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SYNTHESIS OF AMINO SUGARS THROUGH A HIGHLY DIASTEREOSELECTIVE DIPOLAR CYCLOADDITION. ENANTIOSELECTIVE SYNTHESIS OF THE CARBOHYDRATE SEGMENT OF Sch 38516

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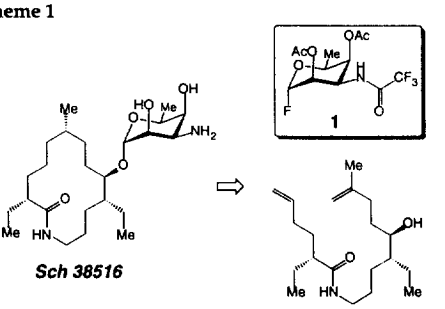
Abstract: A concise and stereoselective route for the synthesis of the carbohydrate moiety of the antifungal agent Sch 38516 is described. The synthesis scheme includes a dipolar cycloaddition, which is rendered diastereoselective through the use of a readily available and easily removable chiral auxiliary. © 1997 Elsevier Science Ltd.

Introduction

Carbohydrates represent one of the most ubiquitous and biologically significant classes of molecules in Nature. A particularly noteworthy constituent of this group of polyhydroxylated natural products are amino sugars; they commonly appear as critical components of medicinally significant entities such as glycoproteins,[1] antibiotics[2] and antigenic determinants.[3] Efficient and stereoselective methods for the synthesis of amino sugars thus remains an important and challenging objective in organic synthesis.

3-Amino-3,6-L-talopyranose monosaccharide **1** is a carbohydrate that makes its debut as part of a natural product in Sch 38516 (Scheme 1).[4] In connection to efforts towards an expeditious and enantioselective total synthesis of this antifungal agent,[5] we required a concise and stereoselective route to optically pure **1**. At the outset, we decided that simply an enantioselective synthesis of the parent carbohydrate would not be sufficient. Instead, a synthesis route towards **1**, suitable for effective material throughput on a large scale was needed.

Scheme 1



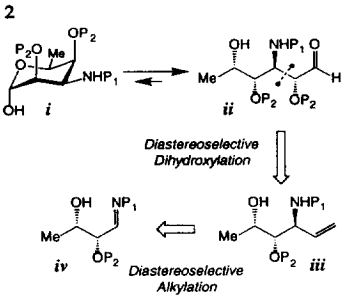
Synthesis of the corresponding carbohydrate, 3-amino-3,6-deoxy-D-talopyranose, has been disclosed by Stanek and Jary.[6] Their reported procedure affords the amino sugar only as a byproduct formed en route to a mixture of various 3-amino-3,6-pyranoses (2.4% of the total mixture). In this Article, we describe two strategies adopted in order to reach **1** in an efficient and enantioselective manner. One of the approaches led to a short and

stereoselective route to the synthesis of optically pure **1**, outfitted in manner that allows for its high yielding union with the aglycon segment of Sch 38516. The synthesis plan highlights a novel and diastereoselective [3+2]-cycloaddition process that leads to an expeditious assembly of the amino sugar skeleton.

Results & Discussion

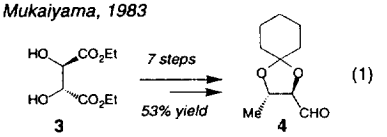
The alkylation-dihydroxylation route. In devising a more efficient synthesis procedure, as illustrated in Scheme 2, we viewed the skeleton of target amino sugar *i* as equivalent to polyhydroxylated aldehyde *ii*, which could be reached through a diastereoselective dihydroxylation of unsaturated amine *iii*. The requisite allylic amine could, in turn, be accessed by a diastereoselective alkylation of chiral imine *iv*.

Scheme 2

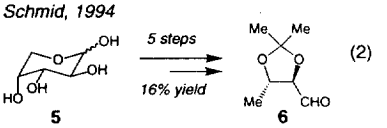


The chiral imine represented by *iv* in Scheme 2 may be obtained from the corresponding carboxaldehyde, a compound that has been utilized as a precursor in the synthesis of daunosamine, the carbohydrate unit of the celebrated antitumor agent daunomycin.[7] The two reported routes for the synthesis of these chiral aldehydes are summarized in eq 1-2. The first route (eq 1), provided by Mukaiyama and coworkers,[8] utilizes tartrate **3** as the starting material and affords optically pure **4** in seven steps and 53% overall yield. A second approach (eq 2), disclosed by the Schmid group,[9] employs D-arabinose **5** as its starting material and delivers **6** in five steps and 16% overall yield.

Mukaiyama, 1983



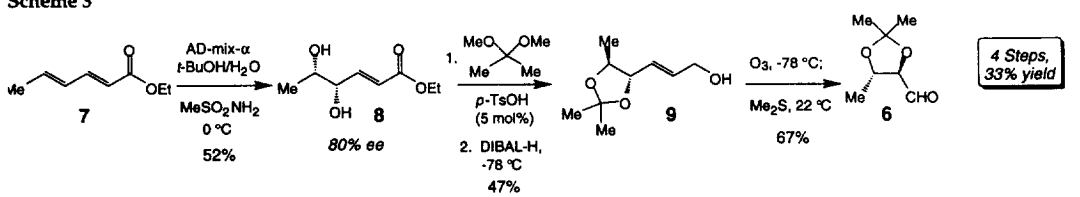
Schmid, 1994



To introduce a more concise and generally applicable synthesis scheme, we decided to avoid the use of carbohydrates or other natural chiral sources. It appeared to us that subsequent modification of these materials en route to the final product often leads to lengthy functional group alterations. We thus devised a four step sequence that uses an inexpensive and commercially available starting material and employs a catalytic and enantioselective process for introduction of chirality. The details of the synthesis route - one that affords non-racemic **6** in 80% ee and 33% overall yield - are put forth in Scheme 3.

Three issues with regard to the sequence illustrated in Scheme 3 merit mention: (1) The Sharpless dihydroxylation of **7**,[10] affords different enantioselectivities, depending upon which diastereomeric chiral oxidant is used (80% ee with AD-mix-α, 96% ee with AD-mix-β). Thus, the present procedure offers *ent*-**6** with a higher level of

Scheme 3



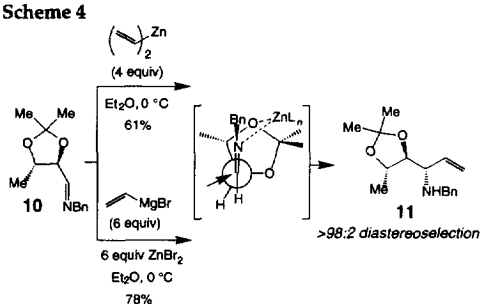
optical purity. (2) The minor stereoisomer obtained in the dihydroxylation reaction can be easily separated from the desired major isomer at a later stage in synthesis (see below). (3) Direct ozonolytic cleavage of protected **8** affords **6** in 40% isolated yield (versus 64% for the two step sequence shown in Scheme 3).

For the synthesis of the requisite allylic amine, the substrate required for testing the stereoselective dihydroxylation strategy, two previous reports suggested that various vinylzinc reagents might be suitable for this purpose. Mukaiyama and coworkers have demonstrated that alkylation of a closely related chiral imine with α-lithio-N,N-dimethylacetamide in the presence of $ZnBr_2$ proceeds with excellent diastereochemical control (little or no selectivity in the absence of the zinc salt).[11a] Fuganti's research team, in the context of synthetic studies on L-daunosamine, have shown that addition of diallylzinc to a chiral phenylsulfenimine that bears an α-alkoxy group proceeds stereoselectively at -78 °C.[11b] In both these studies, exact levels of diastereoselection are not provided, but the diastereomeric ratios are implied to be high.

We prepared chiral imine **10** from **6** ($BnNH_2$, Et_2O, 0 °C, 85%). As illustrated in Scheme 4, we subsequently treated **10** with four equivalents of divinylzinc at 0 °C in Et_2O to obtain **11** in 61% isolated yield and >98% diastereoselectivity (400 MHz ^1H NMR and 100 MHz ^{13}C NMR analysis). When **10** was subjected to a premixed solution of vinylmagnesium bromide and $ZnBr_2$ (6 equiv of each; Et_2O, 0 °C),[12] **11** was obtained, again, in >98% diastereoselectivity, but with an improved 78% isolated yield. The latter *in situ* method for the preparation of divinylzinc proved particularly advantageous, since the need to perform the synthesis of the sensitive divinylzinc reagent could be avoided.

With regard to the sense of observed stereoselectivity in the above alkylation reaction, it is noteworthy that the reactive conformer does not arise from chelation of the imine nitrogen with the α-alkoxy group.[13] Rather, it appears that, as illustrated in Scheme 4, a Felkin-Anh type transition structure,[14] reinforced by Zn chelation with the β-CO bond, is operative.

Scheme 4

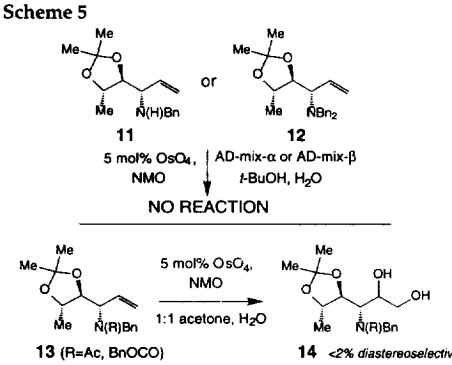


We next turned our attention to the possible diastereocontrolled functionalization of **11**. Stereoselective dihydroxylation of allylic alcohols has been studied extensively, beginning with the pioneering work of Kishi in the mid-eighties.[15] These investigations illustrate that high levels of diastereofacial selectivity can in certain cases be achieved. With regard to extant work on dihydroxylation of allylic amines, the results reported by Hauser indicate that, without an internal directing group, alkene oxidation is often non-selective.[16] We were aware of the findings of Cinquini and Cozzi,[17] observations that have been subsequently utilized by Schreiber in the context of the total synthesis of (-)-hikizimycin.[18] These workers illustrated that addition of chiral cinchanoid alkaloids leads to increase in diastreoselectivity of oxidations of terminal or trans-disubstituted allylic alcohols. However, it was also noted that high selectivities (>20:1) were only achieved when stoichiometric conditions were used, a strategy that we found unattractive. That is, a catalytic dihydroxylation that proceeds with low selectivity (5:1 or less) is unlikely to be improved to high levels of diastereoselection by the addition of a chiral additive. In short, if catalytic

dihydroxylation proved reasonably selective, it could be somewhat improved by the double stereodifferentiation approach.

Somewhat to our surprise, however, as shown in Scheme 5, subjection of allylic amine **11** to a variety of dihydroxylation conditions, both in the presence and absence of chiral additives,[19] led to the complete recovery of the starting material (70-80% mass balance). Similar observations were made when the corresponding dibenzyl derivative **12** was used. To ascertain whether the Lewis basic amine unit poisons the oxidation catalysts, we carried out the dihydroxylation of **7** in the presence of **11**;[19] the former was oxidized smoothly, but the latter was recovered unchanged. As shown in Scheme 5, only after the amine unit was protected as its derived amide or carbamate (**13**), did we observe efficient alkene dihydroxylation, albeit with complete absence of stereochemical control.

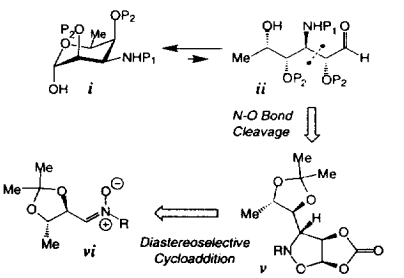
Scheme 5



The [3+2]-cycloaddition route. In light of the difficulties that we faced in connection to our initial strategy (above), we began to search for an alternative approach towards a stereoselective synthesis of the amino sugar. Accordingly, as illustrated in Scheme 6, we realized that the requisite stereochemistry within the amino sugar could be constructed by a selective [3+2]-cycloaddition of a nitrone with an appropriate alkene. As has been expertly demonstrated by DeShong and coworkers,[20] [3+2]-cycloaddition of nitrone ***vi*** (easily prepared from aldehyde **6**) with vinylene carbonate would afford isoxazolidine ***v***. The transformation of ***v*** to ***i*** would be realized by the reductive cleavage of the N-O bond.

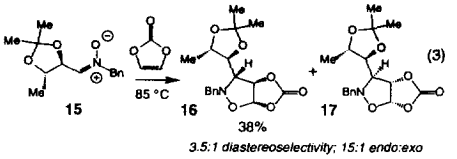
However, we were cognizant of the fact that such a cycloaddition process, only *if rendered highly selective*, would offer a particularly convenient and expeditious route to the desired carbohydrate moiety - one that could be used for effective material throughput in a multistep total synthesis effort. We thus began to explore the possibility of preparing the target amino sugar through the use of DeShong's cycloaddition.

Scheme 6

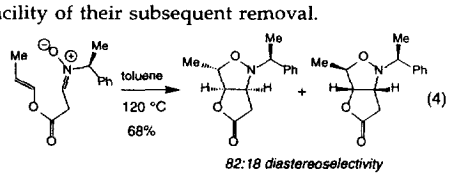


Consistent with previous reports, when nitrone **15** is subjected to cycloaddition conditions (5 equivalents of vinylene carbonate, 85 °C, 22 h),[21] cycloadducts **16** and **17** were obtained with similar selectivity as when the original DeShong procedure is used (eq 3; endo products shown only). The stereochemistry of the major five-membered ring diastereomer **16** is that required for the desired for carbohydrate **1**. Although this chemistry allowed us easy access to an intermediate with the appropriate stereochemical attributes for the amino sugar synthesis, the low levels of diastereochemical control (35-40% isolated yield of **16**) detracted from applications in the total synthesis project. This complication was further exacerbated, when separation of **16** from diastereomer **17** proved difficult and tedious; medium pressure liquid chromatography (MPLC) had to be utilized if **16** was to be obtained in reasonable (>95%) purity. We thus began to contemplate various strategies that would lead to

the improvement of diastereoselectivity in the cycloaddition process.

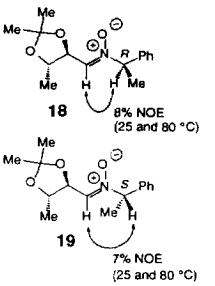


It has been demonstrated that nitrones that carry a chiral auxiliary on nitrogen may display high levels of diastereoselectivity in [3+2]-cycloadditions with a variety of achiral dipolarophiles.[22] Specially relevant, is the work by Wovkulich and Uskokovic, who have reported an asymmetric synthesis of L-acosamine and L-daunosamine, where a key intermediate is prepared by a diastereoselective intramolecular dipolar cycloaddition reaction.[21a] As illustrated in eq 4, the chiral substituent, (*S*)-α-methyl benzyl, induces moderate levels of diastereoselectivity in the cyclization reaction. Therefore, in our case, it was anticipated that by a judicious choice of chiral amine substituents, diastereoselectivity of the cycloaddition reaction could perhaps be enchanced to a more practical level. Both (*R*)- and (*S*)-α-methylbenzyl groups were selected as chiral auxiliaries, due to the ease of their preparation and facility of their subsequent removal.



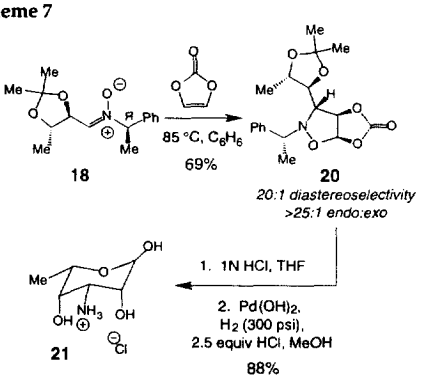
To test the abovementioned hypothesis, nitrone **18** was prepared from non-racemic aldehyde **6** (Scheme 3) according to the procedure reported by Polonski and Chimiak.[23] It was at this juncture that the minor isomer derived from the minor enantiomer of ethyl sorbate dihydroxylation was separated from the major nitrone diastereomer **18**. The desired nitrone was obtained as a single isomer (>98% *Z* isomer at 25 °C), based on nuclear Overhauser effect difference spectroscopy (NOEDS). The preponderance of the *Z* configuration is expected: the majority of nitrones with similar structural properties exist exclusively as their *Z* isomer.[24] We prepared various other diastereomeric nitrones; similar spectroscopic studies indicate that the latter compound adopts the *Z* configuration as well (at 25 and 80 °C); the additional example (**19**)[25] shown in Figure 1 is illustrative.

Figure 1



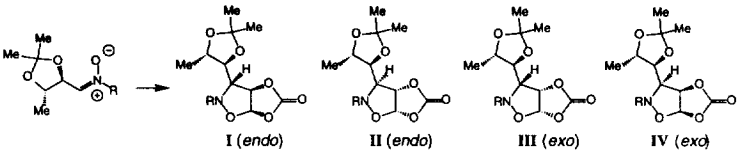
As Scheme 7 illustrates, when optically pure nitrone **18** is treated with 5 equivalents of vinylene carbonate at 85 °C for 20 hours, cycloaddition occurs smoothly (>95% conversion). *Cycloadduct* ***20*** *is obtained in 69% isolated yield with excellent stereochemical control* (20:1; <2% exo product detected by 400 MHz ^{1}H NMR spectrum of the unpurified mixture).

Scheme 7



The stereochemical identity of the derived carbohydrate, and thus the stereochemical course of the cycloaddition reaction was established through conversion of **20** to amino sugar **21**, as shown in Scheme 7. The triacetyl-methoxy acetal derived from **21** proved identical to the material obtained from an authentic sample of the natural product. The exact details of conversion of cycloadducts (*e.g.*, **20**) to carbohydrates (*e.g.*, **21**) will be disclosed in the

Table 1. Diastereocontrol in Nitrone-Vinylene Carbonate Cycloadditions. Effect of Nitrone Auxiliary on Selectivity.[a]



nitrone	R	diastereoselectivity (I:II)	*endo*:*exo* (I+II)/(III+IV)	overall yield (%)
18		20:1	>25:1	72
15		3.5:1	15:1	52
22		1.3:1	10:1	40

a. Reaction conditions: Four equiv of vinylene carbonate, 85 °C, 24 h. *b.* Diastereoselectivity determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified products. *c.* Isolated yields after silica gel chromatography.

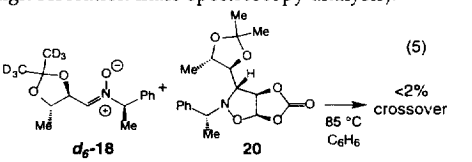
full account of the total synthesis. At this point, we must add that, unless freshly prepared Pearlman's catalyst is used,[26] and the amount of the added acid is diligently controlled, often ten percent or less reaction product is obtained.[27]

In contrast to the cycloaddition reaction with **18**, when **22** is subjected to the same reaction conditions, as summarized in Table 1, the cycloaddition reaction is less efficient than those of **18** or **15** and little or no diastereofacial selectivity is observed (4:3); moreover, the endo:exo ratio is diminished to 10:1 (versus >25:1 for reaction with **18**).

Although the exact mechanistic details of the diastereoselective cycloaddition process must await additional studies, the present studies, in conjunction with previous work in this area, allow us to put forth a plausible working model. Several important factors dictate the preferred transition structure for the [3+2]-cycloaddition reaction:

(1) The nitrone system exists and reacts predominantly in its Z form (see above for spectroscopic evidence).[24]

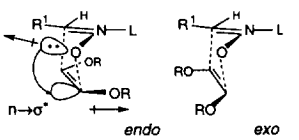
(2) Control experiments indicate that cycloaddition reactions are under kinetic control. When an equimolar mixture of d_6-**18** and **20** are subjected to the reaction conditions (without vinylene carbonate), <2% cross-over products are observed (high resolution mass spectroscopy analysis).



(3) As reactions in the presence and absence of a radical scavenger (2,6-di-*tert*-butyl-4-methylphenol) proceed in an identical fashion, it is unlikely that any radical intermediates are involved to any significant extent.[28]

(4) The endo transition structure is uniformly favored. Minimization of dipole interactions may be partly responsible for this preference (Figure 2). Another plausible argument that has been put forth to rationalize the endo preference, as shown in Figure 2, involves a stereoelectronic communication between the two reaction partners.[29] Thus, electron donation from the nitrone oxygen to the carbonate σ* C-O may lead to lowering of the endo transition state energy. In spite of the thought provoking nature of the present

Figure 2

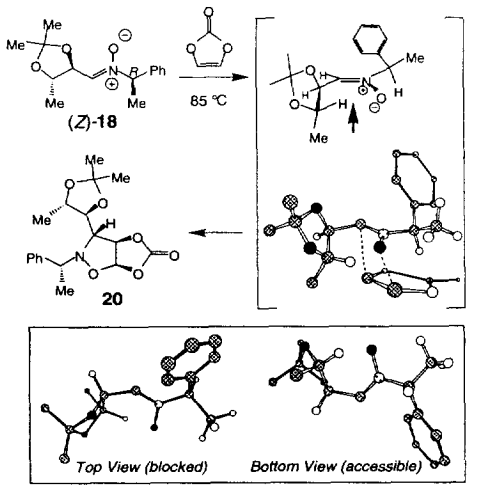


paradigm, it is not clear whether such stereo-electronic interactions can alone lead to appreciable levels of endo selectivity observed in reaction of **18** with vinylene carbonate.

(5) The most reactive conformer of the nitrone, when its reaction partner is the relatively electron rich vinylene carbonate, is one where the electron accepting C-O substituent is perpendicular to the C=N π system.[14] As a result, through electron donation from the π cloud to the low-lying C-O σ*, the C=N bond is rendered more electron deficient and thus more reactive.

(6) A number of mechanistic studies indicate that the cycloaddition reaction is concerted but asynchronous.[30] Furthermore, theoretical studies indicate that, in these types of cycloaddition reactions, formation of the C-C bond is more advanced than that of the C-O bond (nitrone LUMO has larger coefficient at the carbon center).[31] The non-synchronous character of the ring forming transformation suggests that, since the approach to the C=N moiety is significantly developed in the transition state, factors that differentiate the two diastereotopic faces of this π bond are particularly critical to the eventual stereochemical outcome of the reaction.

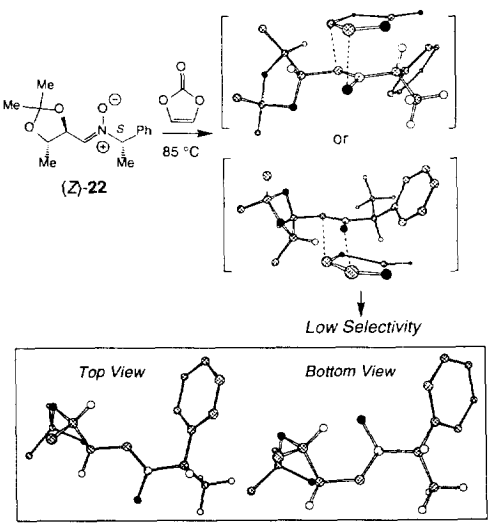
Scheme 8



Accordingly, as illustrated in Scheme 8, reaction of **18** through a more reactive transition state, where the incoming dipolarophile approaches anti to the C-O bond (which in turn is perpendicular to the C=N π cloud), leads to the observed major isomer (Felkin-Anh model).[14] To accommodate the incoming carbonate, the auxiliary moiety is oriented such that the smallest substituent (H) is directed towards the dipolarophile. As a result, the resident phenyl unit effectively blocks attack from the top face of the C=N bond (compare top and bottom views depicted in Scheme 8).[32]

The above mechanistic models provide a plausible rationale for: (i) why reaction with (*S*) chiral auxiliary antipode **22** is non-selective (see Table 1), and (ii) why reactions are less selective with nitrones carrying an achiral benzyl system (*i.e.*, **15**). As illustrated in Scheme 9, with **22** as the starting material, the phenyl group of the auxiliary does not effectively protect one diastereoface of the C=N unit of nitrone.

Scheme 9

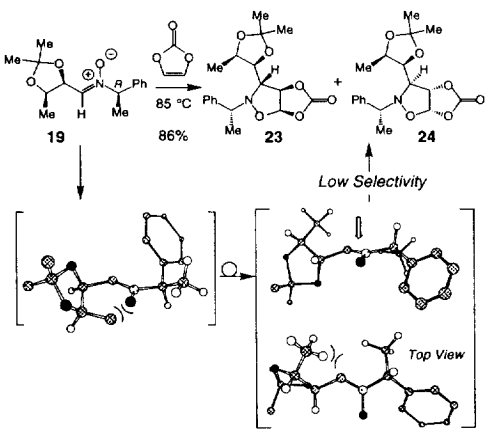


When **15** is used as substrate, transition states similar to those shown in Schemes 8 and 9 become operative (replace Me groups with H), and thus

diastereoselectivity suffers (cf. Table 1). It is important to note that these mechanistic suggestions are based on the premise that electronic effects (overlap of C-O σ^* with C=N π) alone are not sufficient to engender significant levels of stereoselectivity. Only when in concert with appropriate steric effects (proper orientation of one of the substituents of the chiral auxiliary), do we observe high levels of diastereofacial selectivity.

The mechanistic discussions above, as is often the case, are simply rationalizations offered after the fact. Do these hypotheses have any predictive value? The answer to this question must again await extensive additional studies. To test the aforementioned paradigms, however, we did carry out the cycloaddition reaction illustrated in Scheme 10, where **23** and **24** are formed as equal mixtures of isomers. As is also shown in Scheme 10, the above

Scheme 10



model would predict that the transition structure related to that shown in Scheme 8 would engender severe steric interactions between the heterocyclic methyl substituent and the nitrone oxygen. The alternative reactive conformer, where the dipolarophile would attack anti to the C-O bond, according to molecular models, also suffers from unfavorable steric interactions caused by the Me substituent of the neighboring heterocyclic ring.

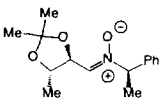
Conclusions

We have provided a convenient, regio- and stereoselective (both enantio- and diastereocontrolled) synthesis scheme that affords amino sugar **21** in 8 steps from commercially available materials (**7**), as a single enantiomer and in 9-10% overall yield. The source of optical purity is a catalytic and enantioselective process (Sharpless dihydroxylation). Other key stereochemical issues were addressed by an efficient cycloaddition reaction which proceeds with excellent diastereoselectivity because of the use of a readily accessible and easily removable chiral auxiliary. Mechanistic hypotheses presented herein suggest that strategic matching of the nitrone streochemistry with an appropriate chiral auxiliary can indeed lead to excellent levels of stereoselectivity. Further studies in connection to the application of other chiral auxiliaries, various nitrone systems and dipolarophiles in the cycloaddition process, the related mechanistic issues and applications to the synthesis of various medicinally important amino sugars are the subject of ongoing investigations.

Experimental Section

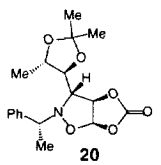
General. Infrared (IR) spectra were recorded on a Perkin Elmer 781 spectophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^1H NMR spectra were recorded on a Varian Unity 300 and 400 (300 and 400 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.24 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, p=pentet, q=quartet, br=broad, m=multiplet),

coupling constants (Hz), and assignment. ^{13}C NMR spectra were recorded on a Varian Unity 300 or 400 (75 or 100 MHz, respectively) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference ($CDCl_3$: δ 77.0 ppm). Microanalyses were performed by Robertson Microlit Laboratories (Madison, New Jersey). High resolution mass spectra were obtained at the Mass Spectrometry Facility of the University of Illinois (Urbana-Champaign, Illinois). All reactions were conducted in oven (135 °C) and flame-dried glassware under an inert atmosphere of dry argon. Tetrahydrofuran, diethyl ether and benzene were distilled from sodium metal/benzophenone ketyl. AD-mix-α, AD-mix-β, *tert*-butyl alcohol and ethyl sorbate were purchased from Aldrich Chemical Co. Vinylene carbonate was purchased from Aldrich Co. and was distilled over CaH_2 before use.



18

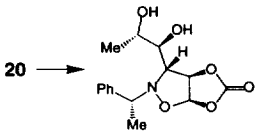
Nitrone 18. Aldehyde **6** (55.0 mg, 0.38 mmol) was dissolved in 4 mL benzene, and (*R*)-N-hydroxy-α-methyl benzylamine (60.0 mg, 0.43 mmol) was added to this solution. The resulting mixture was allowed to reflux for 5 h. The reaction mixture was cooled to 22 °C and solvent was removed *in vacuo* to give a yellow oil. Purification by silica gel chromatography (1:1 hexanes:EtOAc) afforded 84.0 mg of nitrone **18** as a colorless oil (0.32 mmol, 74% yield). IR (NaCl): 3069 (m), 2987 (s), 2924 (s), 2867 (m), 1734 (w), 1590 (s), 1457 (s), 1388 (s), 1250 (s), 1168 (s), 1086 (s), 859.4 (s) cm^{-1}. ^1H NMR: δ 7.4 (m, 5H, aromatic-**H**), 6.88 (d, 1H, J=5.6 Hz, OCHC**H**N), 5.02 (q, 1H, J=6.8 Hz, NC**H**CH_3), 4.87 (dd, 1H, J=7.3, 5.6 Hz, NCHC**H**), 3.97 (qd, 1H, J=6.0, 1.2 Hz, MeC**H**O), 1.80 (d, 3H, J=6.9 Hz, PhCHC**H**$_3$), 1.45 (d, 1H, J=6.4 Hz, C**H**$_3$CHOCH), 1.44 (s, 3H, C**H**$_3$CCH$_3$), 1.35 (s, 3H, CHCC**H**$_3$). ^{13}C NMR: δ 138.1, 135.4, 128.8, 128.7, 127.2, 126.9, 109.5, 77.3, 76.3, 73.5, 53.6, 27.1, 26.3, 19.4, 18.9. HRMS Calcd for: $C_{15}H_{22}NO_3$ (M+H): 264.1599. Found: 264.1600.



20

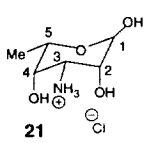
Isoxazolidine 20. Nitrone **18** (106 mg, 0.40 mmol) was placed in a flame-dried round bottom flask equipped with a reflux condenser (under argon). Vinylene carbonate (102 mL, 1.6 mmol), freshly distilled over calcium hydride under vacuum (15 mm Hg), was added to the nitrone substrate. The resulting mixture was heated at 85 °C for 19 h to afford a dark brown oil. Purification by silica gel chromatography with 5:1 hexane/EtOAc afforded 96.4 mg (0.28 mmol) of **20** as a white solid (69% yield). IR (NaCl): 2986 (m), 2936 (w), 2886 (w), 1822 (s), 1463 (w), 1381 (m), 1262 (w), 1168 (m), 1067 (m), 992 (m), 859 (w), 702 (w) cm^{-1}. ^1H NMR: δ 7.27-7.38 (m, 5H, aromatic-**H**), 6.28 (dd, 1H, J=5.2, 0.4 Hz, OC**H**O), 5.48 (d, 1H, J=5.2 Hz, CHC**H**OCO), 4.02 (q, 1H, J=6.0 Hz, PhC**H**Me), 3.45 (d, 1H, J=7.6 Hz, NC**H**), 3.29 (t, 1H, J=7.6 Hz, NC**H**CH), 3.24 (dq, 1H, J=7.6, 6.0 Hz, MeC**H**OCH), 1.57 (d, 3H, J=6.0 Hz, PhCHC**H**$_3$), 1.31 (s, 3H, C**H**$_3$CCH$_3$), 1.23 (s, 3H, CH$_3$CC**H**$_3$), 1.22 (d, 3H, J=6.0 Hz, C**H**$_3$CO). ^{13}C NMR: δ 152.6, 140.7, 128.9, 128.7, 128.1, 109.0, 105.1, 87.2, 79.4, 76.0, 68.4, 67.5, 27.1, 26.5, 21.2, 19.1. HMRS Calcd for $C_{18}H_{23}NO_6$: 349.1525. Found: 349.1527.

Diol isoxazolidine derived from 20. Tricycle (931 mg, 2.66 mmol) was dissolved in 13.3 mL of a 4:1 THF/1M aqueous hydrochloric acid solution. The resulting mixture was heated to 65 °C. Reaction progress was monitored by TLC (1:1 hexanes/EtOAc, R_f=0.75 for starting material, 0.30 for product), which indicated complete

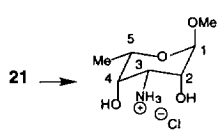


consumption of starting material after 4 h . Reaction was quenched by the addition of 50 mL of a saturated solution of sodium bicarbonate. Aqueous and organic layers were separated and the aqueous layer was washed four times with 50 mL portions of EtOAc. The combined organic layers were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered through a fritted funnel and concentrated *in vacuo* to afford a pale yellow oil, which could be used for next step without purification. When necessary, purification by silica gel chromatography (2:1 hexanes/EtOAc) provide 733 mg (2.50 mmol) of diol as a colorless oil (94% yield). IR (NaCl): 3459 (br), 3069 (w), 3032 (w), 2980 (m), 2936 (w), 1822 (s), 1734 (m), 1495 (m), 1451 (s), 1376 (s), 1313 (m), 1168 (s), 1080 (s), 985 (s) cm^{-1}. ^1H NMR: δ 7.42-7.30 (m, 5H, aromatic-**H**), 6.62 (dd, 1H, J=5.6, 0.8 Hz, OC**H**O), 5.64 (d, 1H, J=5.6 Hz, CHC**H**OCO), 4.02 (q, 1H, J=6.4 Hz, PhC**H**), 3.78 (qd, 1H, J=6.4, 2.0 Hz, CH_3C**H**OH), 3.43 (d, 1H, J=8.8 Hz, NC**H**), 2.95 (dd, 1H, J=8.8, 2.0 Hz MeCHOHC**H**O), 1.40 (d, 3H, J=8.8 Hz, PhCHCH_3), 1.10 (d, 3H, J=6.4 Hz, CH_3CHO). ^{13}C NMR: δ 152.8, 141.0, 129.1, 128.7, 128.1, 105.3, 87.2, 72.6, 67.6, 67.5, 65.6, 21.0, 19.0. HRMS Calcd for $C_{14}H_{17}O_6N$ (M+H): 296.1134 . Found: 296.1129.

3-Amino-3,6-dideoxy-α-L-talopyranose 21. Diol (0.737 mmol) was dissolved in 36 mL of MeOH and brought into a glove box, at which time 50% (by weight) Pearlman's catayst $Pd(OH)_2$ was added. The reaction flask was removed from the glove box and charged with acetyl chloride (143 mL, 2.01 mmol). The resulting mixture was placed in a high pressure bomb which was subsequently purged with hydrogen three times. Hydrogenation was allowed to proceed under 300 psi of hydrogen at 22 °C. After 14 h, the reaction mixture was filtered through celite and concentrated *in vacuo* to provide a light yellow solid, which could be directly submitted to the next step. When necessary, purification by silica gel chromatography (4:1 CH_2Cl_2/MeOH) afforded 120 mg (0.70 mmol) of **76** (7:1 ratio of α/β anomers, 95% yield), the ratio of both anomers varied upon silica gel chromatography. IR (NaCl): 3312 (br, s), 2985 (s), 2938 (s), 1606 (w), 1505 (m), 1380 (w), 1054 (s), 1016 (m), 975 (w), 860 (w) cm^{-1}. ^1H NMR (400 MHz in CD_3OD): δ (α-anomer): 5.20 (s, 1H, C_1-**H**), 4.17 (q, 1H, J=6.2 Hz, C_5-**H**), 3.75 (br, s, 1H, C_2-**H**), 3.69 (br, s, 1H, C_4-**H**), 3.56 (br, s, 1H, C_3-**H**), 1.24 (d, 3H, J=6.5 Hz, C_6-H_3). (β-anomer): 4.75 (s, 1H, C_1-**H**), 3.85 (br, m, 1H, C_2-**H**), 3.71 (br, s, 1H, C_4-**H**), 3.65 (br, s, 1H, C_3-**H**), 1.28 (d, 3H, J=6.0 Hz, C_6-H_3), C_5-**H** hiding underneath one peak of β-anomer. ^{13}C NMR (100 Hz in CD_3OD): δ (α-anomer) 95.6, 70.0, 68.9, 66.8, 50.2, 17.1. HRMS Calcd for $C_6H_{13}O_4N$ (M-Cl): 164.0928. Found: 164.0928.



Methyl-3-amino-3,6-dideoxy-α-L-talopyranose derived from 21. Hydroxy glycoside **21** (128 mg, 0.76 mmol) was placed in a 100 mL round bottom flask, to which was added 36 mL of 10% (by weight) anhydrous methanolic hydrochloric acid solution. Stirring was allowed to continue for 70 h at 22 °C. The resulting reaction mixture was concentrated *in vacuo* to give a light yellow solid, which could be subsequently submitted to next step without purification. Purification by silica gel chromatography (4:1 CH_2Cl_2/CH_3OH) to provide 116 mg (0.63 mmol) of the α-methoxy glycoside (84% yield from the diol). Note: If reaction time is too brief (*e.g.*, 40 h), the product will be contaminated with the α-anomer. IR (NaCl): 3339 (brs), 2949 (s), 2829 (s), 2363 (w), 1621 (w), 1507 (m), 1444 (m), 1381 (m), 1193 (w), 1117 (s), 1067 (s), 1016 (s) cm^{-1}. ^1H NMR (400 MHz in CD_3OD): δ



4.68 (br, s, 1H, C_1-**H**), 3.92 (q, 1H, J=6.5 Hz, C_5-**H**), 3.75 (dd, 1H, J=3.3, 1.6 Hz C_2-**H**), 3.66 (m, 1H, C_4-**H**), 3.47 (t, 1H, J=3.3 Hz, C_3-**H**), 3.34 (s, 3H, OCH_3), 1.20 (d, 3H, J=6.5 Hz, C_6-H_3). ^{13}C NMR (125 MHz in CD_3OD): δ 102.4, 69.7, 67.9, 67.3, 55.8, 50.4, 17.0. HRMS calcd. for $C_7H_{16}O_4N$ (M-Cl): 178.1079. Found: 178.1083.

Methyl-2,4-bis-O-acetyl,3-N-acetyl-3,6-dideoxy-α-L-talopyranose. Into the methoxy glycoside derived from **21** (13 mg, 0.071 mmol) acetic anhydride (80 μL, 85 mmol), pyridine (100 μL, 12.3 mmol) and a ~1 mg of DMAP were subsequently added. The resulting mixture was allowed to stir for 23 hours at 22 °C, then 2.0 mL CH_2Cl_2 was added, and the entire mixture was transferred to a separatory funnel which contained 10 mL of ethyl acetate and 10 mL of saturated aqueous copper sulfate solution. The solution was washed three times with 10 mL portions of ethyl acetate. Organic layers were combined and washed with a saturated solution of sodium bicarbonate (10 mL). The resulting solution was stirred vigorously for 30 minutes and followed by washing with ethyl acetate (10 mL). Organic layers were then combined, dried over $MgSO_4$, filtered through a fritted funnel, and concentrated *in vacuo* to yield a light green oil. Purification by silica gel chromatography (5:1 hexanes:EtOAc) to afford the desired triacetate. IR (NaCl): 3298 (br, w), 2982 (br, w), 2934 (br, w), 2838 (br, w), 2366 (w), 1740 (s), 1648 (s), 1539 (m), 1369 (m), 1231 (s), 1134 (m), 1074 (m), 1028 (m) cm^{-1}. ^1H NMR: δ 5.67 (br, d, J=9.0 Hz, N**H**), 5.10 (dd, J=3.0, 1.0 Hz, C_2-**H**), 4.79 (dd, J=3.9, 1.0 Hz, C_4-**H**), 4.76 (s, C_1-**H**), 4.67 (dt, J=8.8, 3.7 Hz, C_3-**H**), 4.10 (dq, J=6.8, 1.2 Hz, C_5-H), 3.38 (s, 3H, OCH_3), 2.18 (s, 3H, $COCH_3$), 2.16 (s, 3H, $COCH_3$), 1.96 (s, $COCH_3$), 1.16 (d, J=6.6 Hz, C_5-CH_3). ^{13}C NMR: δ 170.7, 170.5, 169.4, 98.2, 70.2, 69.2, 64.8, 55.1, 44.9, 23.2, 21.2, 20.8, 16.4. HRMS calcd. for $C_{13}H_{22}NO_{17}$: 304.1396. Found: 304.1396.

Nitrone 19. Recrystalized from anhydrous Et_2O to obtain a white solid (melting point: 95-97 °C). IR (NaCl) 3089(m), 2981(s), 2934(m) 2872(m), 1605(m), 1460(s), 1382 (s), 1368(s), 1217(s), 1181(s), 1134 (s), 1072(m), 850(m), 705(s) cm^{-1}. ^1H NMR: δ 7.4 (m, 5H aromatic H), 6.84 (d, 1H, J=5.5 Hz, OCHCHN), 5.24 (dd, 1H, J=12.1, 5.5 Hz, NCHC**H**), 5.03 (q, 1H, J=6.9 Hz, NC**H**CH_3) 4.56 (dq, 1H, J=12.8, 6.4 Hz, CH_3CHO), 1.8 (d, 3H, J=6.9 Hz, PhCHC**H**$_3$), 1.44 (s, 3H, CH_3CCH_3), 1.34 (s, 3H, CH_3CCH_3), 0.98 (d, 3H, J=6.2 Hz, C**H**$_3$CHOCH). ^{13}C NMR: δ 137.8, 135.9, 128.9, 128.8, 127.3, 108.7, 74.4, 73.5, 27.7, 24.9, 18.6, 15.3. HRMS calcd. for $C_{15}H_{21}NO_3$ (M+H): 264.1599. Found: 264.1600.

Isooxazolidine 23. IR (NaCl) 2984 (m), 2936 (w), 1819 (s), 1455 (m), 1380 (m), 1214 (m), 1166 (s), 1073 (s), 986 (s), 855 (w), 764 (w), 701 (w) cm^{-1}. ^1H NMR: 7.33 (m, 5H, aromatic H), 6.24 (d, 1H, J=5.3 Hz, OC**H**O), 5.54 (d, 1H, J=5.3 Hz, CHC**H**OCO), 4.20 (dq or apparent pent., 1H, J=6.6, 6.6 Hz, MeC**H**OCH), 4.04 (q, 1H, J=6.4 Hz, PhC**H**Me), 3.94 (dd, 1H, J=6.6, 4.6 Hz, C**H**OCHN), 3.55 (d, 1H, J=4.7 Hz, CHOC**H**N), 1.52 (d, 3H, J=6.4 Hz, PhCHC**H**$_3$), 1.38 (s, 3H, C**H**$_3$CCH$_3$), 1.27 (s, 3H, CH_3C**H**$_3$), 0.71 (d, 3H, 6.6 Hz, C**H**$_3$CHO). ^{13}C NMR: δ 152.8, 141.2, 129.0, 128,4, 128.0, 108.0, 105.5, 87.2, 77.2, 72.7, 67.6, 65.9, 27.1, 24.5, 21.8, 14.7. HRMS calcd. for $C_{18}H_{23}NO_6$ (M+H): 350.1604. Found: 350.1604.

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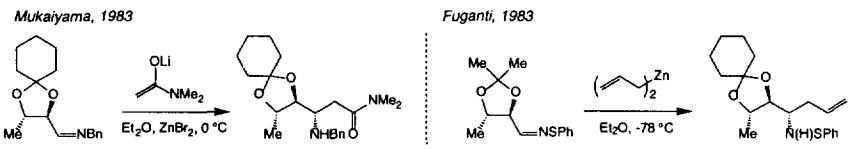

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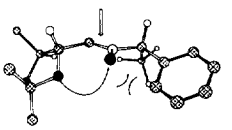
32) Reaction through the alternative conformer is predicted not to be competitive; this conformer suffers from steric and electron-electron repulsion, as illustrated below



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