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Experimental and Theoretical Studies on Stereo- and Regioselectivity in Intramolecular Nitrone−Alkene Cycloaddition of Hept-6-enoses Derived from Carbohydrates

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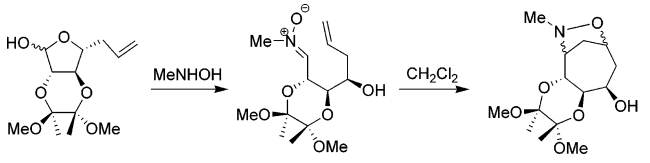
Received February 20, 2006



The effect of blocking groups and stereochemistry of the substituents on the regio- and stereoselectivity in intramolecular nitrone−alkene cycloaddition (INAC) of hept-6-enoses are reported. L-*ribo*-Hept-6-enose **12** and D-*lyxo*-hept-6-enose **15**, both containing a 2,3-*O*-isopropylidene blocking group, and L-*xylo*-hept-6-enose **23** and D-*arabino*-hept-6-enose **30**, both with a 2,3-*O*-trans-diacetal blocking group, were prepared from D-ribose and D-arabinose, respectively. With *N*-alkyl hydroxylamine, lactols **12** and **15** underwent an INAC reaction to give cis-fused isoxazolidines exclusively whereas lactols **23** and **30** gave a mixture of cis-, trans-fused isoxazolidines (cyclohexanols) and bridged isoxazolidines (cycloheptanols). With the 2,3-*O*-trans-diacetal protecting group, the bridged bicyclo[4.2.1]isoxazolidines (cycloheptanols), via the *endo* mode of INAC cyclization, were synthesized for the first time from unbranched sugar derivatives **23** and **30**. The stereochemical outcomes of these reactions were rationalized on the basis of transition state energies obtained by computation. The present INAC showed trivial temperature, but significant solvent dependence. For lactols **23** and **30**, performing the INAC in 2-propanol gave the best yields of fused isoxazolidines (cyclohexanols) whereas in dichloromethane afforded the best yields of bridged isoxazolidines (cycloheptanols).

Introduction

Intramolecular nitrone−alkene cycloaddition (INAC) constitutes a powerful synthetic method for the preparation of polyhydroxylated carbocycles from sugars.[1] The presence of a nitrogen functionality within the cycloadduct is especially attractive for the syntheses of alkaloids and related natural products.[2]

There are two modes of INAC cyclization, the *exo* or the *endo* mode (Scheme 1), which lead to either a fused or a bridged isoxazolidine, respectively.[3] Searching the literature reveals only two examples[4] of the formation of a bridged bicyclo[4.2.1] system from branched sugars and one example[5] of a fused bicyclo[5.3.0] system, i.e., a cycloheptane skeleton, from carbohydrates. A fused bicyclo[5.3.0] system from carbohydrates via an intramolecular nitrile oxide cyclization (INOC) was also

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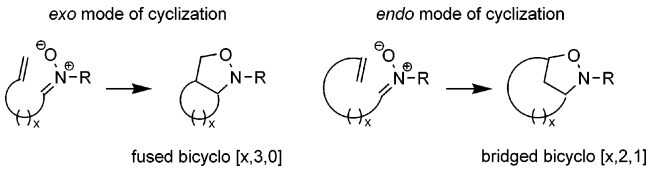
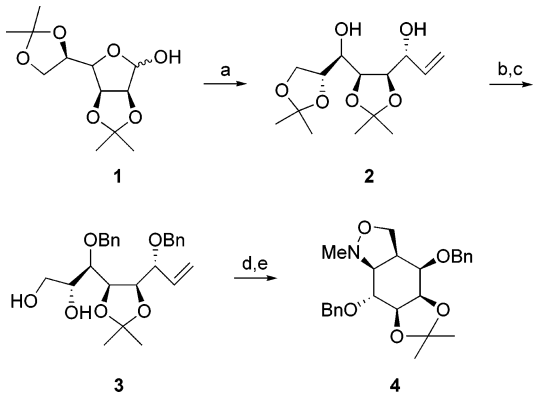
10.1021/jo060348y CCC: $33.50
Published on Web 03/22/2006

SCHEME 1. Two Modes of INAC Cyclization



SCHEME 2. INAC from a D-Mannose Derivative[a]



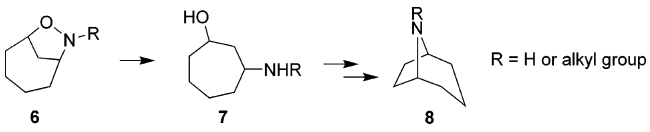
[a] Reagents and conditions: (a) $CH_2CHMgBr$, THF, 93%; (b) BnBr, NaH, THF, 79%; (c) aq AcOH, 64%; (d) $NaIO_4$, aq MeOH; (e) MeNHOH·HCl, $NaHCO_3$, aq EtOH, reflux, 65% from **3**.

reported.[6] However, there are many examples[4c,7−11] of unbranched sugar derivatives giving the fused bicyclo[4.3.0] system, i.e., a cyclohexane skeleton.

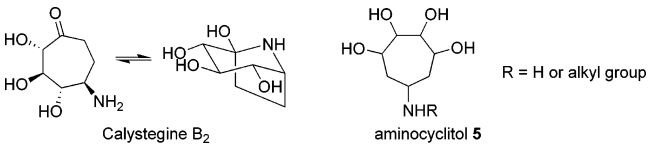
Inspired by the pioneer work from Vasella,[1a] one of us reported a rapid entry to 5- and 6-ring carbocycles from carbohydrates via an INAC reaction (Scheme 2).[11] The strategy involves a Grignard addition of an alkene component to C-1 of acetonide **1**, readily available from D-mannose, and an aldehyde at C-7 was obtained from a glycol cleavage oxidation of the corresponding diol **3**. With *N*-methyl hydroxylamine, an *exo*-mode INAC reaction occurred to yield, exclusively, a fused isoxazolidine, cyclohexane **4**, but its regio- and stereochemical outcomes were not rationalized.[11]

Both the fused and bridged isoxazolidines were shown to be key intermediates in the syntheses of natural products or analogues with biological importance.[3,12−14] Examples are (−)-shikimic acid,[8] β-glucosidase inhibitor cyclophellitol,[15] and nucleoside analogues.[4,5b] The bridged bicyclo[4.2.1] system already encloses the backbone of the new *nor*-tropane alkaloids, calystegines, e.g., calystegine B_2, which exhibit specific glycosidase inhibition.[16] Aminocycloheptanol **5**, proven to be a new

SCHEME 3. Catalytic Hydrogenolysis of the N−O Bond



class of glycosidase inhibitor,[17] also contains a cycloheptane skeleton that is profited from the cleavage of the heterocycle, such as **6**, upon catalytic hydrogenolysis of the N−O bond (Scheme 3).



Further synthetic manipulation performed on the aminocycloheptanol **7** could lead to another class of alkaloids, the tropanes **8**.[18] The regio- and stereoselective formation of the bridged bicyclo[4.2.1] system via the *endo* mode of INAC of hept-6-enose is thus worthy of investigation. However, the rationalization for the regio- and diastereoselectivity of these INAC reactions has not been presented. There are no examples for the construction of the bridged bicyclo[4.2.1] system from unbranched hept-6-enose derivatives. To develop a general synthetic protocol for the construction of enantiopure aminocycloheptanols from carbohydrates, we need to address the stereochemical factors that control the regioselectivity (ring size) as well as the diastereoselectivity of the INAC reactions on hept-6-enose. This is the subject of the present article.

Recent papers[19−21] regarding theoretical studies of intermolecular 1,3-dipolar cycloaddition discovered that solvent effects could modify the regio- and the stereochemical outcome of the reaction. Toward this end, performing the INAC reactions in different solvents is of interest. However, there are no reports on the theoretical studies of the INAC reactions of hept-6-enoses to give carbocycles. In the present Article, we report the first examples of bridged bicyclo[4.2.1] systems by endo dipolar cycloaddition of carbohydrate-derived alkenes. This opens a new route to enantiomerically defined cycloheptane derivatives. Theoretical analysis was carried out and the transition state (TS) energies of all the possible cycloadducts, cyclohexanols and cycloheptanols, were computed.

Results and Discussion

INAC of a D-Ribose Derivative. The acetonide **9**,[22] readily available from D-ribose, reacted with an excess of allylmagnesium bromide in diethyl ether to give triol **10** and its 4-epimer **11** in 17:1 diastereoselectivity, respectively (Scheme 4).

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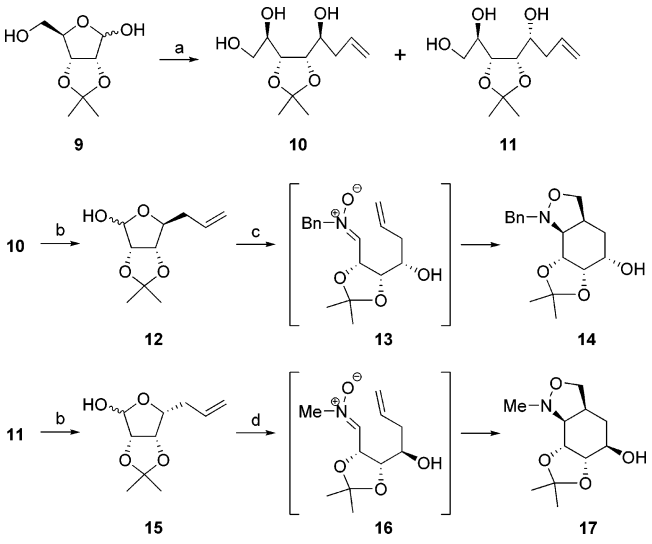
SCHEME 4. Syntheses of Isoxazolidine 14 and 17[a]



[a] Reagents and conditions: (a) allylmagnesium bromide, Et_2O, −78 °C → rt, (**10**:**11** = 17:1), 99%; (b) $NaIO_4$, silica gel, CH_2Cl_2, rt, 100% for **10** and **11**; (c) BnNHOH·HCl, $NaHCO_3$, CH_3CN, reflux, 92%; (d) MeNHOH·HCl, $NaHCO_3$, CH_3CN, reflux, 92%.

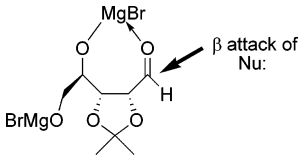


FIGURE 1. Chelation transition model.

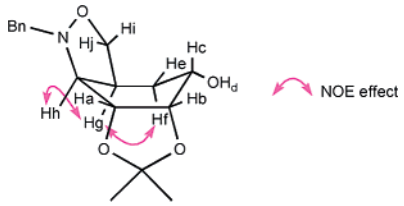
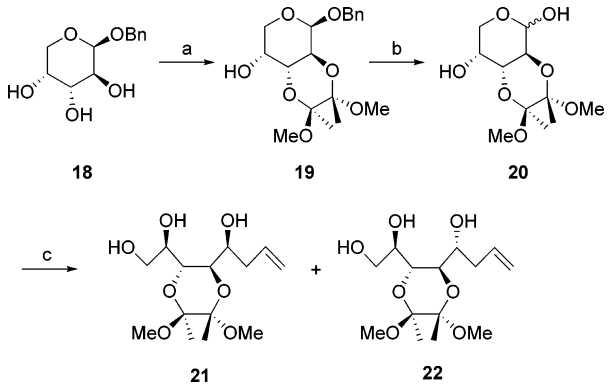


FIGURE 2. Conformation of **14**.

The high selectivity was presumably attributed to the chelation controlled transition model[11] shown in Figure 1. The stereochemistry was confirmed by comparing the ^1H and ^{13}C NMR spectra with the published data.[8] Following the glycol cleavage oxidation procedure developed by our group,[23] lactol **12** was obtained in a quantitative yield. On treatment with BnNHOH, an *exo*-mode of INAC occurred to furnish cyclohexanol **14** in one pot as a single diastereomer. The stereochemistry of the isoxazolidine ring was assigned with the evidence from 1D ^1H NMR, COSY, and NOESY spectra.

The presence of three proton signals in the upfield region (δ 1.0−2.8 ppm) of the ^1H NMR spectrum indicated a cyclohexane ring. The large coupling constant ($J_{c,f}$ = 9.6 Hz) between H_f and H_c suggested a diaxial arrangement. A strong NOE effect between H_h, H_g and a moderate effect between Hg, H_f shown in Figure 2 indicated that the heterocyclic ring was bending upward. The large coupling constant ($J_{g,h}$ = 9.0 Hz) between H_h and H_g demonstrated an eclipsed conformational arrangement. Hence, the cycloadduct **14** should adopt a boatlike conformation.

SCHEME 5. Preparation of Triols 21 and 22[a]



[a] Reagents and conditions: (a) 2,2,3,3-tetramethoxybutane, $CH(OMe)_3$, (±)-CSA, MeOH, reflux, 76%; (b) 10% Pd/C, H_2, EtOH, rt, 100%; (c) allylmagnesium bromide, THF, −78 °C, (**21**:**22** = 1:1), 100%.

Lactol **15**, resulting from glycol cleavage of triol **11**, was reacted with MeNHOH to yield cyclohexanol **17** exclusively through an *exo*-mode of INAC.

INAC of D-Arabinose Derivatives. Benzyl-β-D-arabinopyranoside **18**,[24] prepared from glycosidation of D-arabinose, was protected with a trans-diacetal ring to give acetal **19** (Scheme 5). The benzyl group in **19** was then removed by palladium-catalyzed hydrogenolysis to furnish lactol **20**. Reaction of **20** with an excess of allylmagnesium bromide in THF at −78 °C afforded triols **21** and **22** in equal amounts. The reason for the poor selectivity might be the inherent multichirality of the blocking group, which could offer chelation and complicate the transition state model, making no advance for either side of the nucleophilic attack.

The diastereomers **21** and **22** were separated by flash column chromatography and the individual triol underwent glycol cleavage to give an INAC precursor, lactol **23** (Scheme 6) or **30** (Scheme 7).

INAC reaction of lactol **23** gave three isomers, cis-fused cyclohexanol **25**, trans-fused cyclohexanol **26**, and cycloheptanol **27**, in a ratio of 66:18:16, respectively. The ratio was determined by measuring the integration of the individual *N*-methyl group in the ^1H NMR spectrum of the mixture of cycloadducts. Only isoxazolidine **26** could be isolated pure by flash column chromatography. The remaining alcohols **25** and **27** were converted into silyl ethers **28** and **29**, respectively, for ease chromatographic separation. Desilylation of silyl ether **28** or **29** then afforded pure isoxazolidine **25** or **27**, respectively, for characterization. The assignment of the ring size was based on ^{13}C DEPT experiments. In the ^{13}C DEPT spectra, cyclohexanols **25** and **26**, each having one resonance in the upfield region (δ 25−40 ppm), were assigned to a methylene group showing a distinct difference from cycloheptanol **27**, having two resonances in that region. The structures of **25** and **27** were confirmed by X-ray crystallography and that of **26** could be readily assigned by ^1H NMR analysis. Large coupling constants that fell into the range of axial−axial coupling of H_a with H_c, H_d and those of H_b with H_c, H_e demonstrated the stereochemistry of a trans-fused bicyclic system **26** as shown in Figure 3. The bridged bicyclo[4.2.1] system **27** via a protecting group directed *endo*-

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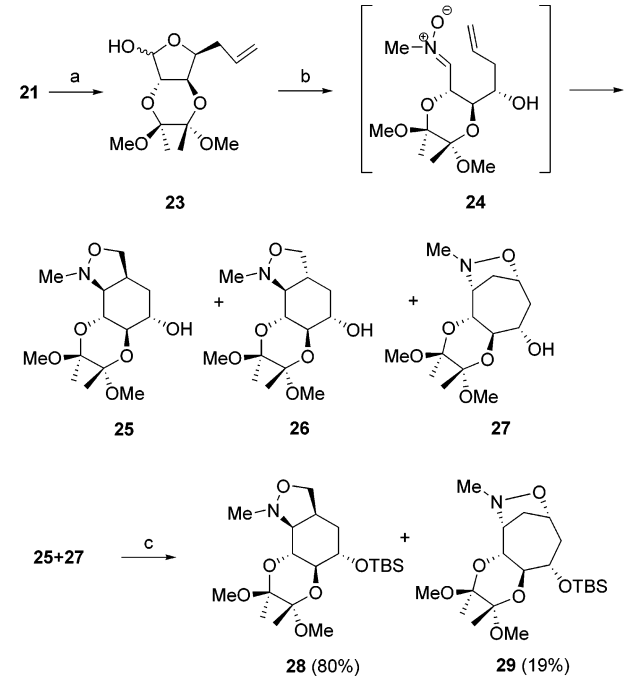
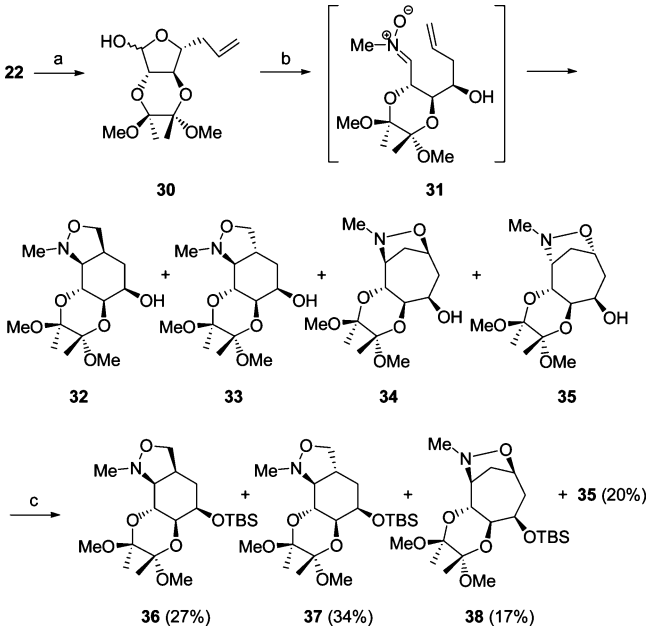
SCHEME 6. INAC of Nitrone 24[a]



[a] Reagents and conditions: (a) $NaIO_4$, silica gel, CH_2Cl_2, rt; (b) MeNHOH·HCl, $NaHCO_3$, CH_3CN, reflux, 98% from **21** (ratio **25**:**26**:**27** = 66:18:16); (c) TBSCl, imidazole, DMF, rt, 99%

SCHEME 7. INAC of Nitrone 31[a]



[a] Reagents and conditions: (a) $NaIO_4$, silica gel, CH_2Cl_2, rt; (b) MeNHOH·HCl, $NaHCO_3$, CH_3CN, reflux, 100% from **22**, (ratio **32**:**33**:**34**:**35** = 27:34:18:21); (c) TBSCl, imidazole, DMF, rt, 98%, 78% conversion.

mode of cyclization was synthesized from an unbranched sugar for the first time.

INAC reaction of lactol **30** gave four cycloadducts, cis-fused cyclohexanol **32**, trans-fused cyclohexanol **33**, along with cycloheptanols **34** and **35** in a ratio of 27:34:18:21, respectively. The ratio was again determined by measuring the integration of the individual *N*-methyl group in the ^{1}H NMR spectrum of

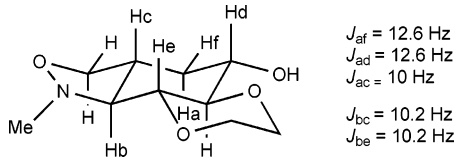


FIGURE 3. Conformation of **26**. The substituents on the trans-acetal ring are omitted for clarity.

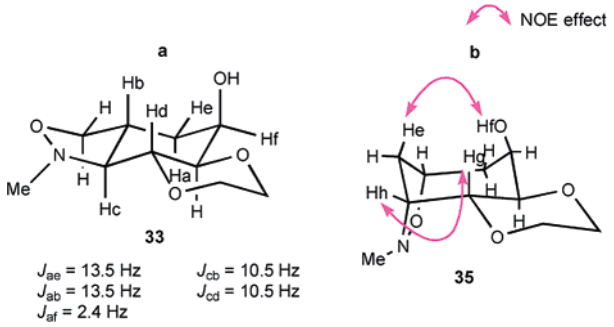


FIGURE 4. Conformation of **33** and **35**. The substituents on the trans-acetal ring are omitted for clarity.

the mixture of cycloadducts. The cycloheptanols **34** and **35** were synthesized in a combined yield of 39%. The four isomers were not separable by flash column chromatography, but using the same method as described above, they were converted into silyl ethers **36**, **37**, and **38** with unreacted **35** recovered. After chromatographic fractionation of the silyl ethers followed by desilylation, individual isoxazolidine **32**, **33**, or **34** could be characterized. The ring size was determined by ^{13}C DEPT experiments as described above. Single crystals of **32** and **34** confirmed their constitution by X-ray crystallography. The axial−axial coupling of H_a with H_b and those of H_c with H_b, H_d indicated the stereochemistry of a trans-fused cycloadduct **33** as illustrated in Figure 4a. The strong NOE effects of H_e with H_f and H_h with H_g in cycloheptanol **35** shown in Figure 4b concluded that the bridgehead was pointing upward.

The purified isoxazolidines **25**−**27** and **32**−**35** were heated individually in a sealed tube to 210 °C in toluene for 24 h and were recovered unchanged. There was no indication of equilibration of the cyclized products.

With a change in the blocking group from isopropylidene in D-ribose to the trans-diacetal ring in D-arabinose, the regio- and stereochemical outcomes of the INAC reactions differ significantly. It is noteworthy that some *endo*-mode of cyclization was induced by the trans-diacetal ring. This was first realized with lactol **23** in which cycloheptanol **27** was obtained in a ratio of 16%. The ratio of *endo*-cyclized products, cycloheptanols, **34** and **35** emerges to 39% for lactol **30**. The next question is on how the blocking group affects the regio- and stereochemistry. Several papers on the theoretical analysis of intermolecular 1,3-dipolar cycloaddition of nitrone and alkene have appeared.[19−21,25] However, there are no reports on the computational studies of the INAC reactions of hept-6-enoses to give hydroxylated

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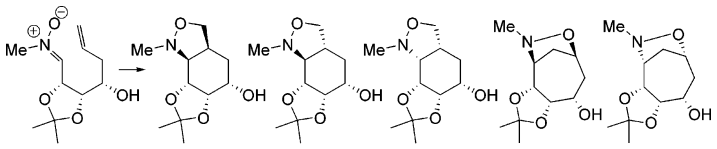
TABLE 1. Theoretical Analysis of INAC of Nitrone 39 from D-Ribose[a]

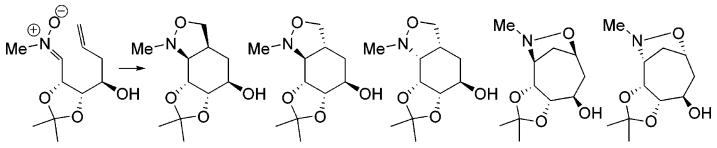


39 40 41 42 43 44

ground state ΔE (ΔG at 80 °C), kcal mol^{-1}	1.34 (0)	4.24 (2.02)	2.75 (3.10)	2.18 (0.92)	0 (0.61)
bond distance in TS, Å[b]	C−C: 2.20 C−O: 2.12	C−C: 2.15 C−O: 2.19	C−C: 2.23 C−O: 2.17	C−C: 2.11 C−O: 2.37	C−C: 2.13 C−O: 2.30
exptl yield,[c] %	92	0	0	0	0
TS ΔE, kcal mol^{-1}	0	4.85	7.77	5.72	4.52
TS ΔG (80 °C), kcal mol^{-1}	0	4.81	7.99	5.82	5.83

[a] B3LYP/6-31G* calculations were performed. Relative energies are shown. [b] The new bonds formed in the INAC reaction. [c] Yield for the *N*-benzyl group **14**.

TABLE 2. Theoretical Analysis of INAC of Nitrone 16[a]



16 17 45 46 47 48

ground state ΔE (ΔG at 80 °C), kcal mol^{-1}	1.56 (0.13)	5.87 (3.07)	4.57 (3.14)	0 (0)	2.30 (0.82)
bond distance in TS, Å[b]	C−C: 2.23 C−O: 2.08	C−C: 2.15 C−O: 2.18	C−C: 2.17 C−O: 2.08	C−C: 2.09 C−O: 2.42	C−C: 2.17 C−O: 2.24
exptl yield, %	92	0	0	0	0
TS ΔE, kcal mol^{-1}	0	4.13	6.40	0.90	5.21
TS ΔG (80 °C), kcal mol^{-1}	0	4.40	7.63	2.69	6.11

[a] B3LYP/6-31G* calculations were performed. Relative energies are shown. [b] The new bonds formed in the INAC reaction

carbocycles. Our present theoretical studies are therefore warranted to determine the transition state energies.

Theoretical Analysis. The TS energies were calculated in the following way. At first, the ground-state structures were calculated with molecular mechanics by using the CONFLEX program for conformational search.[26] Many conformers were obtained and the relatively stable conformers (within 10 kcal mol^{-1} compared to the most stable one) were selected for further analysis. Then the ground states and all the transition states based on the ground-state structures were calculated by B3LYP/6-31G* with a suite of Gaussian 98 programs.[27,28] The obtained TS energies were compared with each other. The obtained structures were similar to previous reports[25,29] and the imaginary frequencies were checked to ensure that the vectors were directed toward the reaction pathway. IRC calculations were performed for the most stable TSs. Only the concerted pathway was calculated since this was reported to be more favorable than the biradical pathway.[25]

The results of nitrone **39** from D-ribose are shown in Table 1. The achiral alkyl group on the nitrogen is usually not crucial for controlling the stereoselectivity in INAC reactions. For simplicity, the benzyl group in **13** was therefore replaced with a methyl moiety in the calculation. Since the reaction was performed in acetonitrile at a boiling range of 80−82 °C, the set of data calculated with single point energy and the Gibbs energy at 80 °C should be considered. The experimental results are consistent with the theoretical analysis since the energy of the TS leading to cyclohexanol **40** is significantly lower than those of the rest of the TSs. Consequently it is not surprising that the cis-fused isoxazolidine **40** was the exclusive product.

For the 4-epimer nitrone **16**, the cis-fused isoxazolidine **17** was synthesized as the only product, which is also in agreement with the theoretical analysis (Table 2). The energy of the TS leading to cyclohexanol **17** is significantly lower than those of the rest of the TSs.

The calculated results for nitrone **24** from D-arabinose in Table 3 suggested that the cis-fused cyclohexanol **25** (ratio 66%) is the major isomer because it had the lowest Gibbs TS energy. The energy differences between the TSs of **25** and **26** and between **25** and **27** were relatively smaller, thus allowing concomitant formation of trans-fused cyclohexanol **26** (ratio 18%) and cycloheptanol **27** (ratio 16%) in low yields. The relatively high TS energy (3.31 kcal mol^{-1}) would not afford an appreciable amount of cycloheptanol **49**. The theoretical analysis is in accord with the experimental results.

The same calculations for nitrone **31** are illustrated in Table 4. Since the energies of the TSs leading to cycloadducts **32**−**35** are similar with a difference not larger than 1.8 kcal mol^{-1}, we would expect the formation of all of them. The amount of cycloheptanols should increase and our experimental results have

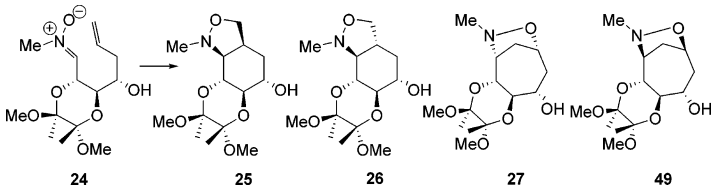
(26) *CONFLEX* Ver 4.0.2, Revision T, Conflex Corp.: Tokyo, Japan, 2000,[26a,b] Although it is well established that the force field approach is useful for the TS search of flexible molecules[26c] and was successfully applied to the 1,3-diplar cyloadddtion,[25e] considering that the CONFLEX does not support the TS MM model and the tricyclic structures investigated in this paper are relatively rigid, TSs were calculated based on the ground state conformers: (a) Goto, H.; Osawa, E. *J. Am. Chem. Soc.* **1989**, *111*, 8950−8951. (b) Goto, H.; Osawa, E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 187−198. (c) Houk, K. N.; Paddon-row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Mets, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108−1117.

(27) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, 37, 785.

(28) Frisch et al. *Gaussian 98*, Revision A.11; Gaussian, Inc.: Pittsburgh, PA, 1998.

(29) Valentin, C. D.; Freccero, M.; Gandolfi, R.; Rastelli, A. *J. Org. Chem.* **2000**, *65*, 6112−6120.

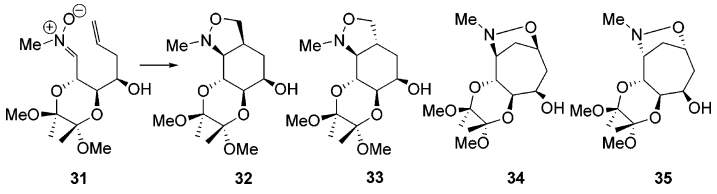
TABLE 3. Theoretical Analysis of INAC of Nitrone 24[a]



ground state ΔE (ΔG at 80 °C), kcal mol^{-1}	0 (0)	0.76 (0.19)	0.12 (0.40)	0.46 (0.91)
bond distance in TS, Å[b]	C−C: 2.21 C−O: 2.15	C−C: 2.15 C−O: 2.18	C−C: 2.19 C−O: 2.23	C−C: 2.13 C−O: 2.31
exptl ratio, %	66	18	16	0
TS ΔE, kcal mol^{-1}	0.08	1.74	0	2.29
TS ΔG (80 °C), kcal mol^{-1}	0	2.72	1.10	3.31

[a] B3LYP/6-31G* calculations were performed. Relative energies are shown. [b] The new bonds formed in the INAC reaction.

TABLE 4. Theoretical Analysis of INAC of Nitrone 31[a]



ground state ΔE (ΔG at 80 °C), kcal mol^{-1}	0.16 (0.05)	0.96 (0.06)	2.29 (2.58)	0 (0)
bond distance in TS, Å[b]	C−C: 2.19 C−O: 2.19	C−C: 2.14 C−O: 2.20	C−C: 2.09 C−O: 2.37	C−C: 2.18 C−O: 2.26
exptl ratio, %	27	34	18	21
TS ΔE, kcal mol^{-1}	0.35	1.55	1.12	0
TS ΔG (80 °C), kcal mol^{-1}	0	1.47	1.75	0.05

[a] B3LYP/6-31G* calculations were performed. Relative energies are shown. [b] The new bonds formed in the INAC reaction.

shown that this is the case. Cycloheptanols **34** and **35** were obtained in a combined yield of 39%.

These calculations also indicate several points. (1) The bridged bicyclo[4.2.1] compounds are equally stable compared with bicyclo[4.3.0] compounds in the ground states, which means that selective *endo*-mode cyclization would be potentially possible by the rational design of the protective group. (2) Stabilization by the intramolecular hydrogen bonding between the free hydroxy group and the oxygen atom of the protective group or nitrone reaches several kilocaloriess per mole, which significantly affects the stability of the conformer in both the ground state and TS. For example, the TS energy of **49** was too high to give the product, whereas a hydrogen bonding between the hydroxy group and nitrone lowered the TS energy of **34** and led to the product. (3) The TS structures of *endo*- and *exo*-cyclizations are very different. In the TS of *exo*-cyclization, the C−C bonds are almost the same length as the C−O bonds. On the contrary, the C−O bonds are much longer than the C−C bonds in the TS of *endo*-cyclization. (4) By comparing the single point energy and the Gibbs free energy with the distribution of the products, the entropy factor would influence the stability of the conformer. It might be considered that one of the main reasons for the deviation from the experimental and theoretical results would be the solvation effect (vide infra).

The conformation of the TSs shown in Figure 5 may provide the rationalization for the effect of the blocking groups on the regioselectivity as well as the diastereoselectivity.

Only the skeleton atom was shown to simplify the figures. For the isopropylidene blocking group of nitrones **39** and **16**,

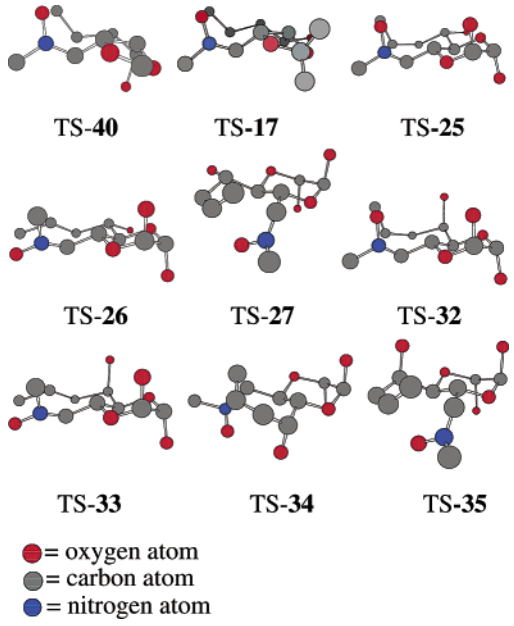


FIGURE 5. TS of **40**, **17**, **25**−**27**, and **32**−**35**.

the TSs leading to the products **40** (TS-40) and **17** (TS-17) respectively adopt a boatlike conformation. The bonding orbitals are therefore aligned to the same plane in space, resulting in better orbital overlap that lowers the TS energy (Figure 6a). In contrast, cyclohexanols **25**, **26**, **32**, and **33** adopt a chairlike conformation, which is imposed by the rigidity of the trans-diacetal blocking group. For a chair conformation, the orienta-

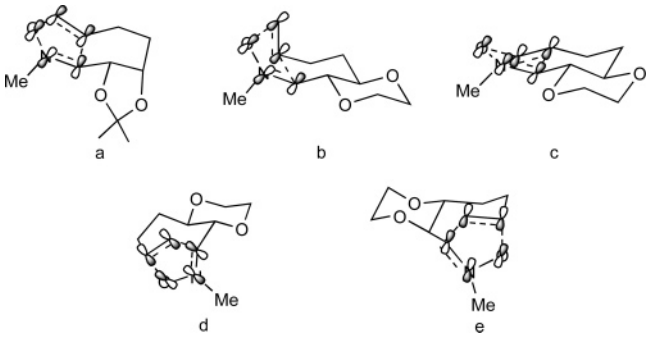
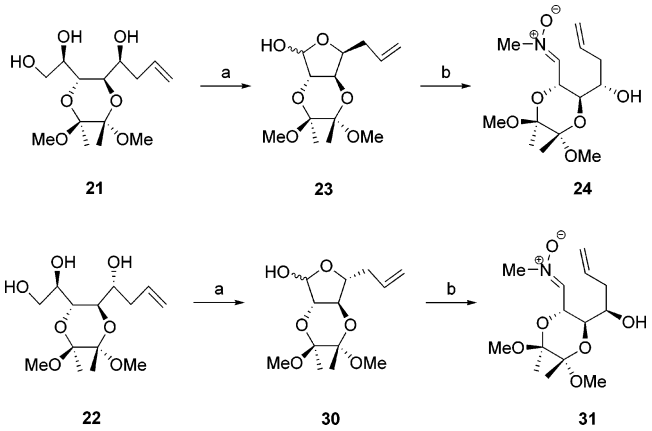


FIGURE 6. Conformation of TS.

SCHEME 8. Preparation of Nitrone 22 and 31[a]



[a] Reagents and conditions: (a) $NaIO_4$, silica gel, CH_2Cl_2, rt; (b) MeNHOH·HCl, $NaHCO_3$, CH_3CN, rt, 100% from **21**, 92% from **22**.

tions of the bonding orbitals are no longer aligned on the same plane as illustrated in Figure 6b,c. The poor overlap of orbitals results in higher TS energies. TS-**32** is further destabilized by the pseudo-1,3-diaxial interaction between the hydroxyl group and the developing isoxazolidine ring. The amount of cyclohexanols from nitrone **31** was therefore the lowest compared to those from nitrones **24**, **39**, and **16**. For the *endo*-cyclized products **27**, **34**, and **35**, the chair conformation of TS allows the orientation of bonding orbitals to be aligned on the same plane (Figure 6d,e). Their TS energies become comparable to those of the *exo*-cyclized ones and they were therefore obtained in considerable amounts.

The cyclohexanol cycloadducts were usually cis-fused as in the case of **25** and **40** resulting from better overlap of bonding orbitals. The unexpected formation of the trans-fused cyclohexanol **33** as the major product was due to the destabilization of the diastereomer **32** by the pseudo-1,3-diaxial interaction between the hydroxyl group and the developing isoxazolidine ring.

Solvent and Temperature Effects. The lactol **23** was allowed to react with MeNHOH at room temperature to afford nitrone **24**, which was isolated and purified for the study of solvent effects. The same operation was performed on lactol **30** to afford nitrone **31** (Scheme 8). The INAC reactions of nitrones **24** and **31** were carried out in toluene, dichloromethane, chloroform, acetonitrile, and 2-propanol at 40 °C and at room temperature. The ratios of the cycloadducts are summarized in Tables 5 (nitrone **24**) and 6 (nitrone **31**).

Lowering the reaction temperature from 40 °C to room temperature exerts no significant effect on the regio- and stereoselectivity, beyond increasing the reaction time. However,

TABLE 5. Solvent and Temperature Effects on INAC of Nitrone 24

entry	solvent	temp, °C	ratio **25**:**26**:**27**	ratio *exo*:*endo*	yield, %	reaction time
1a	CH_3CN[a]	80−82	66:18:16	85:15	98	1 h
2a	CH_3CN	80−82	74:12:14	86:14	100	1 h
3a	toluene	40	78:11:11	89:11	100	24 h
4a	CH_2Cl_2	40	65:17:18	82:18	86	68 h
5a	CH_3CN	40	71:12:17	83:17	100	40 h
6a	$CHCl_3$	40	73:13:14	86:14	99	40 h
7a	2-propanol	40	78:13:9	91:9	89	36 h
8a	toluene	rt	80:10:10	90:10	100	5 d
9a	CH_2Cl_2	rt	62:17:21	79:21	98	13 d
10a	CH_3CN	rt	73:13:14	86:14	97	11 d
11a	$CHCl_3$	rt	74:12:14	86:14	99	10 d
12a	2-propanol	rt	79:13:8	92:8	86	6 d

[a] INAC reaction performed without isolation of the nitrone.

TABLE 6. Solvent and Temperature Effects on INAC of Nitrone 31

entry	solvent	temp, °C	ratio **32**:**33**:**34**:**35**	ratio *exo*:*endo*	yield, %	reaction time
1b	CH_3CN[a]	80−82	27:35:17:21	62:38	99	1 h
2b	CH_3CN	80−82	25:39:15:21	64:36	98	1 h
3b	toluene	40	35:35:8:22	70:30	100	72 h
4b	CH_2Cl_2	40	21:37:21:21	58:42	99	72 h
5b	CH_3CN	40	26:35:18:21	61:39	100	72 h
6b	$CHCl_3$	40	26:43:14:17	68:32	100	72 h
7b	2-propanol	40	20:50:7:23	70:30	99	48 h
8b	toluene	rt	35:36:8:21	71:29	98	23 d
9b	CH_2Cl_2	rt	20:37:21:22	57:43	100	17 d
10b	CH_3CN	rt	24:38:16:22	62:38	92	14 d
11b	$CHCl_3$	rt	23:43:16:18	66:34	94	22 d
12b	2-propanol	rt	19:51:6:24	70:30	100	14 d

[a] INAC reaction performed without isolation of the nitrone.

an interesting feature is an increment of the *endo*-cyclized product (cycloheptanol) of around 10% when the solvent is switched from 2-propanol (entries 12a and 12b) or toluene (entries 8a and 8b) to CH_2Cl_2 (entries 9a and 9b). The stereochemistry of the cycloadducts is also modified by different solvents. For nitrone **24**, the ratio of cis-fused cyclohexanol **25** to trans-fused cyclohexanol **26** is 3.6:1 in CH_2Cl_2 (entry 9a), which increased to 8:1 in toluene (entry 8a); whereas with nitrone **31**, the ratio of cis-fused cyclohexanol **32** to trans-fused cyclohexanol **33** (**32**:**33** = 1:1) in toluene (entry 8b) decreased to 1:2.7 in 2-propanol (entry 12b).

Conclusion

From the experimental results and theoretical studies, the regio- and stereochemical outcomes of the INAC reactions of hep-6-enoses derived from D-ribose and D-arabinose derivatives were significantly affected by the blocking group and the stereochemistry of the substituents. The stereochemical outcomes of these reactions were rationalized on the basis of transition state energies obtained by computation. The nitrones **13** and **16** containing a 2,3-*O*-isopropylidene ring afforded *exo*-cyclized cis-fused isoxazolidines (cyclohexanol) **13** and **17** exclusively. The *endo*-cyclization mode was enhanced when the TS is restricted to adopt a chair conformation imposed by the blocking group. Hence, unbranched sugar nitrones **24** and **31**, both containing a 2,3-trans-acetal ring, afforded appreciable amounts of *endo*-cyclized bicyclo[4.2.1] isoxazolidines (cycloheptanols) for the first time. For the transformation of nitrone **31** into cis-fused isoxazolidine **32**, the formation of **32** was

decreased, attributable to 1,3-diaxial steric interaction between OH-4 and the developing C−C bond. The intramolecular hydrogen bonding between the free hydroxy group and the oxygen atom of the protective group or nitrone significantly increases the stability of the conformer both in the ground state and TS, which was shown in the formation of cycloheptanol **34** but not cycloheptanol **49**. Moreover, the TS structures of *endo*- and *exo*-cyclizations are very different. In the TS of *exo*-cyclization, the lengths of the C−C bonds and C−O bonds are almost the same. On the contrary, the C−O bonds are much longer than the C−C bonds in the TS of *endo*-cyclization. The present INAC showed trivial temperature, but significant solvent dependence. For lactols **23** and **30**, performing the INAC in 2-propanol gave the best yields of fused isoxazolidines (cyclohexanols) whereas that in dichloromethane afforded the best yields of bridged isoxazolidines (cycloheptanols).

In summary, we describe a novel blocking group strategy in controlling the mode of cyclization of INAC reactions. With 2,3-trans-acetal as the protecting group, cycloheptanols **27**, **34**, and **35** were synthesized from unbranched hept-6-enoses for the first time. The regio- and stereoselectivity can be further modified by an appropriate solvent. Following this discovery, other protecting groups are under active investigation with an aim to develop INAC reactions of unbranched sugar derivatives into a general synthetic avenue for the construction of enantiopure polyhydroxylated aminocycloheptanols.

Experimental Section

1,2,3-Trideoxy-5,6-*O*-isopropylidene-D-*allo*-oct-1-enitol (10). To a stirred solution of 2,3-*O*-isopropylidene-D-ribofuranose (**9**) (119 mg, 0.626 mmol) in dry Et_2O (25 mL) was added a 1 M Et_2O solution of allylmagnesium bromide (5.0 mL, 5.01 mmol) dropwise at −78 °C under N_2. After the addition, the mixture was allowed to rise to room temperature and stirred for another 12 h. The mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (hexane:EtOAc, 3:2) to afford first alkene **10** (135 mg, 93%) and second its 4-epimer **11** (8.0 mg, 6%) as colorless oils. Data for **10**: $[\alpha]^{20}_D$ +17.6 (*c* 1.14, $CHCl_3$); R_f 0.11 ($CHCl_3$:MeOH, 20:1); IR (thin film) 3304, 2981, 2935, 1642. 1371, 1221, 1067, 872 cm^{-1}; ^1H NMR δ 1.33 (3H, s), 1.38 (3H, s), 2.22 (1H, dt, J = 16.5, 8.4 Hz), 2.54 (1H, s), 2.64 (1H, dddd, J = 14.4, 6.3, 3, 1.5 Hz), 3.36 (1H, d, J = 2.4 Hz), 3.70−3.72 (1H, m), 3.85−3.88 (3H, m), 3.02 (1H, dd, J = 9.3, 5.4 Hz), 4.13 (1H, dd, J = 9.3, 5.4 Hz), 4.20 (1H, s), 5.18 (1H, s), 5.23 (1H, d, J = 3.9 Hz), 5.82−5.93 (1H, m); ^{13}C NMR δ 25.8, 28.4, 38.9, 64.8, 68.9, 69.8, 78.1, 80.0, 109.2, 119.5, 134.3; MS (FAB) *m*/*z* (rel intensity) 232 ($[M]^-$, 11), ($[M - H]^-$, 100); HRMS (FAB) calcd for $C_{11}H_{20}O_5$ $[M - H]^-$ 231.1238, found 231.123154.

1,2,3-Trideoxy-5,6-*O*-isopropylidene-D-*altro*-oct-1-enitol (11). $[\alpha]^{20}_D$ +11.6 (*c* 0.82, $CHCl_3$) {lit.[8] $[\alpha]^{20}_D$ +9.6 (*c* 1.66, $CHCl_3$}; R_f 0.11 ($CHCl_3$:MeOH, 20:1); IR (thin film) 3392, 2936, 1642, 1382, 1217, 1057, 873 cm^{-1}; ^1H NMR δ 1.35 (3H, s), 1.47 (3H, s), 2.07−2.11 (1H, m), 2.41−2.47 (3H, m), 3.47 (1H, br s), 3.64−3.68 (1H, m), 3.84−3.89 (1H, m), 3.97 (1H, d, J = 9 Hz), 3.98 (1H, d, J = 9.6 Hz), 4.05−4.14 (2H, m), 5.13−5.20 (2H, m), 5.86 (1H, ddt, J = 17.4, 10.2, 7.2 Hz); ^{13}C NMR δ 25.6, 27.9, 40.3, 64.9, 68.5, 69.9, 77.5, 78.6, 108.6, 118.5, 134.9; MS (FAB) *m*/*z* (rel intensity) 233 ($[MH]^+$, 100), 175 (56), 93 (47); HRMS (FAB) calcd for $C_{11}H_{20}O_5$ $[MH]^+$ 233.1384, found 233.139379.

5,6,7-Trideoxy-2,3-*O*-isopropylidene-α,*β*-L-*ribo*-hept-6-enofuranose (12). $NaIO_4$ (228 mg, 1.07 mmol) was dissolved in a minimum amount of hot water (∼80 °C, 0.5 mL) followed by the addition of silica gel (230−400 mesh, 1 g) with vigorous swirling and shaking. The mixture was suspended in CH_2Cl_2 (5 mL) and then a solution of alkene **10** (98.9 mg, 0.426 mmol) in CH_2Cl_2 (3 mL) was added. After vigorous stirring at room temperature for 1 h, the mixture was filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (hexane:EtOAc, 2:1) to give lactol **12** (85.0 mg, 100%) as a colorless oil: $[\alpha]^{20}_D$ +6.77 (*c* 3.52, $CHCl_3$) {lit.[10] $[\alpha]^{24}_D$ −3.9 (*c* 0.36, $CHCl_3$)}; R_f 0.41 (hexane:Et_2O, 1:1); IR (thin film) 3431, 2942, 1375, 1211, 1074, 870 cm^{-1}; ^1H NMR (mixture of α and *β* isomer with ratio α:*β* = 1:11) δ 1.32 (3.0H, s), 1.38 (0.27H, s), 1.48 (3.0H, s), 1.57 (0.27H, s), 2.26−2.53 (2.19H, m), 2.84 (1.0H, d, J = 2.7 Hz), 3.89 (0.09H, d, J = 9.3 Hz), 4.14 (0.09H, td, J = 6.9, 3 Hz), 4.25 (1.0H, t, J = 7.5 Hz), 4.49 (0.09H, dd, J = 6.6, 2.4 Hz), 4.61−4.66 (2.09H, m), 5.10−5.16 (2.19H, m), 5.29 (0.09H, dd, J = 9.1, 4.2 Hz), 5.45 (1.0H, d, J = 2.4 Hz), 5.74−5.88 (1.09H, m); ^{13}C NMR δ 25.3, 26.6, 26.8, 37.5, 40.3, 79.8, 80.2, 83.4, 84.0, 86.4, 86.7, 96.2, 103.4, 112.7, 118.1, 118.6, 133.5, 134.5; MS (CI) *m*/*z* (rel intensity) 201 ($[MH]^+$, 11), 183 (100), 125 (40); HRMS (CI) calcd for $C_{10}H_{16}O_4$ $[MH]^+$ 201.1121, found 201.112458.

Isoxazolidine 14. *N*-Benzylhydroxylamine hydrochloride (620 mg, 3.88 mmol) and $NaHCO_3$ (544 mg, 6.47 mmol) were added to a solution of lactol **12** (259 mg, 1.30 mmol) in CH_3CN (15 mL). The reaction mixture was stirred at room temperature for 48 h until the disappearance of the starting material as shown on TLC. The mixture was then heated under reflux for 16 h. After cooling, the mixture was partitioned between CH_2Cl_2 (30 mL) and water (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (hexane:EtOAc, 1:1) gave isoxazolidine **14** (362 mg, 92%) as a colorless oil: $[\alpha]^{20}_D$ −98.8 (*c* 0.74, $CHCl_3$); R_f 0.28 (hexane:EtOAc, 1:2); IR (thin film) 3457, 2932, 1377, 1210, 1057, 866 cm^{-1}; ^1H NMR δ 1.33−1.40 (4H, m), 1.47 (3H, s), 2.07 (1H, ddd, J = 13.8, 9.6, 7.5 Hz), 2.28 (1H, d, J = 6.3 Hz), 2.99−3.09 (1H, m), 3.22 (1H, dd, J = 8.7, 3.6 Hz), 3.58 (1H, dd, J = 8.4, 5.7 Hz), 3.95 (1H, d, J = 13.8 Hz), 4.01 (1H, d, J = 13.8 Hz), 4.13−4.29 (4H, m), 7.25−7.40 (5H, m); ^1H NMR (C_6D_6) δ 1.02 (1H, ddd, J = 13.5, 4.8, 2.7 Hz), 1.13 (3H, s), 1.32 (3H, s), 1.80 (1H, ddd, J = 13.5, 9.6, 7.5 Hz), 2.20 (1H, d, J = 6.3 Hz), 2.68 (1H, hextet, J = 7.8 Hz), 3.12 (1H, dd, J = 9, 4.2 Hz), 3.23 (1H, dd, J = 8.4, 6 Hz), 3.73 (1H, t, J = 8.1 Hz), 3.75 (1H, d, J = 14.1 Hz), 3.81 (1H, d, J = 14.1 Hz), 3.99 (1H, dd, J = 7.5, 4.2 Hz), 4.08−4.12 (2H, m), 7.05−7.19 (11H, m), 7.36−7.38 (2H, m); ^{13}C NMR δ 24.5, 26.6, 29.1, 38.2, 61.5, 64.9, 66.2, 72.5, 74.9, 75.1, 108.8, 127.7, 128.7, 129.1, 137.6; MS (FAB) *m*/*z* (rel intensity) 306 ($[MH]^+$, 47), 185 (100), 93 (86); HRMS (FAB) calcd for $C_{17}H_{23}O_4N$ $[MH]^+$ 306.1700, found 306.170960. Anal. Calcd for $C_{17}H_{23}O_4N$: C, 66.86; H, 7.59; N, 4.58. Found: C, 67.36; H, 7.71, N, 4.57.

5,6,7-Trideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hept-6-enofuranose (15). Following the glycol cleavage procedure for alkene **10**, triol **11** (33.1 mg, 0.165 mmol) was converted into lactol **15** (34.9 mg, 100%) as a colorless oil. $[\alpha]^{20}_D$ +15.8 (*c* 3.00, $CHCl_3$) {lit.[8] $[\alpha]^{20}_D$ +15.9 (*c* 1.48, $CHCl_3$)}; R_f 0.58 (hexane:EtOAc, 1:1); IR (thin film) 3423, 2982, 2941, 1374, 1210, 1064, 1013, 917, 871 cm^{-1}; ^1H NMR δ 1.33 (3H, s), 1.47 (3H, s), 2.45−2.50 (2H, m), 2.56 (1H, br s), 4.19 (1H, td, J = 6.9, 3.3 Hz), 4.61 (1H, d, J = 6 Hz), 4.69 (1H, dd, J = 5.7, 3.6 Hz), 5.08−5.12 (1H, m), 5.18 (1H, dq, J = 17.1, 1.5 Hz), 5.36 (1H, d, J = 2.4 Hz), 5.88 (1H, ddt, J = 17.1, 10.2, 6.9 Hz); ^{13}C NMR δ 25.3, 26.5, 33.4, 80.0, 80.6, 86.0, 101.3, 112.8, 117.6, 134.8; MS (CI) *m*/*z* (rel intensity) 201 ($[MH]^+$, 99), 183 (100), 177 (27), 159 (40), 125 (23), 91 (57); HRMS (CI) calcd for $C_{10}H_{16}O_4$ $[MH]^+$ 201.1121, found 201.112621.

Isoxazolidine 17. *N*-Methylhydroxylamine hydrochloride (138 mg, 1.65 mmol) and $NaHCO_3$ (139 mg, 1.65 mmol) were added to a solution of lactol **15** (33.1 mg, 0.165 mmol) in CH_3CN (6 mL). The reaction mixture was stirred at room temperature for 24 h until the disappearance of the starting material as shown on TLC.

$NaHCO_3$ (27.8 mg, 0.331 mmol) was added to acquire a basic medium and the mixture was then heated under reflux for 8 h. After cooling, the mixture was partitioned between EtOAc (10 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography ($CHCl_3$:MeOH, 50:1) gave isoxazolidine **17** (34.9 mg, 92%) as a colorless oil: $[\alpha]^{20}_D$ −113.2 (*c* 1.63, $CHCl_3$) {lit.[8] $[\alpha]^{20}_D$ −115.6 (*c* 1.45, $CHCl_3$)}; R_f 0.20 (EtOAc); IR (thin film) 3418, 3987, 2937, 2880, 1679, 1457, 1382, 1215, 1060, 862 cm^{-1}; ^1H NMR δ 1.34 (3H, s), 1.46 (3H, s), 1.59 (1H, ddd, J = 14.1, 6.3, 3.6 Hz), 2.01 (1H, ddd, J = 14.1, 7.5, 2.7 Hz), 2.74 (3H, s), 2.91−2.95 (2H, m), 3.73−3.77 (2H, m), 4.18−4.24 (2H, m), 4.31 (1H, dd, J = 7.2, 2.4 Hz); ^{13}C NMR δ 24.6, 27.2, 29.2, 37.7, 44.2, 68.2, 69.0, 72.7, 73.6, 77.5, 108.6; MS (ESI) *m*/*z* (rel intensity) 230 ($[MH]^+$, 100), 185 (2); HRMS (ESI) calcd for $C_{11}H_{19}O_4N$ $[MH]^+$ 230.1387, found 230.138771.

Benzyl-2,3-*O*-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-*β*-D-arabinopyranoside (19). To a suspension of benzyl-*β*-D-arabinopyranoside **18** (501 mg, 2.09 mmol) in methanol (25 mL) were added 2,2,3,3-tetramethoxybutane (483 mg, 2.71 mmol), trimethylorthoformate (0.91 mL, 8.34 mmol), and (±)-10-camphorsulfonic acid (48.4 mg, 10 mol %) and the mixture was heated under reflux for 12 h. Powered $NaHCO_3$ (0.1 g) was then added to the cooled reaction mixture, which was stirred for 5 h. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc and the solution was washed with saturated $NaHCO_3$ solution. The organic layer was dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash chromatography (hexane:EtOAc, 1:1) to afford glycoside **19** (558 mg, 76%) as a white solid. Recrystallization from EtOAc−hexane gave white crystals: mp 144−145 °C; $[\alpha]^{20}_D$ −3.94 (*c* 1.27, $CHCl_3$); R_f 0.33 (hexane:EtOAc, 1:1); IR (thin film) 3465, 2938, 1132, 1057, 884 cm^{-1}; ^1H NMR δ 1.31−1.33 (6H, 2s), 2.59 (1H, s), 3.22 (3H, s), 3.26 (3H, s), 3.71 (1H, dd, J = 12.6, 1.5 Hz), 3.81 (1H, d, J = 12.6 Hz), 3.93 (1H, s), 4.13 (1H, dd, J = 10.5, 2.7 Hz), 4.19 (1H, dd, J = 10.5, 3.3 Hz), 4.67 (1H, d, J = 12.3 Hz), 4.75 (1H, d, J = 12.6 Hz), 4.95 (1H, d, J = 3 Hz), 7.28−7.42 (5H, m); ^{13}C NMR δ 18.2, 48.3, 48.4, 63.4, 65.6, 66.3, 68.4, 69.8, 97.3, 100.6, 100.7, 128.1, 128.5, 128.8, 138.0; MS (FAB) *m*/*z* (rel intensity) 377 ($[M + Na]^+$, 27), 323 ($[M - OCH_3]^+$, 26), 101 (60), 91 (100); HRMS (FAB) calcd for $C_{18}H_{26}O_7$ $[M + Na]^+$ 377.1571, found 377.157871.

***O*-[(2*S*,3*S*)-2,3-Dimethoxybutan-2,3-dioxy]-α,*β*-D-arabinose (20).** To a solution of glycoside **19** (4.17 g, 11.8 mmol) in EtOH (80 mL) was added 10% Pd-on-charcoal (626 mg, 5% mol) and the mixture was stirred under an atmosphere of H_2 (balloon). After being stirred at room temperature under H_2 for 12 h, the mixture was filtered and the filtrate was concentrated. Flash chromatography (hexane:EtOAc, 1:3) of the residue gave lactol **20** (3.11 g, 100%) as a white solid: mp 189−190 °C; $[\alpha]^{20}_D$ +92.7 (*c* 2.69, MeOH); R_f 0.30 (EtOAc); IR (thin film) 3435, 2947, 1379, 1133, 1060, 1001 cm^{-1}; ^1H NMR (mixture of α and *β* isomer with ratio α:*β* = 1:1.3) δ 1.31−1.33 (10.8H, m), 2.59 (1.0H, br s), 2.72 (0.8H, br s), 3.20 (1.0H, br s), 3.25−3.29 (10.8H, m), 3.60−3.64 (1.6H, m), 3.72−4.20 (8.2H, m), 4.66 (0.8H, t, J = 6.3 Hz), 5.30 (1.0H, s); ^{13}C NMR δ 17.9, 18.0, 48.3, 48.3, 63.3, 65.6, 65.8, 67.5, 67.8, 68.3, 68.7, 70.2, 92.1, 95.9, 100.1, 100.5, 100.5; MS (FAB) *m*/*z* (rel intensity) 233 ($[M - OCH_3]^+$, 37), 185 (100), 93 (93); HRMS (FAB) calcd for $C_{11}H_{20}O_7$ $[M - OCH_3]^+$ 233.1020, found 233.102450.

1,2,3-Trideoxy-5,6-*O*-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-D-*gluco*-oct-1-enitol (21) and 1,2,3-Trideoxy-5,6-*O*-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-D-*manno*-oct-1-enitol (22). A 1 M THF solution of allylmagnesium bromide (44.0 mL, 44.0 mmol) was added dropwise to a stirred solution of lactol **20** (2.90 g, 11.0 mmol) in THF (200 mL) at −78 °C under N_2 over 30 min. After being stirred at −78°C for another 1 h, the mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography ($CHCl_3$:EtOAc, 1:4) to afford first triol **22** (1.68 g, 50%) and second triol **21** (1.68 g, 50%) as colorless oils. Data for **21**: $[\alpha]^{20}_D$ +148.0 (*c* 1.7, $CHCl_3$); R_f 0.24 ($CHCl_3$:EtOAc, 1:3); IR (thin film) 3385, 2946, 1379, 1130, 1038 cm^{-1}; ^1H NMR δ 1.26−1.28 (6H, 2s), 2.32−2.51 (2H, 1dt, J = 14.1, 6.6 Hz, 1dt, J = 14.1, 7.2 Hz), 2.83−2.95 (2H, m), 3.23−3.25 (6H, 2s), 3.59 (1H, d, J = 5.7 Hz), 3.67−3.78 (4H, m), 3.91 (1H, br s), 4.00 (1H, dd, J = 9.9, 6 Hz), 5.08−5.16 (2H, m), 5.84 (1H, ddt, J = 17.4, 10.2, 7.2 Hz); ^{13}C NMRδ17.8, 17.9, 37.9, 48.5, 48.5, 63.8, 69.7, 70.5, 71.5, 72.2, 99.0, 99.2, 118.0, 135.5; MS (FAB) *m*/*z* (rel intensity) 329 ($[M + Na]^+$, 100), 243 (45), 115 (55), 101 (33); HRMS (FAB) calcd for $C_{14}H_{26}O_7$ $[M + Na]^+$ 329.1571, found 329.157304.

Data for **22**: $[\alpha]^{20}_D$ +148.7 (*c* 1.43, $CHCl_3$); R_f 0.33 ($CHCl_3$:EtOAc, 1:3); IR (thin film) 3381, 2947, 1378, 1129, 1038 cm^{-1}; ^1H NMR δ 1.27−1.28 (6H, 2s), 2.15 (1H, dt, J = 14.4, 9 Hz), 2.49 (1H, br s), 2.81 (1H, dddd, J = 14.1, 5.7, 2.7, 1.2 Hz), 3.14−3.15 (1H, m), 3.26−3.27 (6H, 2s), 3.55 (1H, dd, J = 9.8, 8.1 Hz), 3.71−3.91 (5H, m), 4.46 (1H, br s), 5.18−5.22 (2H, m), 5.84 (1H, dddd, J = 17.7, 9.3, 8.4, 6 Hz); ^{13}C NMR δ 17.8, 17.8, 37.8, 48.6, 63.7, 70.4, 70.7, 73.8, 98.8, 99.1, 119.7, 134.9; MS (FAB) *m*/*z* (rel intensity) 329 ($[M + Na]^+$, 100), 115 (92), 101 (70), 57 (69), 43 (70); HRMS (FAB) calcd for $C_{14}H_{26}O_7$ $[M + Na]^+$ 329.1571, found 329.157350.

5,6,7-Trideoxy-2,3-*O*-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-α,*β*-L-*xylo*-hept-6-eneofuranose 23. Following the glycol cleavage procedure for alkene **10**, triol **21** (811 mg, 2.65 mmol) was converted into lactol **23** (723 mg) as a colorless oil. It was used in the next step without characterization.

Isoxazolidines 25, 26, and 27. *N*-Methylhydroxylamine hydrochloride (660 mg, 7.91 mmol) and $NaHCO_3$ (1.11 g, 13.2 mmol) were added to a solution of lactol **23** (723 mg) in CH_3CN (80 mL). The reaction mixture was stirred at room temperature for 30 min until the disappearance of the starting material as shown on TLC. The mixture was then heated under reflux for 1 h. After being cooled, the mixture was partitioned between EtOAc (100 mL) and water (60 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography ($CHCl_3$:MeOH, 30:1) gave a mixture of isoxazolidines **25**, **26**, and **27** (783 mg, 98% from **21**) as a colorless oil. Flash chromatography (EtOAc:hexane, 2:1) afforded first a mixture of **25** and **27** (0.643 g, 80%) as a colorless oil and second isoxazolidine **26** (0.134 g, 17%) as a white solid.

Data for **26**: mp 174−175 °C; $[\alpha]^{20}_D$ +159.6 (*c* 0.40, $CHCl_3$); R_f 0.14 (EtOAc); IR (thin film) 3419, 2950, 1134, 1034, 974, 868 cm^{-1}; ^1H NMR (C_6D_6) δ 1.08 (1H, td, J = 12.6, 10.8 Hz), 1.27 (3H, s), 1.33 (3H, s), 1.60 (1H, dt, J = 12.3, 3.6 Hz), 1.98−2.09 (1H, m), 2.13−2.16 (1H, br d, J = 9.6), 2.21 (1H, t, J = 10.5 Hz), 2.94 (3H, s), 3.09−3.10 (6H, 2s), 3.25 (1H, dd, J = 10.2, 6.0 Hz), 3.47−3.64 (3H, m), 3.82 (1H, t, J = 9.3 Hz); ^1H NMR (C_6D_6−D_2O) δ 1.07 (1H, td, J = 12.6, 10.5 Hz), 1.27 (3H, s), 1.32 (3H, s), 1.59 (1H, dt, J = 12.9, 4.8 Hz), 2.02−2.12 (1H, m), 2.21 (1H, t, J = 10.2 Hz), 2.94 (3H, s), 3.09−3.10 (6H, 2s), 3.24 (1H, dd, J = 10.5, 6.3 Hz), 3.50 (1H, td, J = 9.3, 4.8 Hz), 3.58 (1H, d, J = 6.6 Hz), 3.61 (1H, t, J = 9.3 Hz), 3.82 (1H, t, J = 9.3 Hz); ^{13}C NMR δ 18.1, 18.1, 31.1, 44.8, 47.5, 48.4, 48.5, 69.2, 70.4, 70.7, 72.0, 75.7, 99.7, 100.2; ^{13}C DEPT135 NMR δ 18.1 (+ve), 18.1 (+ve), 31.1 (−ve), 44.8 (+ve), 47.5 (+ve), 48.4 (+ve), 48.5 (+ve), 69.2 (−ve), 70.4 (+ve), 70.7 (+ve), 72.0 (+ve), 75.7 (+ve); MS (FAB) *m*/*z* (rel intensity) 304 ($[MH]^+$, 65), 303 ($[M]^+$, 52), 272 ($[M - OCH_3]^+$, 16), 154 (57), 83 (56), 69 (90), 57 (100); HRMS (FAB) calcd for $C_{14}H_{25}O_6N$ $[MH]^+$ 304.1755, found 304.175464.

Anal. Calcd for $C_{14}H_{25}O_6N$: C, 55.43; H, 8.31; N, 4.62. Found: C, 55.04; H, 8.42, N, 4.43.

Silyl Ethers 28 and 29. A solution of a mixture of isoxazolidines **25** and **27** (643 mg, 2.12 mmol), imidazole (721 mg, 10.6 mmol), and TBSCl (798 mg, 5.30 mmol) in dry DMF (4 mL) was stirred at room temperature for 24 h. The mixture was quenched with saturated $NaHCO_3$ solution and the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (hexane:Et_2O, 1:2) to afford first silyl ether **28** (708 mg, 80%) and second silyl ether **29** (172 mg, 19%) as white solids. Data for **28**: mp 99−100 °C; $[\alpha]^{20}_D$ +103.8 (*c* 2.67, $CHCl_3$); R_f 0.67 (hexane:EtOAc, 1:2); IR (thin film) 2952, 2857, 1463, 1373, 1252, 1129, 1037, 836 cm^{-1}; ^1H NMR δ 0.05 (3H, s), 0.09 (3H, s), 0.87 (9H, s), 1.28−1.29 (6H, 2s), 1.51 (1H, dt, J = 14.1, 4.8 Hz), 1.88 (1H, ddd, J = 14.7, 9.6, 5.4 Hz), 2.75 (3H, s), 2.78 (1H, t, J = 8.4 Hz), 2.97−3.06 (1H, m), 3.28 (6H, s), 3.38 (1H, t, J = 7.8 Hz), 3.55 (1H, dd, J = 11.4, 6.3 Hz), 3.64 (1H, dd, J = 11.4, 8.4 Hz), 3.92 (1H, q, J = 5.1 Hz), 4.14 (1H, t, J = 8.4 Hz); ^{13}C NMR δ −4.4, −4.2, 18.1, 18.2, 18.4, 26.2, 33.1, 38.4, 45.7, 48.3, 48.5, 69.2, 69.5, 70.1, 71.3, 75.0, 99.4; MS (EI) *m*/*z* (rel intensity) 418 ($[MH]^+$, 12), 417 ($[M]^+$, 40), 386 ($[M - OCH_3]^+$, 17), 286 ($[M - OTBS]^+$, 16), 85 (57), 75 (98), 57 (99), 43 (100); HRMS (EI) calcd for $C_{20}H_{39}O_6NSi$ $[M]^+$ 417.2541, found 417.253508.

Data for **29**: mp 53−54 °C $[\alpha]^{20}_D$ +132.3 (*c* 2.65, $CHCl_3$); R_f 0.60 (hexane:EtOAc, 1:2); IR (thin film) 2950, 1465, 1374, 1251, 1127, 1036, 842, 777 cm^{-1}; ^1H NMR (C_6D_6) δ 0.13 (3H, s), 0.22 (3H, s), 1.01 (9H, s), 1.13 (1H, d, J = 12.9 Hz), 1.36 (3H, s), 1.40 (3H, s), 1.79 (1H, ddd, J = 14.7, 6.9, 4.2 Hz), 1.85−1.98 (1H, m), 2.39 (3H, s), 2.92 (1H, dd, J = 7.5, 2.4 Hz), 3.10 (3H, s), 3.13 (3H, s), 3.36 (1H, dd, J = 9, 2.7 Hz), 3.65 (1H, td, J = 9.3, 7.2 Hz), 4.12 (1H, dd, J = 8.7, 2.4 Hz), 4.29 (1H, t, J = 9.6 Hz); ^{13}C NMR δ −4.8, −3.9, 17.8, 18.6, 26.2, 31.0, 42.3, 46.9, 48.2, 67.4, 68.6, 71.0, 72.9, 74.2, 98.8, 99.6; MS (FAB) *m*/*z* (rel intensity) 418 ($[MH]^+$, 23), 417 ($[M]^+$, 10), 386 ($[M - OCH_3]^+$, 46), 286 ($[M - OTBS]^+$, 12), 95 (60), 73 (75), 69 (83), 55 (100), 43 (66); HRMS (FAB) calcd for $C_{20}H_{39}O_6NSi$ $[MH]^+$ 418.2619, found 418.262570.

Isoxazolidine 25. To a solution of silyl ether **28** (29.0 mg, 0.0694 mmol) in THF (3 mL) was added a 1 M THF solution of TBAF (0.14 mL, 0.139 mmol). The reaction mixture was stirred at room temperature for 12 h and the solvent was removed under reduced pressure. Flash chromatography of the residue ($CHCl_3$:MeOH, 30:1) afforded isoxazolidine **25** (21.0 mg, 100%) as a white solid: mp 141−142 °C; $[\alpha]^{20}_D$ +144.8 (*c* 0.93, $CHCl_3$); R_f 0.15 (EtOAc); IR (thin film) 3445, 2950, 1123, 1035 cm^{-1}; ^1H NMR δ 1.32 (6H, s), 1.66 (1H, ddd, J = 15.9, 9.6, 6 Hz), 2.11 (1H, dt, J = 14.4, 4.8 Hz), 2.48 (1H, br s), 2.67 (3H, s), 2.99 (1H, t, J = 8.4 Hz), 3.08−3.17 (1H, m), 3.29−3.30 (6H, 2s), 3.44 (1H, t, J = 8.4 Hz), 3.46 (1H, d, J = 9.0 Hz), 3.59 (1H, t, J = 10.5 Hz), 3.86 (1H, td, J = 8.7, 5.4 Hz), 4.16 (1H, dd, J = 9.3, 7.5 Hz); ^{13}C NMR δ 18.0, 29.8, 37.7, 45.6, 48.4, 48.6, 67.3, 68.6, 68.8, 70.2, 74.0, 99.5, 99.6; ^{13}C DEPT135 NMR δ 18.0 (+ve), 29.8 (−ve), 37.7 (+ve), 45.6 (+ve), 48.4 (+ve), 48.6 (+ve), 67.3 (+ve), 68.6 (+ve), 68.8 (+ve), 70.2 (−ve), 74.0 (+ve); MS (FAB) *m*/*z* (rel intensity) 304 ($[MH]^+$, 65), 303 ($[M]^+$, 65), 272 ($[M - OCH_3]^+$, 42), 154 (77), 55 (100); HRMS (FAB) calcd for $C_{14}H_{25}O_6N$ $[MH]^+$ 304.1755, found 304.176525.

Isoxazolidine 27. According to the desilylation procedure for silyl ether **28**, silyl ether **29** (91.3 mg, 0.219 mmol) gave isoxazolidine **27** (66.2 mg, 100%) as a white solid: mp 207−208 °C; $[\alpha]^{20}_D$ +220.9 (*c* 1.10, $CHCl_3$); R_f 0.18 (EtOAc); IR (thin film) 3415, 2961, 1462, 1378, 1125, 1026 cm^{-1}; ^1H NMR (C_6D_6) δ 1.08 (1H, d, J = 13.2 Hz), 1.21 (3H, s), 1.35 (3H, s), 1.85 (1H, ddd, J = 12.9, 9.3, 8.1 Hz), 1.96 (1H, dd, J = 8.1, 3 Hz), 2.34 (3H, s), 2.88 (1H, dd, J = 7.8, 2.7 Hz), 2.95 (3H, s), 3.08 (3H, s), 3.21 (1H, br s), 3.33 (1H, dd, J = 9, 2.7 Hz), 3.60 (1H, td, J = 9.9, 8.4 Hz), 4.11 (1H, dt, J = 8.7, 2.7 Hz), 4.31 (1H, t, J = 9.6 Hz); ^{13}C NMR δ 17.85, 17.96, 30.97, 38.94, 47.01, 48.36, 67.13, 71.00, 72.82, 74.04, 99.07, 99.96; ^{13}C NMR (C_6D_6) δ 18.0, 18.2, 31.0, 40.0, 46.8, 47.9, 67.4, 67.7, 71.2, 73.6, 74.1, 99.1, 100.0; ^{13}C DEPT135 NMR (C_6D_6) δ 18.0 (+ve), 18.2 (+ve), 31.0 (−ve), 40.0 (−ve), 46.8 (+ve), 47.9 (+ve), 67.4 (+ve), 67.7 (+ve), 71.2 (+ve), 73.6 (+ve), 74.1 (+ve); MS (FAB) *m*/*z* (rel intensity) 304 ($[MH]^+$, 28), 303 ($[M]^+$, 14), 272 ($[M - OCH_3]^+$, 24), 154 (100), 137 (72), 69 (69), 55 (66); HRMS (FAB) calcd for $C_{14}H_{25}O_6N$ $[MH]^+$ 304.1755, found 304.175796.

5,6,7-Trideoxy-2,3-*O*-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy]-α,β-D-*arabino*-hept-6-eneofuranose (30). Following the glycol cleavage procedure for alkene **10**, triol **22** (852 mg, 2.78 mmol) was converted into lactol **30** (0.763 g) as a colorless oil. It was used in the next step without characterization.

Isoxazolidines 32, 33, 34, and 35. Following the INAC procedure for lactol **23**, lactol **30** (763 mg) was converted into a mixture of isoxazolidines **32, 33, 34,** and **35** (843 mg, 100% from **22**) as a colorless oil.

Silyl Ethers 36, 37, and 38. Following the silylation procedure for isoxazolidines **25** and **27,** isoxazolidines **32**, **33**, **34**, and **35** (843 mg, 2.78 mmol) were converted into silyl ethers **36**, **37**, and **38**. Purification by flash chromatography (hexane:EtOAc, 4:1 to 1:5) afforded first silyl ether **37** (395 mg, 34%) as a colorless oil, second silyl ether **38** (197 mg, 17%) as a colorless oil, third silyl ether **36** (309 mg, 27%) as a white solid, and finally the starting isoxazolidine **35** (232 mg, 20%) as a colorless oil.

Data for **36**: mp 62−63 °C; $[\alpha]^{20}_D$ +100.7 (*c* 1.31, $CHCl_3$); R_f 0.19 (hexane:EtOAc, 2:1); IR (thin film) 2951, 1462, 1375, 1253, 1126, 1044, 838 cm^{-1}; ^1H NMR (C_6D_6) δ 0.12 (3H, s), 0.27 (3H, s), 1.01 (9H, s), 1.18 (1H, ddd, J = 15, 6.9, 3 Hz), 1.31 (3H, s), 1.39 (3H, s), 1.59 (1H, dd, J = 15, 1.2 Hz), 2.40 (1H, pentet, J = 8.4 Hz), 2.74 (1H, t, J = 7.8 Hz), 3.10 (3H, s), 3.33−3.37 (4H, m), 3.84 (1H, q, J = 3 Hz), 3.89 (1H, dd, J = 9.6, 6.6 Hz), 4.13 (1H, dd, J = 9.3, 6.6 Hz), 4.28 (1H, dd, J = 10.5, 9.6 Hz); ^{13}C NMR δ −4.9, −4.4, 17.9, 18.2, 18.6, 26.2, 29.7, 38.3, 46.1, 48.1, 48.2, 65.9, 69.4, 69.6, 71.1, 71.2, 99.4, 99.6; MS (FAB) *m*/*z* (rel intensity) 418 ($[MH]^+$, 84), 417 ($[M]^+$, 67), 386 ($[M - OCH_3]^+$, 17), 109 (57), 95 (79), 83 (81), 69 (100), 55 (98); HRMS (FAB) calcd for $C_{20}H_{39}O_6NSi$ $[MH]^+$ 418.2619, found 418.261484.

Data for **37**: $[\alpha]^{20}_D$ +91.5 (*c* 0.70, $CHCl_3$); R_f 0.54 (hexane:EtOAc, 2:1); IR (thin film) 2946, 2763, 375, 1251, 1133, 837, 775 cm^{-1}; ^1H NMR δ 0.04 (3H, s), 0.10 (3H, s), 0.87 (9H, s), 1.23 (3H, s), 1.26 (3H, s), 1.43 (1H, td, J = 12.9, 2.1 Hz), 1.80 (1H, dt, J = 13.2, 3.3 Hz), 2.33 (1H, t, J = 10.2 Hz), 2.93−3.01 (1H, m), 3.19 (3H, s), 3.22 (3H, s), 3.49 (1H, dd, J = 9.6, 2.4 Hz), 3.61 (1H, dd, J = 11.1, 6 Hz), 3.96 (1H, t, J = 6.6 Hz), 4.04 (1H, q, J = 2.7 Hz), 4.10 (1H, t, J = 9.6 Hz); ^{13}C NMR δ −4.8, −4.3, 18.0, 18.2, 18.6, 26.1, 32.5, 42.8, 47.6, 48.0, 48.1, 68.9, 69.5, 69.6, 72.8, 73.1, 99.2, 100.2; MS (FAB) *m*/*z* (rel intensity) 418 ($[MH]^+$, 100), 417 ($[M]^+$, 70), 386 ($[M - OCH_3]^+$, 12), 101 (25), 73 (43); HRMS (FAB) calcd for $C_{20}H_{39}O_6NSi$ $[MH]^+$ 418.2619, found 418.261854.

Data for **38**: $[\alpha]^{20}_D$ +62.4 (*c* 1.41, $CHCl_3$); R_f 0.38 (hexane:EtOAc, 2:1); IR (thin film) 2951, 2855, 1125, 1040, 836 cm^{-1}; ^1H NMR δ 0.03 (3H, s), 0.09 (3H, s), 0.91 (9H, s), 1.23 (3H, s), 1.25 (3H, s), 1.45 (1H, ddd, J = 15, 4.5, 1.5 Hz), 2.01 (1H, dt, J = 15.3, 3.3 Hz), 2.22 (1H, d, J = 13.2 Hz), 2.48 (1H, dt, J = 13.5, 8.4 Hz), 2.62 (3H, s), 3.09 (1H, d, J = 6.9 Hz), 3.20 (3H, s), 3.22 (3H, s), 3.64 (1H, dd, J = 9.6, 1.2 Hz), 3.97 (1H, t, J = 2.1 Hz), 4.28 (1H, d, J = 9.3 Hz), 4.58 (1H, dd, J = 8.7, 4.5 Hz); ^{13}C NMR δ −4.9, −4.4, 17.7, 18.1, 18.6, 26.2, 32.2, 39.9, 47.9, 48.1, 68.5, 72.0, 76.3, 99.1, 99.3; MS (FAB) *m*/*z* (rel intensity) 418 ($[MH]^+$, 100), 417 ($[M]^+$, 76), 386 ($[M - OCH_3]^+$, 20), 154 (53), 95 (56), 69 (67), 55 (69); HRMS (FAB) calcd for $C_{20}H_{39}O_6NSi$ $[MH]^+$ 418.2619, found 418.262098.

Data for **35**: $[\alpha]^{20}_D$ +169.4 (*c* 1.72 $CHCl_3$); R_f 0.38 (EtOAc:MeOH, 10:1); IR (thin film) 3432, 2948, 1127, 1039, 756 cm^{-1}; ^1H NMR (C_6D_6) δ 1.31 (3H, s), 1.40 (3H, s), 1.72 (1H, ddd, J = 15.6, 3.6, 1.2 Hz), 1.89 (1H, dd, J = 15.6, 5.1 Hz), 2.04 (1H, dt,

J = 12.3, 8.4 Hz), 2.27 (1H, br s), 2.35 (1H, d, J = 12.6 Hz), 2.39 (3H, s), 2.97 (3H, s), 3.05 (1H, dd, J = 7.8, 2.7 Hz), 3.11 (3H, s), 3.96 (1H, d, J = 6 Hz), 4.05 (1H, dd, J = 9.3, 2.7 Hz), 4.23 (1H, d, J = 9.3 Hz), 4.44 (1H, dd, J = 9.6, 1.5 Hz); ^{13}C NMR δ 18.0, 30.4, 38.1, 47.2, 48.2, 67.8, 69.3, 70.7, 70.9, 75.1, 99.4, 99.6; ^{13}C DEPT135 NMR δ 18.0 (+ve), 30.4 (−ve), 38.1 (−ve), 47.2 (+ve), 48.2 (+ve), 67.8 (+ve), 69.3 (+ve), 70.7 (+ve), 70.9 (+ve), 75.1 (+ve); MS (FAB) *m*/*z* (rel intensity) 326 ([M + Na]$^+$, 30), 304 ([MH]$^+$, 26), 303 ([M]$^+$, 55), 272 ([M − OCH_3]$^+$, 40), 95 (56), 69 (77), 55 (100); HRMS (FAB) calcd for $C_{14}H_{25}O_6N$ [M]$^+$ 303.1676, found 303.167070. Anal. Calcd for $C_{14}H_{25}O_6N$: C, 55.43; H, 8.31; N, 4.62. Found: C, 55.26; H, 8.16, N, 4.04.

Isoxazolidine 32. According to the desilylation procedure for silyl ether **28**, silyl ether **36** (27.5 mg, 0.0659 mmol) gave isoxazolidine **32** (19.9 mg, 100%) as a white solid: mp 161−162 °C; $[\alpha]^{20}_D$ +149.4 (*c* 1.60, $CHCl_3$); R_f 0.19 (EtOAc); IR (thin film) 3479, 3390, 2947, 1117, 1037 cm^{-1}; ^{1}H NMR (C_6D_6) δ 1.19 (1H, ddd, J = 15.3, 6.3, 4.5 Hz), 1.33 (3H, s), 1.38 (3H, s), 1.80 (1H, dt, J = 15.3, 2.4 Hz), 2.26−2.37 (1H, m), 2.52 (3H, s), 2.58 (1H, br s), 2.70 (1H, dd, J = 9, 7.8 Hz), 3.08 (3H, s), 3.33 (3H, s), 3.45 (1H, dd, J = 10.8, 3.0 Hz), 3.85 (1H, d, J = 6.6 Hz), 3.87 (1H, dd, J = 9.9, 7.2 Hz), 4.09 (1H, dd, J = 9.0, 7.2 Hz), 4.34 (1H, dd, J = 10.8, 9.3 Hz); ^{13}C NMR (C_6D_6) δ 18.1, 18.4, 27.9 (2H), 37.8, 45.4, 48.0, 48.2, 65.8, 68.5, 69.6, 71.2 (2H), 71.5, 99.9, 100.3; ^{13}C NMR δ 17.9, 18.2, 28.1, 37.9, 45.8, 48.4, 65.5, 68.0, 69.4, 70.7, 71.4, 99.7, 100.0; ^{13}C DEPT135 NMR δ 17.9 (+ve), 18.2 (+ve), 28.1 (−ve), 37.9 (+ve), 45.8 (+ve), 48.4 (+ve), 65.5 (+ve), 68.0 (+ve), 69.4 (+ve), 70.7 (+ve), 71.4 (−ve); MS (FAB) *m*/*z* (rel intensity) 304 ([MH]$^+$, 43), 303 ([M]$^+$, 37), 272 ([M − OCH_3]$^+$, 23), 154 (100), 136 (73), 55 (74); HRMS (FAB) calcd for $C_{14}H_{25}O_6N$ [MH]$^+$ 304.1755, found 304.175692.

Isoxazolidine 33. According to the desilylation procedure for silyl ether **28**, silyl ether **37** (56.0 mg, 0.134 mmol) gave isoxazolidine **33** (40.6 mg, 100%) as a colorless oil: $[\alpha]^{20}_D$ +86.8 (*c* 0.96, $CHCl_3$); R_f 0.14 (EtOAc); IR (thin film) 3449, 2947, 1381, 1132, 1036 cm^{-1}; ^{1}H NMR ($CDCl_3$:C_6D_6, 1:3) δ 0.94 (1H, td, J = 13.5, 2.4 Hz), 1.18 (3H, s), 1.24 (3H, s), 1.73 (1H, dt, J = 13.5, 3.3 Hz), 2.14 (1H, t, J = 10.5 Hz), 2.41 (1H, br s), 2.88−2.98 (4H, m), 3.03 (3H, s), 3.08 (3H, s), 3.31 (1H, dd, J = 10.8, 6 Hz), 3.51 (1H, dd, J = 9.6, 3 Hz), 3.73 (1H, t, J = 6.9 Hz), 3.80 (1H, q, J = 2.7 Hz), 4.19 (1H, t, J = 9.9 Hz); ^{13}C NMR (C_6D_6) δ 14.2, 26.3, 39.2, 43.8, 43.9, 64.9, 65.2, 65.5, 69.2, 69.6, 95.8, 96.9; ^{13}C NMR δ 18.1, 18.2, 30.3, 42.9, 47.6, 48.3, 48.4, 68.7, 69.1, 69.4, 72.5, 73.0, 99.7, 100.8; ^{13}C DEPT135 NMR δ 18.1 (+ve), 18.2 (+ve), 30.3 (−ve), 42.9 (+ve), 47.6 (+ve), 48.3 (+ve), 48.4 (+ve), 68.7 (+ve), 69.1 (+ve), 69.4 (−ve), 72.5 (+ve), 73.0 (+ve); MS (FAB) *m*/*z* (rel intensity) 304 ([M]$^+$, 100), 303 ([M]$^+$, 74), 272 ([M − OCH_3]$^+$, 25), 154 (80), 55 (86); HRMS (FAB) calcd for $C_{14}H_{25}O_6N$ [MH]$^+$ 304.1755, found 304.175664. Anal. Calcd for $C_{14}H_{25}O_6N$: C, 55.43; H, 8.31; N, 4.62. Found: C, 55.19; H, 8.55, N, 4.42.

Isoxazolidine 34. According to the desilylation procedure for silyl ether **28**, silyl ether **38** (66.3 mg, 0.159 mmol) gave isoxazolidine **34** (37.6 mg, 78%) as a white solid: mp 157−158 °C; $[\alpha]^{20}_D$ +104.3 (*c* 1.12, $CHCl_3$); R_f 0.26 (EtOAc); IR (thin film) 3254, 2960, 1125, 1045, 847 cm^{-1}; ^{1}H NMR (C_6D_6) δ 1.04 (1H, ddd, J = 15.3, 4.2, 2.4 Hz), 1.35 (3H, s), 1.41 (3H, s), 1.73 (1H, dt, J = 12.9, 7.8 Hz), 1.89 (1H, d, J = 12.6 Hz), 2.10 (1H, dt, J = 15.0, 3.0 Hz), 2.32 (3H, s), 2.73 (1H, d, J = 9.0 Hz), 3.03 (3H, s), 3.05 (3H, s), 3.76 (1H, d, J = 8.7 Hz), 4.06−4.11 (2H, m), 4.25 (1H, d, J = 8.4 Hz); ^{13}C NMR δ 18.0, 33.0, 39.2, 46.4, 48.0, 48.1, 67.8, 71.0, 71.3, 72.5, 78.0, 100.3, 100.4; ^{13}C DEPT135 NMR δ 18.0 (+ve), 33.0 (−ve), 39.2 (−ve), 46.4 (+ve), 48.0 (+ve), 48.1 (+ve), 67.8 (+ve), 71.0 (+ve), 71.3 (+ve), 72.5 (+ve), 78.0 (+ve); MS (FAB) *m*/*z* (rel intensity) 304 ([MH]$^+$, 22), 303 ([M]$^+$, 16), 272 ([M − OCH_3]$^+$, 7), 95 (61), 69 (92), 55 (100); HRMS (FAB) calcd for $C_{14}H_{25}O_6N$ [MH]$^+$ 304.1755, found 304.176109.

Nitrone 24. Following the glycol cleavage procedure for alkene **10**, triol **21** (178 mg, 0.582 mmol) was converted into lactol **23** (160 mg) as a colorless oil. *N*-Methylhydroxylamine hydrochloride (146 mg, 1.75 mmol) and $NaHCO_3$ (244 mg, 2.91 mmol) were added to a solution of lactol **23** (160 mg) in CH_3CN (10 mL). After being stirred at room temperature for 30 min the reaction mixture was partitioned between EtOAc (20 mL) and water (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography ($CHCl_3$:MeOH, 15:1) gave nitrone **24** (269 mg, 100% from **21**) as a colorless oil: $[\alpha]^{20}_D$ +175.4 (*c* 1.35, $CHCl_3$); R_f 0.31 (EtOAc:MeOH, 30:1); IR (thin film) 3362, 2950, 1642, 1378, 1214, 1120, 1036, 957 cm^{-1}; ^{1}H NMR δ 1.29 (3H, s), 1.35 (3H, s), 2.28 (1H, dt, J = 13.2, 6.3 Hz), 2.56 (1H, dt, J = 14.4, 6.6 Hz), 3.25 (3H, s), 3.26 (3H, s), 3.45−3.52 (1H, m), 3.62 (1H, dd, J = 9.9, 2.1 Hz), 3.37 (3H, s), 4.70 (1H, d, J = 4.8 Hz), 5.03−5.13 (2H, m), 5.20 (1H, dd, J = 9.9, 6.6 Hz), 5.89 (1H, ddt, J = 17.1, 10.2, 6.9 Hz), 6.80 (1H, d, J = 6.6 Hz); ^{13}C NMR δ 17.8, 18.0, 36.4, 48.7, 53.3, 65.9, 69.9, 71.5, 99.1, 99.5, 117.0, 136.2, 138.4; MS (FAB) *m*/*z* (rel intensity) 304 ([MH]$^+$, 74), 303 ([M]$^+$, 22), 272 ([M − OCH_3]$^+$, 36), 116 (100), 115 (66), 101 (96), 73 (55); HRMS (FAB) calcd for $C_{14}H_{25}O_6N$ [MH]$^+$ 304.1755, found 304.175680.

Nitrone 31. Following the procedure for the generation of nitrone **24**, triol **22** (129 mg, 0.421 mmol) was converted into nitrone **31** (117 mg, 92% from **22**) as a colorless oil: $[\alpha]^{20}_D$ +141.8 (*c* 1.26, $CHCl_3$); R_f 0.33 (EtOAc:MeOH, 15:1); IR (thin film) 3379, 2950, 1638, 1376, 1212, 1121, 1036, 888 cm^{-1}; ^{1}H NMR δ 1.29−1.31 (6H, 2s), 2.14 (1H, dt, J = 15.3, 8.1 Hz), 2.62 (1H, br d, J = 14.1 Hz), 3.25−3.26 (6H, 2s), 3.49 (1H, dd, J = 9.9, 8.7 Hz), 3.67 (3H, s), 3.76 (1H, td, J = 8.4, 3.3 Hz), 4.91 (1H, dd, J = 9.9, 6.3 Hz), 5.05−5.14 (2H, m), 5.52 (1H, br s), 5.91 (1H, ddt, J = 17.1, 10.2, 6.9 Hz), 6.85 (1H, d, J = 6.3 Hz); ^{13}C NMR δ 17.7, 17.9, 37.8, 48.7, 48.9, 53.0, 67.5, 70.6, 71.8, 98.5, 98.7, 117.4, 135.7, 140.8; MS (FAB) *m*/*z* (rel intensity) 304 ([MH]$^+$, 100), 272 ([M − OCH_3]$^+$, 55), 185 (70), 93 (92), 101 (53); HRMS (FAB) calcd for $C_{14}H_{25}O_6N$ [MH]$^+$ 304.1755, found 304.175944.

General Procedure for Performing INAC Reactions in Different Solvents. Nitrone **24** or **31** was dissolved in the selected solvent and the solution was either stirred at room temperature or heated at 40°C. After the completion of the reaction, the solvent was removed under reduced pressure and the residue was purified by flash chromatography ($CHCl_3$:MeOH, 30:1) to give a mixture of cycloadducts. The ratios of the cycloadducts were determined by ^{1}H NMR spectral analysis.

General Procedure for Studying Equilibration of the Cyclized Products 25−27 and 32−35. A solution of the individual cycloadduct in toluene in a sealed tube was degassed and heated at 210 °C (sand bath temperature) for 24 h. The reaction was cooled to room temperature and the solvent was removed under reduced pressure. The cycloadduct was recovered almost quantitatively.

Acknowledgment. This work was partially supported by a CERG from the Research Grants Council of the Hong Kong SAR, China (project no. 402805). This work was also partially supported by a Grant-in-Aid for the 21st century COE program "KEIO LCC" from the Ministry of Education, Culture, Sports, Science and Technology, Japan. The authors thank the Research Center for Computational Science, Okazaki National Institute, for their support of the DFT calculations.

Supporting Information Available: Complete ref 28, general experimental methods, copies of ^{1}H and ^{13}C NMR spectra of all compounds, X-ray crystallographic structure of **25**, **27**, **32**, and **34** (including CIF files), conformers used for the TS search obtained by CONFLEX, and Cartesian coordinates and energies of the most stable ground state and some transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060348Y