}H_{35}N_3O_3$ 437.2678, found 437.2678.

Synthesis of α-Benzyloxyaldehydes 26−30: General Procedure. Dry ozone was bubbled through a cooled (−78 °C) solution of α-benzyloxyhydrazone **21−25** (0.5 mmol) in CH_2Cl_2 (5 mL) until the appearance of a permanent blue color arose. After addition of Me_2S (0.5 mL), the mixture was allowed to reach room temperature and concentrated, and the residue was purified by flash chromatography. Compounds **26−28** were identified by a comparison of their spectral and analytical data with those previously reported.[14] Representative spectral and analytical data for compound **30** are as follows.

(2*S*,3*S*)-2-Benzyloxy-3-(*tert*-butoxycarbonylamino)-5-methylhexanal (30). Flash chromatography (1:2 Et_2O/hexane) gave 104 mg (62%) of **30** as an oil: $[\alpha]^{25}_D$ −38.6 (*c* 0.6, CH_2Cl_2); ^{1}H NMR (DMSO-d_6, 75 °C, 300 MHz) δ 0.86 (d, 3H, J = 6.7 Hz), 0.89 (d, 3H, J = 6.7 Hz), 1.29−1.35 (m, 2H), 1.39 (s, 9H), 1.56−1.62 (m, 1H), 3.87−3.91 (m, 1H), 4.45 (d, 1H, J = 12.0 Hz), 4.58−4.63 (m, 1H), 4.69 (d, 1H, J = 12.0 Hz), 6.61 (bs, 1H), 7.25−7.35 (m, 5H), 9.58 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 °C, 75 MHz) δ 21.4, 22.6, 23.9, 27.9, 48.7, 71.7, 85.3, 126.2, 127.3, 127.9, 128.4, 137.8, 155.1, 201.6; IR (film, cm^{-1}) 1713; MS (CI) 336 (M^+ + 1, 40), 306 (35), 294 (35), 280 (70); HRMS *m*/*z* calcd for $C_{19}H_{29}NO_4$ 335.2089, found 335.2083.

Synthesis of *O*-Benzylcyanohydrins 31−35: General Procedure. A solution of MMPP·$6H_2O$ (1.25 mmol) in MeOH (4 mL) was added dropwise to a cooled (0 °C) solution of α-benzyloxyhydrazone **21−25** (0.5 mmol) in MeOH (1 mL). After completion (5 min), CH_2Cl_2 (10 mL) and H_2O (10 mL) were added, and the organic layer was washed with brine (2 × 5 mL) and H_2O (5 mL), dried (Na_2SO_4), and concentrated. The resulting residue was purified by flash chromatography. Representative spectral and analytical data for compounds **31** and **34** are as follows.

3,5-Di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*gluco*-hexofuranurononitrile (31). Flash chromatography (1:5 Et_2O/hexane) gave 176 mg (89%) of crystalline **31**: mp 93−95 °C; $[\alpha]^{25}_D$ −61.8 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.38 (s, 3H), 1.56 (s, 3H), 4.12 (d, 1H, J = 1.7 Hz), 4.51 (d, 1H, J = 11.1 Hz), 4.51 (dd, 1H, J = 3.3, 8.3 Hz), 4.57 (d, 1H, J = 11.8 Hz), 4.60 (d, 1H, J = 8.3 Hz), 4.66 (d, 1H, J = 4.8 Hz), 4.71 (d, 1H, J = 11.1 Hz), 4.91 (d, 1H, J = 11.8 Hz), 6.02 (d, 1H, J = 3.7 Hz), 7.33−7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.2,

26.8, 65.9, 72.2, 72.5, 79.1, 80.6, 81.7, 105.3, 112.4, 116.8, 127.4, 128.0, 128.2, 128.5, 128.5, 128.6, 134.5, 136.8; IR (film, cm^{-1}) 2221, 1442; MS (EI) 395 (M^+, 1), 91 (100). Anal. Calcd for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.75; H, 6.58; N, 3.47.

(2*S*,3*S*)-2-Benzyloxy-3-(*tert*-butoxycarbonylamino)-4-phenylbutyronitrile (34). Flash chromatography (1:2 Et_2O/hexane) gave 170 mg (93%) of crystalline **34**: mp 112−114 °C; $[\alpha]^{23}_D$ +4.1 (*c* 1, CH_2Cl_2); ^{1}H NMR (DMSO-d_6, 70 °C, 300 MHz) δ 1,29 (s, 9H), 2.80 (dd, 1H, J = 10.1, 14.1 Hz), 2.92 (dd, 1H, J = 4.3, 14.1 Hz), 4.01−4.10 (m, 1H), 4.54 (d, 1H, J = 4.6 Hz), 4.62 (d, 1H, J = 11.7 Hz), 4.78 (d, 1H, J = 11.7 Hz), 6.88 (bs, 1H), 7.13−7.39 (m, 10H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 27.8, 33.6, 52.6, 70.5, 71.6, 74.7, 117.1, 126.0, 127.3, 127.6, 127.8, 128.1, 128.8, 137.0, 137.6, 155.1; IR (film, cm^{-1}) 3379, 2143, 1690; MS (EI) 375 (M^+, 1), 360 (3), 269 (18), 211 (11), 91 (100). Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 71.77; H, 7.27; N, 7.32.

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Supporting Information Available: Spectral and analytical data for compounds **4a**,**c**,**d**, **5a**−**d**, **6a**, **7a**−**c**, (2*S*,3*R*)-**9**, (2*R*,3*R*)-**9**, (2*S*,3*S*)-**13**, (2*R*,3*S*)-**13**, **14**, **15**, **17**, **18**, **20**, **29**, **32**, **33**, **35**, **36**, and **37**, and the ^{13}C NMR spectra for compounds **4a**,**c**,**d**, **5a**−**d**, **7a**−**c**, (2*S*,3*R*)-**9**, (2*R*,3*R*)-**9**, (2*S*,3*S*)-**12**, (2*R*,3*S*)-**13**, **17**, **22**, **24**, **25**, **29**, **30**, and **35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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