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Chiral *N*-Acyloxazolidines: Synthesis, Structure, and Mechanistic Insights†

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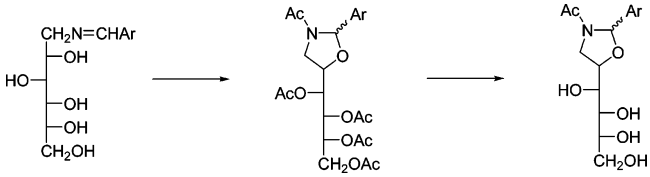

A series of chiral imines derived from 1-amino-1-deoxyalditols such as D-glucamine, a rather unexplored raw material from the chiral pool, have been serendipitiously transformed into a novel family of *N*-acetyl-1,3-oxazolidines by means of an unexpected acetylation. The structure of these substances is supported by spectroscopic and crystallographic data. The acetylates also trigger a complex dynamic transformation, in which an initially configured trans oxazolidine converts into a more stable cis-configured derivative. Both isomers can also exist as rotational conformers (*E*,*Z*) as a consequence of the restricted rotation around the *N*-acetyl bond. The barriers to rotation have been determined by variable-temperature experiments. Overall, this transformation most likely involves the intermediacy of a chiral iminium ion, which has been documented in the synthesis of nitrogen heterocycles, thus explaining the experimental facts.

Introduction and Background

It should be largely unnecessary to emphasize the role played by carbohydrates in contemporary organic synthesis, a convenient source of both chiral synthons and densely functionalized raw materials for varied purposes. As starting materials for the preparation of enantiomerically pure compounds, carbohydrates often provide advantages of availability and low cost. However, to be truly practical, carbohydrate-based synthetic methodology must also be efficient and in particular should avoid lengthy protection/deprotection protocols.[1] It is in this context that the search for inexpensive and available chirons from sugars, and methods to convert them into building blocks constitutes our current challenge and this study concentrates on the use of aminopolyols to this end.

It is somewhat surprising that while the chemistry of reducing aminosugars, particularly 2-amino-2-deoxyaldoses, is well established,[2] that of aminopolyols remains quite underexploited. Early preparations of 1-amino-1-deoxypolyols include catalytic hydrogenation in the presence of Pt, Pd, or Raney Ni of the corresponding glycosylamines[3] or hydrazones,[4] hydrogenation of 1-deoxy-1-nitropolyols over Ag_2O,[5] as well as chemical[3] or electrolytic[6] reduction of monosaccharide oximes.

Recently we turned our attention to the preparation of some protected derivatives of the readily available 1-amino-1-deoxy-D-glucitol (**1**), commonly referred to as D-glucamine.[7] In following well-known protocols, its condensation with aromatic

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(1) (a) Bols, M. *Carbohydrate Building Blocks*; John Wiley & Sons: New York, 1995. (b) *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997.

(2) (a) Horton, D. In *The Amino Sugars*; Jeanloz, R. W., Ed.; Academic Press: New York, 1969; Vol. IA, Chapter 1, pp 3−211. (b) Horton, D.; Wander, J. D. In *The Carbohydrates*; Pigman, W., Horton, D., Wander, J. D., Eds.; Academic Press: New York, 1980; Vol. IB, Chapter 16, pp 643−760.

(3) (a) Kagan, F.; Rebenstorf, M. A.; Heinzelman, R. V. *J. Am. Chem. Soc*. **1957**, *79*, 3541. (b) Neuberg, C.; Marx, F. *Biochem. Z.* **1907**, *3*, 539.

(4) Wolfrom, M. L.; Shafizadeh, F.; Wehrmüller, J. O.; Armstrong, R. K. *J. Org. Chem.* **1958**, *23*, 571.

(5) Angus, H. J. F.; Richtmyer, N. K. *Carbohydr. Res*. **1967**, *4*, 7.

(6) Ryan, G.; Utley, H. P.; Jones, H. F. *Tetrahedron Lett.* **1988**, *29*, 3699.

(7) Avalos, M.; Babiano, R.; Cintas, P.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; Palacios, J. C.; Pérez, E. M. S. *Eur. J. Org. Chem*. **2006**, 657.

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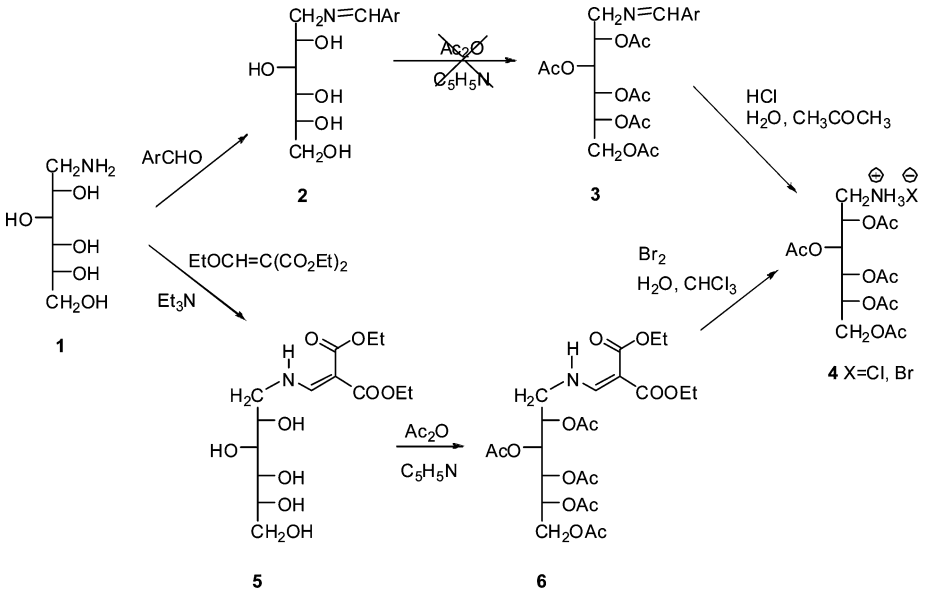


aldehydes led to the corresponding Schiff bases (**2**), which serve as a suitable protecting group of the amino function (Scheme 1). Such substrates could also be employed as stereodifferentiating elements in asymmetric syntheses, although again this potentiality has scarcely been employed. Thus, Barton et al. did recognize the usefulness of acyclic imines derived from D-glucosamine in the Staudinger synthesis of optically active β-lactams.[8,9] Kunz and his associates have successfully employed imines derived from *O*-protected glycosylamines in numerous asymmetric reactions,[10] such as Strecker,[11] Ugi,[12] Mannich,[13] tandem Mannich−Michael,[14] hetero-Diels−Alder,[15] organometallic additions,[16] or Staudinger.[17] Likewise, glycosylimines have been used in the stereoselective synthesis of α-amino acids.[18]

Further interest on Schiff bases as ligands, not related to carbohydrates nevertheless, is illustrated by metallosalen complexes (especially Mn- and Cr-salen complexes) having a structure of *N*,*N*-ethylenebis(salicylideneaminato) that catalyze the epoxidation of a wide range of olefins.[19]

We did initially envisage that Schiff bases **2** could conveniently be *O*-protected by acylation yielding **3** and then converted into **4**. The latter is a useful intermediate that can be employed as starting material en route to sugar isocyanates and their ureas.[7] Quite unexpectedly, the conventional *O*-acetylation of imines **2** did not lead to compounds **3**, but to anomalous substances, namely polyol-based oxazolidines, which constitute the subject of the present work. Compounds **4** could actually be prepared by an alternative strategy that involves *N*-protection as an enamine derivative (**5**) followed by *O*-acylation (**6**) and further *N*-deprotection under mild conditions. It should be noted that enantiomerically pure 1,3-oxazolidines (as well as their *N*-acyl derivatives and other oxazolidinones), which can be generated from 1,3-amino alcohols and functionalized aldehydes (or aldehyde equivalents), have been explored as chiral auxiliaries in asymmetric synthesis.[20] Our research might therefore add novel chirons suitable for synthetic design.

Results and Discusion

Schiff Bases Derived from D-Glucamine. Formation of imines was initially conducted by dissolving D-glucamine in water and adding, under stirring, the corresponding aldehyde, either solvent-free with liquid aldehydes or dissolved in methanol. However, improved yields (~90%) could be obtained when a mixture of D-glucamine and aldehyde was refluxed in benzene with azeotropic removal of water. Insoluble materials can be obtained within short reaction times. Thus, Schiff bases **7**−**15** were prepared by condensation of **1** with substituted benzaldehydes and cinnamaldehyde (Table 1).

The structures of these substances have been confirmed by analytical and spectroscopic data. The most prominent IR

(8) Barton, D. H. R.; Gateau-Olesker, A.; Anaya-Mateos, J.; Cleophax, J.; Géro, S. D.; Chiaroni, A.; Riche, C. *J. Chem. Soc., Perkin Trans. I* **1990**, 3211.

(9) Anaya, J.; Barton, D. H. R.; Géro, S. D.; Grande, M.; Hernando, J. I. M.; Laso, N. M. *Tetrahedron*: *Asymmetry* **1995**, *6*, 609.

(10) Kunz, H. In *Selectivities in Lewis Acid Promoted Reactions*; Schinzer, D., Ed.; Kluwer Academic: Dordrecht, The Netherlands, 1989; pp 189−202.

(11) Kunz, H.; Sager, W. *Angew. Chem., Int. Ed. Engl*. **1987**, *26*, 557.

(12) Kunz, H.; Pfrengle, W. *J. Am. Chem. Soc*. **1988**, *110*, 651.

(13) Kunz, H.; Pfrengle, W. *Tetrahedron* **1988**, *44*, 5487.

(14) Kunz, H.; Schanzenbach, D. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1068.

(15) Kunz, H.; Pfrengle, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1067.

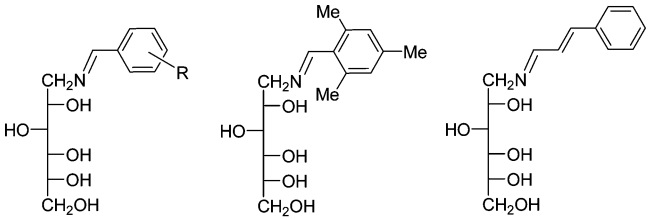
(16) Pfrengle, W.; Kunz, H. *J. Org. Chem*. **1989**, *54*, 4261.

(17) Laschat, S.; Kunz, H. *J. Org. Chem*. **1991**, *56*, 5883.

(18) (a) Georg, G. I.; Akgün, E.; Mashava, P. M.; Milstead, M.; Ping, H.; Wu, Z.; Velde, D. V. *Tetrahedron Lett.* **1992**, *33*, 2111. (b) Ross, G. F.; Herdwetck, E.; Ugi, I. *Tetrahedron* **2002**, *58*, 6127.

(19) Katsuki, T. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 6B, pp 295−314.

(20) (a) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley & Sons: New York, 1995; Chapter 1.3. (b) Steif, F.; Wibbeling, B.; Meyer, O.; Hoppe, D. *Synthesis* **2000**, 743−753. (c) Vega-Pérez, J. M.; Vega, M.; Blanco, E.; Iglesias-Guerra, F. *Tetrahedron*: *Asymmetry* **2001**, *12*, 3189−3203. (d) Shen, M.; Li, C. *J. Org. Chem.* **2004**, *69*, 7906−7909. (e) Spino, C.; Tremblay, M.-C.; Gobdout, C. *Org. Lett.* **2004**, *6*, 2801−2804. (f) Elzner, S.; Maas, S.; Engel, S.; Kunz, H. *Synthesis* **2004**, 2153−2164. (g) Gessier, F.; Schaeffer, L.; Kimmerlin, T.; Flögel, O.; Seebach, D. *Helv. Chim. Acta* **2005**, *88*, 2235−2249. (h) Hein, J. E.; Geary, L. M.; Jaworski, A. A.; Hultin, P. G. *J. Org. Chem.* **2005**, *70*, 9940−9946. (i) Coumbarides, G. S.; Dingjan, M.; Eames, J.; Flinn, A.; Motevalli, M.; Northen, J.; Yohannes, Y. *Synlett* **2006**, 101−105. (j) Gnas, Y.; Glorius, F. *Synthesis* **2006**, 1899−1930. (k) Bruschi, M.; Orlandi, M.; Rindone, B.; Rummakko, P.; Zoia, L. *J. Phys. Org. Chem.* **2006**, *19*, 592−596. (l) Chavda, S.; Coumbarides, G. S.; Dingjan, M.; Eames, J.; Flinn, A.; Northen, J. *Chirality* **2007**, *19*, 313−320.



7 R=4-HO
8 R=4-MeO
9 R=4-Me
10 R=H
11 R=4-Cl
12 R=3-Br
13 R=4-NO_2

14 **15**

TABLE 1. Isolated Yields (%) for Compounds 7−20 by Methods A and B

compd	method A[a]	method B[b]
7	92	99
8	55	93
9	95	98
10	63	90
11	87	99
12	73	99
13	91	91
14	26	95
15	86	96
16	95	98
17	58	94
18	90	*c*
19	89	98
20	89	*c*

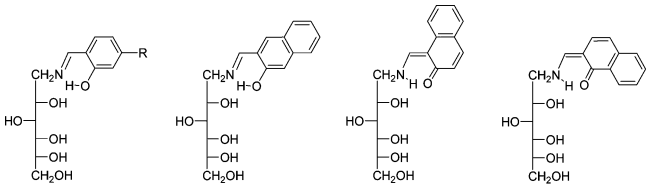
[a] In water. [b] In benzene. [c] Not determined.

absorption appeared at ∼1640 cm^{-1} and can be attributed to the imino group.[21] ^1H NMR spectra showed the imino proton resonating at ∼8.0−8.2 ppm, either as singlet for compounds **7**−**14** or doublet for **15** due to the coupling of that imino proton with those of the olefinic group. Five OH groups were observed in the range 4.2−5.0 ppm whereas all the protons of the sugar moiety appeared more highfield (∼3.2−4.0 ppm).

^{13}C NMR spectra revealed the existence of the iminic carbon at ∼162 ppm. The terminal methylene carbons of D-glucamine showed almost coincidental chemical shifts at ∼64 ppm while the remaining sugar carbons resonated around ∼72 ppm, a fact usually typical of acyclic polyhydroxyalkyl chains. It is noteworthy that the C-1 carbon, i.e., the position linked to the imino function, appeared unusually downfield, whereas D-glucamine derivatives show the same C-1 carbon at ∼43 ppm.[22]

When D-glucamine was treated with 2-hydroxybenzaldehyde, 2,4-dihydroxybenzaldehyde, and 2-hydroxy-3-naphthaldehyde, the corresponding imines **16**−**18** could also be isolated. In stark contrast, the condensation of the parent aminoalditol with 2-hydroxy-1-naphthaldehyde and 1-hydroxy-2-naphthaldehyde yielded the enamine structures **19** and **20**, respectively.

Spectroscopic data for compounds **16**−**18** are similar to those found for **7**−**14**, thereby supporting imine skeleta: a typical IR absorption at ∼1640 cm^{-1} ($\nu_{C=N}$) as well as proton and carbon signals at ∼8.5 and ∼167 ppm, respectively, which can be attributed to the imino function. The *o*-hydroxyl groups at the aromatic rings are highly deshielded (δ_{OH} >13 ppm), a fact consistent with a strong intramolecular hydrogen bonding. Overall, the above results agree with literature data indicating that most adducts (>90% according to our database searching) generated from amines and 2-hydroxybenzaldehyde adopt imine structures in the solid state,[23−25] whereas other crystal data support enamine structures,[23,26−29] and all have invariably iminic structures in solution.[29] On the other hand, there are a few adducts solved by X-ray crystallography, arising from amines and 3-hydroxy-2-naphthaldehydes, but they correspond again to imine skeleta.[30,31]



16 R=H
17 R=OH

18 **19** **20**

The enamino structure associated with compounds **19** and **20** can easily be inferred from spectroscopic data; a strong IR absorption at ∼1635 cm^{-1} points to the stretching vibration of the enamine carbonyl group, while weaker absorptions are to be expected for the corresponding imines. The methine proton coupled to the NH proton appeared as a doublet signal at ∼9 ppm. The ^{13}C NMR spectrum equally confirms the enamine structure on showing the carbonyl group at ∼180 ppm. As noted above, the NH proton, shifted downfield at δ_{NH} >13 ppm, suggests the participation of this group within a strong intramolecular hydrogen bond.

In this context, it is convenient to note that most structures elucidated by X-ray diffraction analyses involving adducts between amines and 2-hydroxy-1-naphthaldehyde correspond to enamines,[32−42] while compounds adopting iminic arrange-

(21) Nakanishi, K.; Solomon, P. *Infrared Absorption Spectroscopy*, 2nd ed.; Holden-Day: San Francisco, CA, 1997; p 33.
(22) Bock, K.; Pedersen, Ch. *Adv. Carbohydr. Chem. Biochem.* **1983**, *41*, 27.
(23) Paredes-García, V.; Venegas-Yazigi, D.; Lough, A. J.; Latorre, R. *Acta Crystallogr.* **2000**, *C56*, 283.
(24) Dominiak, P. M.; Grech, E.; Barr, G.; Teat, S.; Mallinson, P.; Wozniak, K. *Chem. Eur. J.* **2004**, *9*, 963.
(25) Ozeryanskii, V. A.; Pozharskii, A. F.; Schiff, W.; Kamiénski, B.; Sawka-Dobrowolska, W.; Sobczyk, L.; Grech, E. *Eur. J. Org. Chem.* **2006**, 782.
(26) (a) Cungen, Z.; Peizi, Z.; Dan, W.; Kaibei, Y. *J. Chem. Res.* **2000**, 402. (b) Odabasoglu, M.; Albayrak, Ç.; Büyükgüngör, O.; Lönnecke, P. *Acta Crystallogr.* **2003**, *C59*, 616.
(27) Albayrack, Ç.; Odabasoglu, M.; Büyükgüngör, O.; Lönnecke, P. *Acta Crystallogr.* **2004**, *C60*, 318.
(28) Ensali, C. C.; Albayrak, Ç.; Odabasoglu, M.; Endönmez, A. *Acta Crystallogr.* **2003**, *C59*, 601.
(29) Kia, R.; Esmazilbeig, A.; Harkema, S. *Acta Crystallogr.* **2004**, *A60*, 267.
(30) Fernández-G., J. M.; Rosales, M. J.; Toscano, R. A.; Tapia, R. G. *Acta Crystallogr.* **1986**, *C42*, 1313.
(31) Lin, J.; Cui, G.-H.; Li, J. R.; Xu, S.-S. *Acta Crystallogr.* **2005**, *E61*, 627.
(32) Pavlovic, G.; Sosa, J. M. *Acta Crystallogr.* **2000**, *C56*, 1117.
(33) Yüce, S.; Ozëk, A.; Albayrak, Ç.; Odabasoglu, M.; Büyükgüngör, O. *Acta Crystallogr.* **2004**, *E60*, 1217.
(34) Ozëk, A.; Yüce, S.; Albayrak, Ç.; Odabasoglu, M.; Büyükgüngör, O. *Acta Crystallogr.* **2004**, *E60*, 826.
(35) Odabasoglu, M.; Albayrak, Ç.; Büyükgüngör, O. *Acta Crystallogr.* **2004**, *E60*, 142.
(36) Dilovic, I.; Matkovic-Calogovic, D.; Popovic, Z.; Roje, V. *Acta Crystallogr.* **2005**, *C61*, 351.
(37) Ozëk, A.; Yüce, S.; Albayrak, Ç.; Odabasoglu, M.; Büyükgüngör, O. *Acta Crystallogr.* **2004**, *E60*, 1162.
(38) Ozëk, A.; Yüce, S.; Albayrak, Ç.; Odabasoglu, M.; Büyükgüngör, O. *Acta Crystallogr.* **2004**, *E60*, 828.
(39) Acevedo-Aranz, E.; Fernández-G., J. M.; Rosales-Hoz, M. J.; Toscano, R. A. *Acta Crystallogr.* **1992**, *C48*, 115.

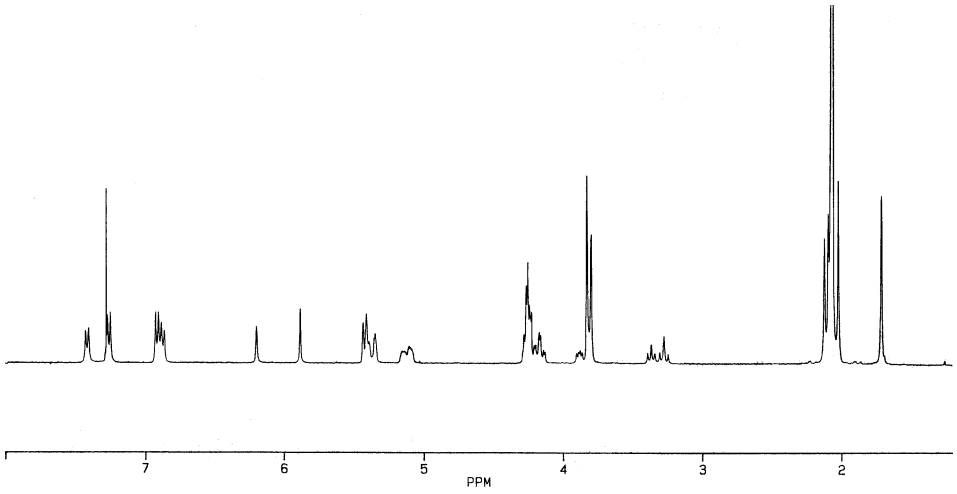
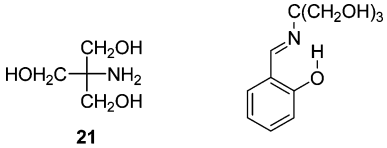


FIGURE 1. ^{1}H NMR spectrum in $CDCl_3$ for compound **25**.

ments in the solid state[43,44] behave contrarily as enamines in solution.[44]

In a further attempt to obtain simplified models, at least from a spectroscopic viewpoint, the imine derivative **22** has been obtained starting from α,α,α-tris(hydroxymethyl)methylamine (**21**). By virtue of the symmetry of the latter, compounds such as **22** show spectra that can easily be interpreted: the stretching vibration of the C═N bond ($\nu_{C=N} \approx 1640$ cm^{-1}), singlet signals at ∼8.5 ($\delta_{CH=N}$) and 14.5 ppm (δ_{OH},phenol), and a carbon resonance at ∼165 ppm all support an iminic structure in solution. Conversely, crystallographic data point to an enamine derivative in the solid state as evidenced by recent studies.[26] In contrast, the adduct generated from **21** and 2-hydroxy-1-naphthaldehyde shows an enamine structure (**23**) as inferred from its carbonyl resonance at ∼180 ppm and those of the NH proton (∼14 ppm) and the C═CH−N group (∼8.9 ppm), both as doublets. The large downfield shifts for the phenolic OH group and the NH of the enamine moiety in **22** and **23**, respectively, suggest again the existence of strong intramolecular hydrogen bonds.



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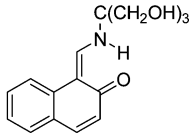
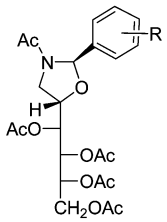
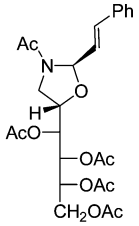


23

Synthesis of Chiral Oxazolidines. When imines **7**−**13**, **15**, and **16** were treated with acetic anhydride in pyridine, the resulting acetyl derivatives show spectroscopic data that rule out the expected structure of per-*O*-acetylimines (**3**) (with overall yields ranging from 40% to 86%). Such data are rather consistent with *N*-acyloxazolidines (**24**−**32**). This behavior is clearly distinct from that of D-glucamine-based enamines, which produce the corresponding per-*O*-acetyl derivatives under the same reaction conditions.[7]



24 R=4-$MeCO_2$
25 R=4-MeO
26 R=4-Me
27 R=H
28 R=4-Cl
29 R=3-Br
30 R=4-NO_2
32 R=2-$MeCO_2$



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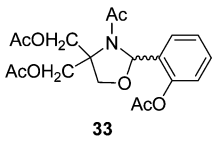


33

A preliminary inspection of their IR spectra shows a strong absorption at ∼1750 cm^{-1}, resulting from the acetate groups, and a medium intensity band at ∼1652 cm^{-1} characteristic of the stretching vibration of the amide carbonyl. However, NMR data provide the most significant data supporting the formation of a ring system (Figure 1). At first glance the observed multiplicity of signals in both the ^{1}H and ^{13}C NMR spectra, having similar chemical shifts and multiplicities, suggested the existence of two isomers for **24**−**27** and **32** and four isomers in the remaining cases. In the latter compounds **28**−**31** could be isolated by recrystallization, as an isomer couple each, in a similar way to that of **24**−**27** and **32**. If these compounds had an imine structure, this functional group would be expected to give rise to NMR signals at ∼8.3 and ∼161 ppm, corresponding to the iminic proton and carbon, respectively. In contrast, resonances at ∼6.0 and ∼90 ppm were found. Such shifts agree with those of saturated groups and their magnitude is consistent with the typical values found for the C-2 position of an oxazolidine ring (90 ppm)[45] and its proton (∼5.30−6.00 ppm).[45−47]

(40) Elerman, Y.; Kabak, M.; Elmali, A.; Svoboda, I. *Acta Crystallogr.* **1998**, *E54*, 128.
(41) Ozëk, A.; Yüce, S.; Albayrak, Ç.; Odabasoglu, M.; Büyükgüngör, O. *Acta Crystallogr.* **2004**, *E60*, 356.
(42) Kaitner, B.; Pavlovic, G. *Acta Crystallogr.* **1996**, *C52*, 2573.
(43) Popovic, Z.; Roje, V.; Pavlovic, G.; Matkovic-Calogovic, D.; Giester, G. *J. Mol. Struct.* **2001**, *597*, 39.
(44) Pavolic, G.; Sosa, J. M.; Vikic-Topic, D.; Leban, I. *Acta Crystallogr.* **2002**, *E58*, 317.
(45) Neuvonen, K.; Fülöp, F.; Neuvonen, H.; Koch, A.; Kleinpeter, E.; Pihlaja, K. *J. Org. Chem.* **2001**, *66*, 4132.
(46) (a) Fülöp, F.; Pihlaja, K. *Tetrahedron* **1993**, *49*, 6701. (b) Fülöp, F.; Pihlaja, K.; Neuvonen, K.; Bernáth, G.; Argay, G.; Kálmán, A. *J. Org. Chem.* **1993**, *58*, 1967.

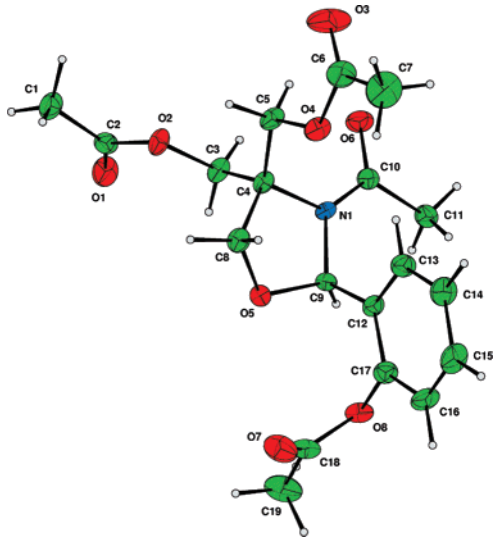


FIGURE 2. ORTEP diagram for *N*-acyloxazolidine **33**.

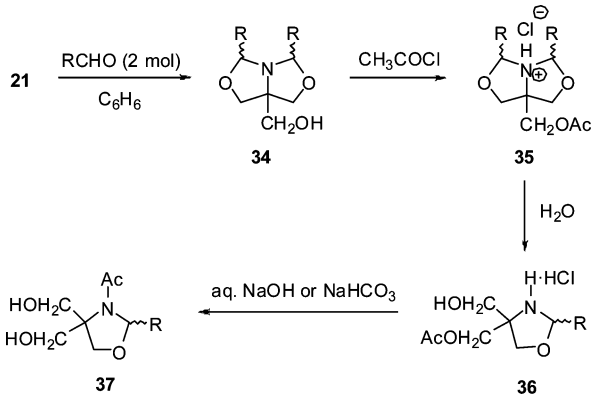
A similar behavior was found in imines derived from α,α,α-tris(hydroxymethyl)methylamine. Thus, acetylation of **22** led to compound **33**, an *N*-acyloxazolidine derivative whose structure could be unambiguously elucidated by single-crystal X-ray diffraction (Figure 2).[48] The solid-state structure also reveals an *E* configuration around the amide bond.

Since compound **33** show spectroscopic data similar to those of **24**−**32**, the latter substances should equally be oxazolidine derivatives. Characteristic signals are the amide band in their IR spectra at 1661 cm^{-1} and resonances at ∼87 (C-2) and ∼6.3 ppm as mentioned above. The methylene protons of the acetoxymethyl groups are diastereotopic and give rise to AB-type splitting patterns centered at 4.74 and 4.57 ppm. The heterocyclic methylene gives an AB splitting too having chemical shifts markedly different for its protons ($\Delta\delta$ ∼0.25 ppm). It is noteworthy that the acetamido resonance occurs at unusually high field around ∼1.84 ppm. If compound **33** had in solution a structure identical with that of the solid state, the methyl group of the acetamido function would be placed next to the aromatic ring and would undergo an appreciable shielding.

It is also interesting to point out that *N*-acyloxazolidines derived from **21** had been previously synthesized using a lengthier route (Scheme 2).[49] Condensation of **21** with 2 equiv of aldehyde in refluxing benzene with concomitant water elimination leads to 1-aza-3,7-dioxabicyclo[3.3.0]octano (**34**),[50,51] whose acetylation with acetyl chloride and further hydrolysis gives rise to an oxazolidine hydrochloride (**36**). Neutralization with aqueous solutions of sodium hydroxide or sodium hydrogen carbonate also causes migration of the acetyl group to yield *N*-acetyloxazolidines (**37**).[51]

The present synthesis of *N*-acetyloxazolidines such as **33**, which can further be easily deacetylated, envisages a strategy

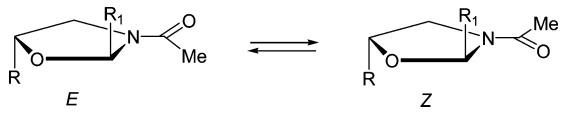
SCHEME 2



to obtain the unprotected oxazolidines **37** having a greater atom-economy orientation.[52]

Rotational Equilibria of *N*-Acetyloxazolidines. As mentioned before on the basis of NMR data, compounds **24**−**32** exist in solution as isomeric couples that could not be separated. After repeated crystallizations, these mixtures remain in the same ratio, a fact pointing to rotational isomers. This surmise could be assessed by means of variable-temperature experiments. Thus, the broad NMR signals observed at room temperature become increasingly sharp and well-differentiated resonances by decreasing the temperature. On heating, the signals become increasingly broad again until they merge to form simplified spectra showing only one signal set (Figure 3). The existence of such isomers should be reasonably linked to the restricted rotation around the amide bond. Assuming that this function should adopt a coplanar arrangement with the oxazolidine ring, thereby facilitating the electronic delocalization between the lone pair on the nitrogen atom and the carbonyl group, this system could in principle have the possibility to exist in two orientations as depicted in Scheme 3: either placing the carbonyl oxygen close to the C-4 position of the heterocycle (*E* configuration) or pointing the former group to the C-2 position of the ring (*Z* configuration).

SCHEME 3



The protons of the C-2 and C-4 positions will undergo the influence of the carbonyl group in a different way for each rotamer. This assumption correlates well with the chemical shift ranges observed experimentally. Thus, the *geminal* C-4 protons exhibit chemical shift differences of about 1 ppm for one of the rotamers and approximately 0.5 ppm for the other. The C-2 protons show typical shift differences of 0.3 ppm for both rotamers.

A similar behavior has been previously reported for glycosides derived from 5-acetamido-5-deoxypyranoses (**38**),[53] 6-acylamino-2,6-anhydro-2-deoxyheptitols (**39**),[54] and glycosides or nucleosides from 4-acetamido-4-deoxyfuranoses (**40** and **41**).[53,55]

(47) Maireanu, C.; Darabantu, M.; Plé, G.; Berghian, C.; Condamine, E.; Ramondenc, Y.; Silaghi- Dumitrescu, I.; Mager, S. *Tetrahedron* **2002**, *58*, 2681.

(48) Crystal data for compound **33** have been deposited with the Cambridge Crystallographic Data Centre (CCDC-644232) and can be obtained, upon request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

(49) For a revision in the synthesis of oxazolidines see: Bergmann, E. D. *Chem. Rev.* **1953**, *53*, 309.

(50) Senkus, M. *J. Am. Chem. Soc.* **1945**, *67*, 1515.

(51) Pierce, J. S.; Lunsford, C. D.; Raiford, R. W., Jr.; Rush, J. L.; Riley, D. W. *J. Am. Chem. Soc.* **1951**, *73*, 2595.

(52) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

(53) Szarek, W. A.; Wolfe, S.; Jones, J. K. N. *Tetrahedron Lett.* **1964**, 2743.

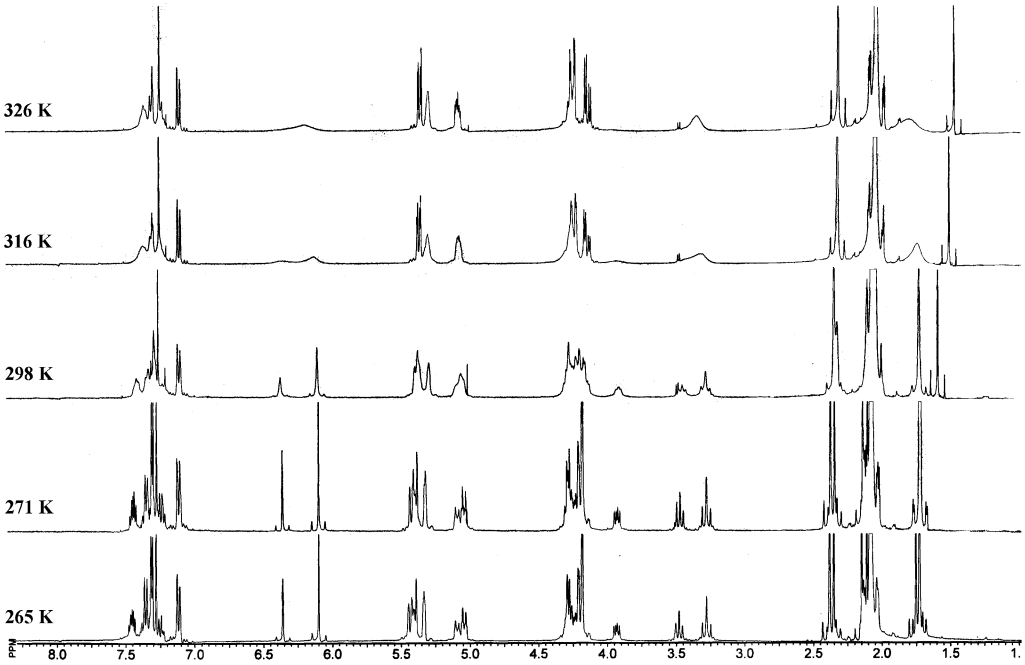
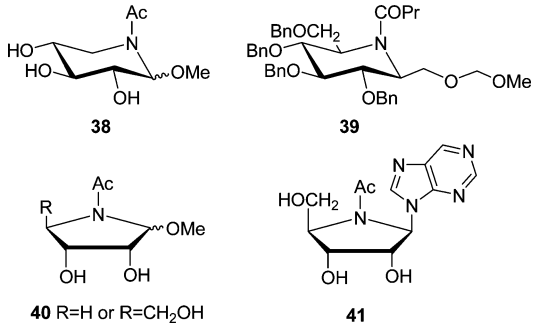


FIGURE 3. ^{1}H NMR spectra of compound **32** at the temperatures indicated (recorded in $CDCl_3$).



For compound **33** only one rotamer could be observed in solution, which should be correlated with its solid-state structure (Figure 2). It seems obvious that in the indicated *E* configuration, the oxygen atom of the amide group bisects the angle between the two acetoxymethyl groups at C-4, and such an arrangement is less sterically encumbered than its *Z* counterpart, for which the bulkier methyl group would bisect the acetoxymethyl groups.

Estimation of Rotational Barriers. Temperature-dependent NMR spectra enabled the measurement of the interconversion barriers between rotational isomers, by determining experimentally the coalescence temperature for some signals, in both $CDCl_3$ and DMSO-d_6. It is well-known that the rate constant at the coalescence point between exchanging systems in equilibrium with NMR signals showing no coupling and being of the same intensity follows the equation:[56]

$$k = \pi 2^{1/2} \Delta\nu = 2.221 \Delta\nu$$

where $\Delta\nu$ represents the full width at half-maximum of the signal at the coalescence point T_C; it also corresponds to the difference in chemical shift observed for slow exchange. Although this expression is not accurate when equilibria occur between unequally populated states, errors are usually small and it gives an approximate estimation of the barriers to rotation.

By combining the above expression with the Eyring equation, according to which the exchange rate constant decreases exponentially with the free molar activation enthalpy, and after substitution of the fundamental constants, one gets the following expression for the free molar activation enthalpy for the exchange process:[57]

$$\Delta G^{\ddagger}\ (\text{cal·mol}^{-1}) = 1.987 T_C [22.96 + \ln(T_C/\Delta\nu)]$$

Table 2 collects the different data obtained for compounds **25**, **27**, **28**, and **32**, which are quite similar in both solvents.

TABLE 2. Dynamic NMR Data for the Interconversion of the *Z*,*E* Rotamers

product	solvent	$\Delta\nu$ (Hz)	k (s^{-1})	T_C (K)	$\Delta G^{\ddagger}$ [a]	$\Delta G^{\ddagger}$ [b]
25	$CDCl_3$	116.0	257.6	328	65.2	15.6
	DMSO-d_6	26.0	57.7	317	64.4	15.4
27	$CDCl_3$	119.6	265.6	327	65.1	15.6
	DMSO-d_6	29.6	65.7	320	67.4	16.1
28	$CDCl_3$	107.6	239.0	325	65.0	15.5
	DMSO-d_6	48.82	108.4	325	67.1	16.0
32	$CDCl_3$	104.2	231.4	321	63.4	15.2
	DMSO-d_6	30.4	67.5	318	66.0	15.8

[a] In kJ mol^{-1}. [b] In kcal mol^{-1} (1 cal = 4.183 J).

Geometric Isomerization of 1,3-Oxazolidines. It was intriguing to see that the rotational pair observed for **25** converted slowly and gradually in $CDCl_3$ into a novel rotamer couple (Figure 4). This transformation should be associated with a stereochemical change of the new chiral center at C-2, generated during the imine cyclization that occurs by acetylation. Such a

(54) Saavedra, O. M.; Martin, O. R. *J. Org. Chem.* **1996**, *61*, 6987.
(55) Reist, E. J.; Gueffroy, D. E.; Blackford, R. W.; Goodman, L. *J. Org. Chem.* **1966**, *31*, 4025.
(56) (a) Breitmaier, E. *Structure Elucidation by NMR in Organic Chemistry. A Practical Guide*; John Wiley & Sons: New York, 1993; pp 63−64. (b) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; p 503.
(57) Williams, D. H.; Fleming, I. *Spectroscopic Methods in Organic Chemistry*, 4th ed.; McGraw-Hill: New York, 1984; p 103.

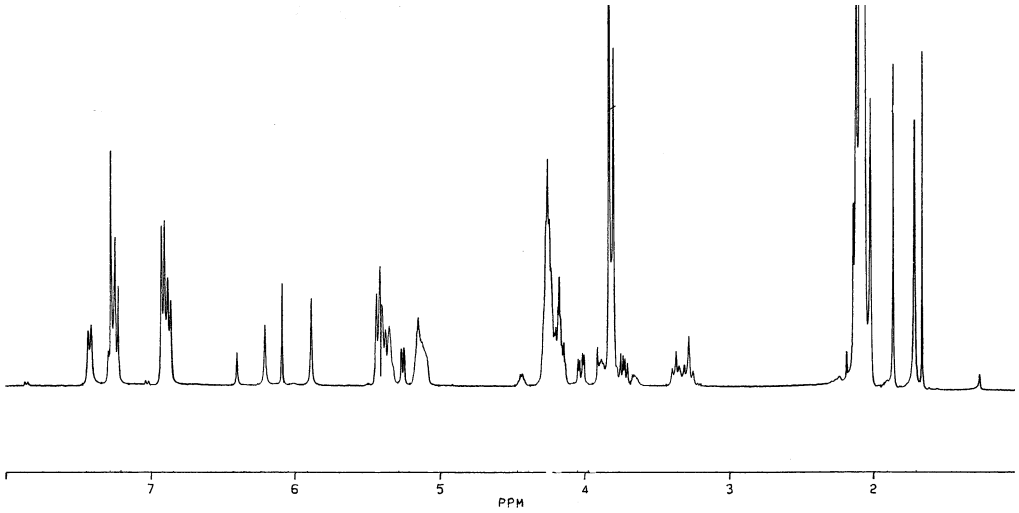


FIGURE 4. ^{1}H NMR spectrum in $CDCl_3$ of compound **25** after equilibration.

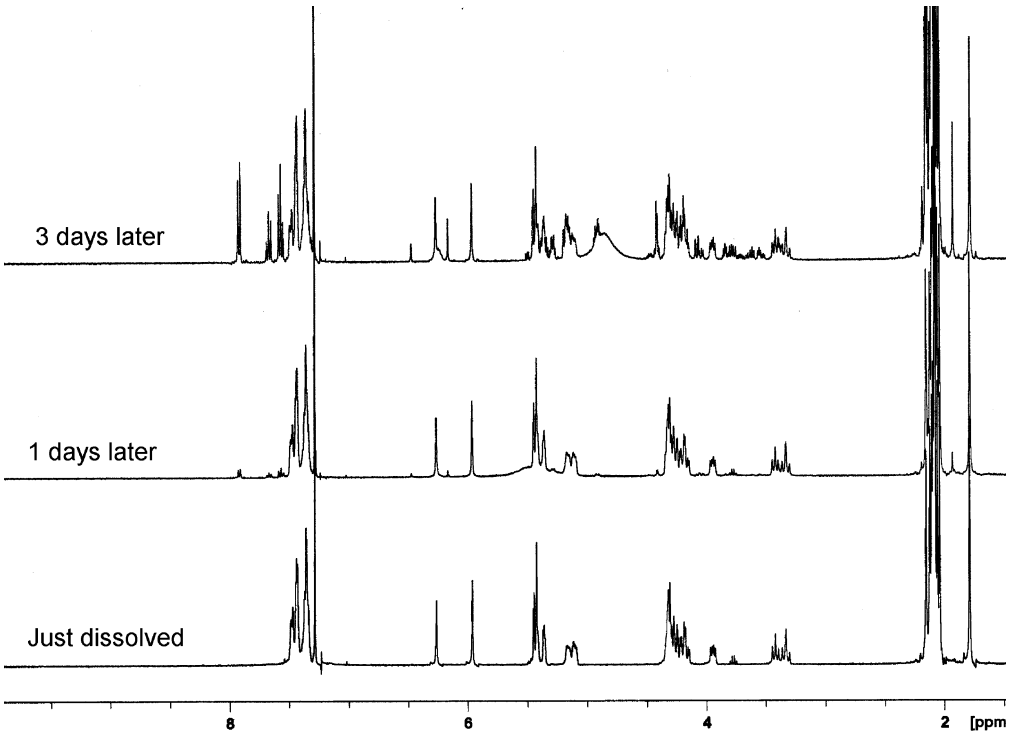


FIGURE 5. Equilibration of *Z,E* rotamers derived from **45** with their *Z,E* partners of the new isomer in $CDCl_3$ acidified with trifluoroacetic acid.

ring closure affords a kinetically favored mixture of rotamers, which further evolves into the products of thermodynamic control. This isomerization, however, was not detected in DMSO-d_6 at room temperature.

The crude mixture of synthetic **28**−**31** showed ^{1}H and ^{13}C NMR spectra similar to those obtained in the equilibration of **25** (Figure 4). On the basis of these results, it was thought that this isomerization took place via acid catalysis promoted by DCl traces in $CDCl_3$. To verify this surmise, we studied the fate of diverse oxazolidine solutions in $CDCl_3$ acidified with trifluoroacetic acid. It was shown that a slow equilibration of *Z,E* rotamers derived from the starting oxazolidine with their *Z,E* partners of the new isomer (Figure 5). The presence of the aldehydo group reveals that such an isomerization is accompanied by a degradation of the heterocyclic ring.

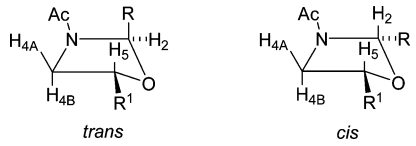


FIGURE 6. Oxazolidine ring conformations (R^1= D-*arabino*-$(CHOAc)_3CH_2OAc$, R = Ar or PhCH=CH−).

Absolute Configuration at C-2 of Chiral Oxazolidines. There are some antecedents dealing with the steric course of imine cyclization to produce oxazolidines,[58−60] although they are not completely applicable to the present case. In a further attempt to label the absolute stereochemistry at C-2, a series of NOE experiments involving the heterocyclic protons at C-2, C-4, and C-5 have been carried out.

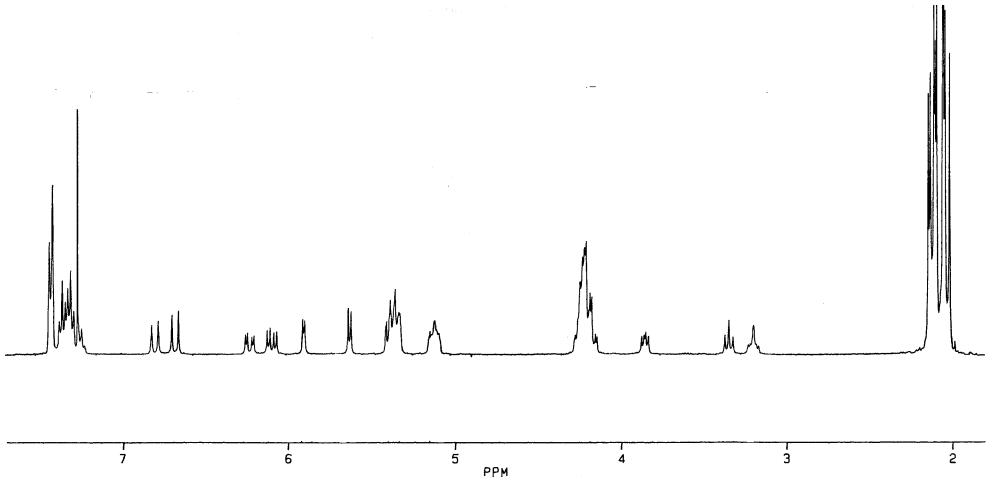


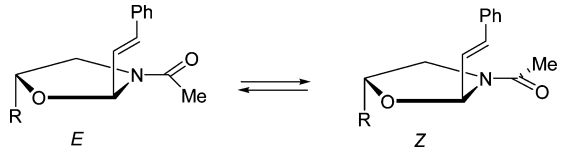
FIGURE 7. ^{1}H NMR spectrum of compound **31** (recorded in $CDCl_3$)

Had the substituent at C-2 adopted a trans relationship relative to the substituent at C-5 (polyhydroxyl chain), the oxazolidine ring would exhibit either $^5T_1$ or E_1 conformations. In such circumstances, the bulkier polyhydroxyl side chain and the H-2 proton adopt pseudoequatorial dispositions, while the substituent at C-2 would be at a pseudoaxial arrangement. This does mean that the H-2 proton lies far away with respect to the remaining oxazolidine protons and, accordingly, no appreciable NOE effects would be expected among them (Figure 6). A distinctive behavior would take place if the substituents at C-2 and C-5 had adopted a cis relationship, which would lead to pseudoequatorial configurations for such groups. The steric effect decreases and the H-2 proton lies closer to the H-5 proton and one of the protons on the C-4 position; then significant NOE effects should be observed.[61]

When such decoupling experiments are conducted on the initial rotamers (kinetic control products), no NOEs are observed for the H-2 signal and the rest of the heterocyclic protons, thus suggesting the presence of a trans isomer. Assuming that the absolute configuration at C-5 is known to be *S* (coming from D-glucamine), the stereochemistry at C-2 should logically be *R* (**24**−**32**).

Absolute Stereochemistry of Rotational Pairs. Further analysis of NMR data provides further evidence for the stereochemistry of these rotamers around the C−N bond of the amide linkage. As noted above, compound **33** exists exclusively as its *E* rotamer in solution with the methyl group of the acetamide function appearing unusually upfield (δ_{MeCON} ∼1.84 ppm), and that shielding results from the spatial arrangement of this methyl group with respect to the aromatic ring (Figure 2). Obviously this effect will be absent in the case of the *Z* rotamer, in which the methyl group lies far from the aryl substituent. For compounds **25** and **32** the ^{1}H NMR spectrum of the kinetically controlled rotamers (2*R* isomer) shows a signal for the acetyl group of one rotamer (δ_{MeCON} ∼1.72 ppm) matching that of *E*-**33**. The latter signal should therefore belong

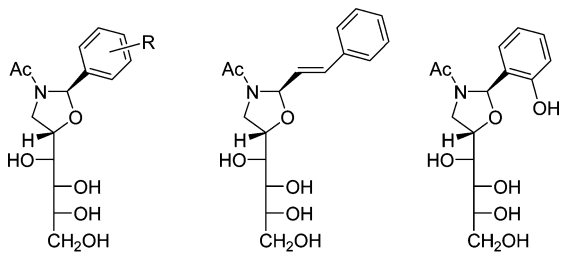
SCHEME 4



to rotamers having a similar spatial environment for the acetamido group, i.e., the *E* rotamers of **25** and **32**. These conjectures could also be confirmed by assessing the NMR spectra of the rotamers from **31** (Figure 7). This styryloxazolidine shows spectra analogous to those observed for **25** and **32**, and with a similar rotamer distribution (Scheme 4). However, there are no proton signals at chemical shifts less than 1.98 ppm. Due to the CH═CH linkage, the *N*-acetyl group is located outside of the shielding zone of the aromatic ring, and therefore this methyl group will be expected to be more deshielded as compared to the *E* rotamers of **25** and **32**.

When both kinetically controlled rotamers (2*R*-oxazolidines) of **25** isomerize to the corresponding thermodynamic products (2*S*-oxazolidines), the major rotamer shows again a shielded acetyl group (δ_{MeCON} 1.86 ppm), for which the *E* conformation has been assigned (Figure 4).

Scheme 5 displays a plausible rationale consistent with experimental data. Thus, acetylation of imines **7**−**17** does initially produce their corresponding trans isomers (**24**−**32**), having the 2*R* absolute configuration and existing as a mixture of *E* and *Z* conformers in equilibrium, the former being

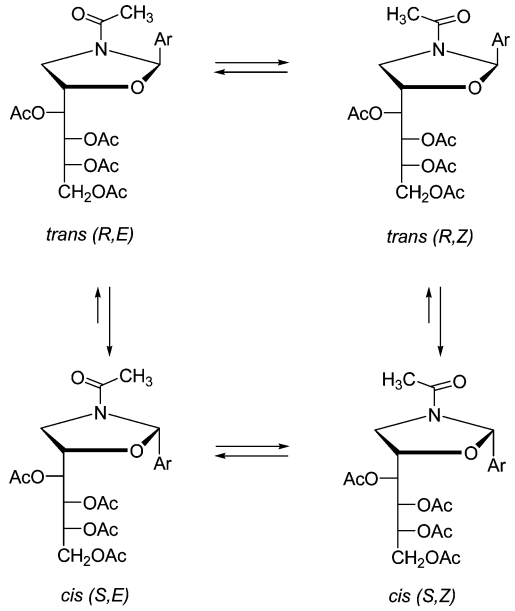


42 R=4-OH
43 R=4-MeO
44 R=4-Me
45 R=H
46 R=4-Cl
47 R=3-Br
48 R=4-NO_2

49 **50**

(58) For a revision on the cyclization of iminium ions in the synthesis of chiral heterocycles see: Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311.
(59) Just, G.; Potvin, P.; Uggowitzer, P. *J. Org. Chem.* **1983**, *48*, 2923.
(60) Khruscheva, N. S.; Loim, N. M.; Sokolov, V. I.; Makhaev, V. D. *J. Chem. Soc., Perkin Trans. I* **1997**, 2425.
(61) (a) Santiesteban, F.; Grimaldo, C.; Contreras, R.; Wrackmeyer, B. *J. Chem. Commun.* **1983**, 1486. (b) Hussain, A.; Wyatt, P. B. *Tetrahedron* **1993**, *49*, 2123.

SCHEME 5



prevalent. Under appropriate conditions, these compounds could be partially converted into the more stable cis isomers of 2*S* absolute configurations and exist again as a mixture of two conformers (Scheme 5).

Synthesis of Polyhydroxyalkyl Oxazolidines. Deacetylation of compounds **24**−**32** can easily be carried out by treatment with saturated solutions of ammonia in methanol, which affords the corresponding D-*arabino*-tetrahydroxybutyl oxazolidines **42**−**50** in good to excellent yields (68−100%). These substances maintain unaffected their trans (2*R*) stereochemistry, because deacetylation in basic medium has no effect on that chiral center.

Synthesis of *N*-acyloxazolidines by reaction of *N*-acylamino alcohols with aldehydes under acid catalysis has been reported. Therefore, we have attempted an alternative synthesis of the above substances using *N*-acetyl-D-glucamine (**51**)[62] as raw material, easily generated by reaction of **1** with acetic anhydride in methanol, which was further treated with the corresponding aldehydes in refluxing benzene with azeotropic removal of water (Scheme 6). Unfortunately, the entire range of aldehydes tested, both in the presence and the absence of *p*-toluenesulfonic acid as catalyst, failed to give *N*-acyloxazolidines (**52**), the precursor being recovered unaffected.

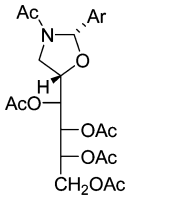
The spectroscopic data of **42**−**50** clearly support the *O*-unprotected structures, particularly a broad IR absorption of the OH groups (ν_{OH} 3600−3100 cm^{-1}) along with the amide band (ν_{CO} ∼1623 cm^{-1}) of the oxazolidine moiety. Both ^{1}H and ^{13}C NMR spectra showed duplicated signals, with singlets at ∼6 and ∼85 ppm characteristic of the heterocyclic ring. The acetamido groups appeared with distinctive chemical shifts, for instance, 1.59, 167.2, and 22.2 ppm for the major rotamer of **50**, while resonances at 2.01, 167.9, and 23.4 ppm were observed for the minor one.

Stability of *N*-Acetyloxazolidines. To test the validity of Scheme 5 as a working hypothesis representing the possible equilibria of the *N*-acetyloxazolidine rotamers in solution, a series of theoretical calculations have also been performed. Estimations have been obtained at the DFT level (B3LYP/6-31G*),[63] on compounds **25**, **27**, **30**, **32**, and their 5*S* isomers. Table 3 shows the calculated energies for the trans isomers (2*R* configured) and the corresponding cis isomers (2*S* configured).

TABLE 3. Calculated Relatives Energies of Cis/Trans and *Z*/*E* Configurations of Some 1,3-Oxazolidines[a,b]

	cis (5*S*)		trans (5*R*)	
product	*E*	*Z*	*E*	*Z*
25	0.00	1.21	8.85	14.56
27	1.42	0.00	0.40	13.46
30	0.00	2.60	0.11	15.95
32	0.00	0.94	3.70	12.05

[a] At DFT level (B3LYP/6-31G*) in the vacuum. [b] In kcal mol^{-1}.



53 R=4-MeOC$_6$H$_4$
54 R=C$_6$H$_5$
55 R=4-NO$_2$C$_6$H$_4$
56 R=2-Me$_2$COC$_6$H$_4$

The above results are consistent with our experimental observations and stereochemical conclusions. The trans oxazolidines are less stable and should therefore be the kinetic product, the energy difference relative to its cis isomers, thereby accounting for the conversion, being the thermodynamic product.

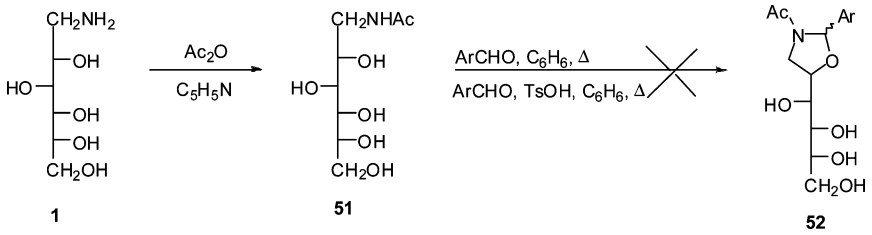
Formation of Oxazolidine Rings: Mechanistic Considerations. At first sight, the most intuitive mechanistic hypothesis explaining the formation of oxazolidines **24**−**32** should first involve cyclization of imine derivatives followed by acetylation as shown in Scheme 7. However, imines such as **25**, **31**, or **32** were stable in pyridine-d_5 solutions for prolonged reaction times and no oxazolidine formation could be observed by NMR monitoring.

These results clearly suggest that formation of oxazolidines from imines under acetylating conditions should be occurring by a mechanism other than that of Scheme 7. An alternative hypothesis, both plausible and consistent with the whole range of experiments, is depicted in Scheme 8. Given the inherent basicity of the iminic nitrogen, formation of the corresponding acetyliminium ion **60** should be occurring quickly, which would give rise to the heterocyclic derivative, a step presumably

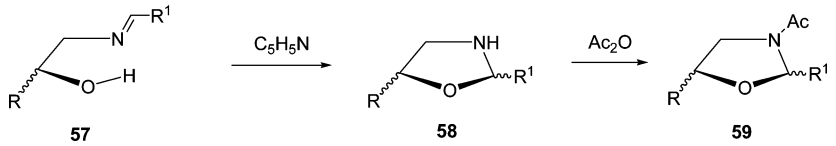
(62) Whistler, R. C.; Pauzer, H. P.; Roberts, H. J. *J. Org. Chem*. **1961**, *26*, 1583.

(63) (a) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 2004 User's Reference*; Gaussian, Inc.: Wallingford, CT, 2004. (b) Becke, A. D. *J. Chem. Phys*. **1993**, *98*, 5648. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1998**, *37*, 75. (d) Hehre, W. J.; Radom, L.; Scheleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

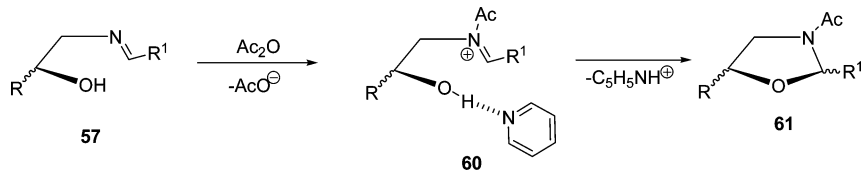
SCHEME 6



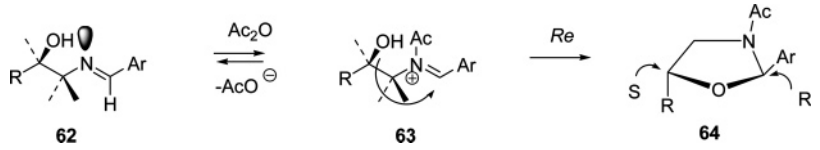
SCHEME 7



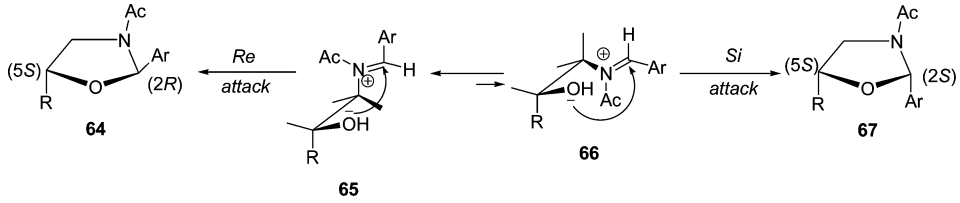
SCHEME 8



SCHEME 9



SCHEME 10



favored by basic catalysis from solvent molecules. Formation of 1,3-oxazolidines arises from a *5-endo-trig* cyclization[64] is entropically favored with respect to the alternative *6-endo-trig* that leads to a 1,3-oxazine ring.

The stereochemical outcome can be rationalized assuming that cyclization of the acetyliminium cation takes place through the most stable conformation. Iminium ion cyclization has in fact become a useful strategy in the synthesis of chiral heterocycles, particularly alkaloid skeleta.[58]

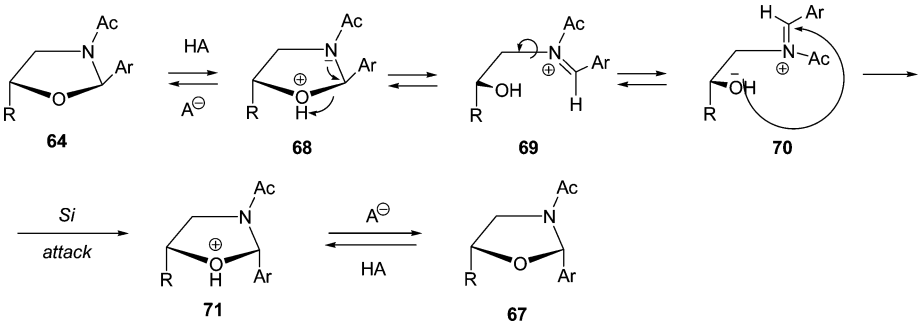
The first chiral center of D-glucamine has the *S* configuration and its hydroxyl substituent lies in the *Re* face of the acetyliminium ion. If the subsequent cyclization took place through such a face, the newly created chiral center would be *R* and the relative stereochemistry between the polyhydroxyl chain at C-5 and the aromatic substituent at C-2 would be trans, thus generating the kinetic product (Scheme 9). The starting conformations **65** and **66** would lead by attack to the Re or *Si* faces to the corresponding transition structures, which would ultimately evolve into the oxazolidine derivatives (Scheme 10). A conformation such as **66** (and hence the corresponding transition structure) should be less stabilized than **65**, because the bulkier acetyliminium group bisects the angle between the hydroxyl substituent and the sugar chain, thus generating two strong *gauche* interactions; conversely, only one *gauche* interaction with the hydroxyl group occurs in **65**. Further transformation into the more stable cis isomer **67** (of 2*S* configuration) should be occurring under acid catalysis, a fact that regenerates the cation intermediate, which slowly and irreversible cyclizes via the *Si* face (Scheme 11). The requirement for acid catalysis is also supported by other experimental observations. Thus, elimination of acid substances in $CDCl_3$, by passing the solution through alumina, inhibits the isomerization. Likewise, no isomerization takes place when the process is conducted in DMSO-d_6, lacking acid properties.

Conclusions

This work demonstrates that condensation of aromatic aldehydes with 1-amino-1-deoxypolyols, exemplified here by D-glucamine, produces either imine or enamine skeleta. The former derivatives, under conventional *O*-acetylation, give rise to

(64) Alva, M. E.; Chokotho, N. C. J.; Jarvis, T. C.; Johnson, C. D.; Lewis, C. C.; McDonnell, P. D. *Tetrahedron* **1985**, *41*, 5919.

SCHEME 11



unexpected *N*-acetyl-1,3-oxazolidine chirons, whose structures are supported by spectroscopic data. This behavior can also be extended to an imine derived from tris(hydroxymethyl)methylamine and salicylaldehyde; the resulting oxazolidine structure (**33**) has been elucidated unambiguously by X-ray diffraction analysis. The *N*-acetyloxazolidines undergo dynamic equilibria in solution where an initial mixture of *E*,*Z* rotamers (around the *N*-acetyl bond) of a trans oxazolidine evolves into a more stable cis isomer that equally exists as a mixture of rotational isomers, in which the *E* rotamer is preferentially formed. By means of theoretical calculations and NMR experiments, we have now figured out how these transformations occur and a mechanistic rationale satisfactorily accounts for all the experimental observations. Such functionalized chiral oxazolidines bearing a polyhydroxyl side chain constitute appropriate raw materials for further use in asymmetric methodologies.

Experimental Section

Compound **51** was synthesized as described.[62]

Condensation of D-Glucamine with Arylaldehydes. Method A: To a solution of D-glucamine (10.0 g, 55.2 mmol) in water (70 mL) was added slowly a solution of the corresponding aldehyde (55.0 mmol) in the minimal volume of methanol. The reaction mixture was kept at room temperature under stirring until the appearance of a solid within a few minutes. Precipitation was continued at the refrigerator, then the solid was filtered and washed successively with water, cold ethanol, and diethyl ether.

Method B: A mixture of D-glucamine (0.91 g, 5.0 mmol) and the corresponding aldehyde (7.5 mmol) in benzene (15 mL) was refluxed with azeotropic separation of water during 5 h. Then the solid was filtered and washed with benzene.

1-Deoxy-1-(4-hydroxybenzylidene)amino-D-glucitol (7): method A 92%, method B 99%; mp 227−228 °C; $[\alpha]^{23}_D$ +12.8 (*c* 0.5, DMSO); IR (KBr) ν_{max} 3400−2900 (OH), 1642 (C═N), 1608, 1587 (aryl), 1104, 1084, 1020 cm^{-1} (C−O); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.70 (1H, bs, OH-arom), 8.16 (1H, s, CH═N), 7.55 (2H, d, J = 8.4 Hz, H-arom), 6.81 (2H, d, J = 8.0 Hz, H-arom), 4.67−4.31 (4H, bs, OH), 3.82 (1H, c, $J_{1,2} = J_{2,3} = J_{C2,OH}$ = 4.8 Hz, H-2), 3.68 (2H, m, H-1, H-3), 3.60 (1H, dd, $J_{5,6}$ = 2.4 Hz, $J_{6,6'}$ = 8.8 Hz, H-6′), 3.51 (1H, m, H-1), 3.39 (1H, m, H-4, H-5, H-6′); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.7 (C═N), 160.2, 130.1, 127.9, 115.9 (C-arom), 73.0 (C-2), 72.4 (C-4), 71.9 (C-5), 70.3 (C-3), 64.0 (C-6), 63.6 (C-1). Anal. Calcd for $C_{13}H_{19}NO_6$ (285.29): C, 54.73, H, 6.71, N, 4.91. Found: C, 54.58; H, 6.56, N, 4.95.

Acetylation of D-Glucamine Schiff Bases: Synthesis of Chiral Oxazolidines. To a solution of the corresponding 1-(arylmethylene)-amino-1-deoxy-D-glucitol (5.0 mmol) in pyridine (6.7 mL) was added acetic anhydride (6.5 mL). The reaction mixture was kept at 0 °C for 24 h, and then it was poured into ice−water. If the resulting product was an oil this was extracted with chloroform (3 × 50 mL), and the organic layer was sequentially washed with 1 N HCl (2 × 50 mL), a saturated solution of $NaHCO_3$ (2 × 50 mL), and distilled water (2 × 50 mL). The organic layer was dried ($MgSO_4$) and evaporated. If the resulting product was a solid this was separated by filtration and washed with water.

(2*R*,5*S*)-2-(4-Acetoxyphenyl)-3-acetyl-5-(1,2,3,4-tetra-*O*-acetyl-D-*arabino*-tetritol-1-yl)oxazolidine (24*E*,*Z*): 42%; recrystallized from ethanol had mp 149−151 °C; $[\alpha]^{24}_D$ −33.0 (*c* 0.5, chloroform); IR (KBr) ν_{max} 1747 (C═O), 1652 (C═O, amide), 1225 (C−O−C, ester), 1082, 1034 cm^{-1} (C−O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (2H, d, J = 7.6 Hz, H-arom), 7.34 (2H, d, J = 7.6 Hz, H-arom), 7.13 (2H, d, J = 7.2 Hz, H-arom), 7.05 (2H, d, J = 7.6 Hz, H-arom), 6.29 (1H, s, H-2$_E$), 5.96 (1H, s, H-2$_Z$), 5.42 (1H, m, H-2′$_E$), 5.39 (1H, m, H-2′$_Z$), 5.39 (1H, m, H-1′$_E$), 5.31 (1H, m, H-1′$_Z$), 5.13 (1H, m, H-3′$_E$), 5.08 (1H, m, H-3′$_Z$), 4.29−4.16 (4H, m, H-4$_Z$, H-4′$_Z$, H-5$_Z$, H-5$_E$, H-4″$_Z$ and H-4″$_E$), 3.90 (1H, dd, $J_{4,4}$ = 9.2 Hz, $J_{4,5}$ 5.6 Hz, H-4$_E$, oxaz), 3.31 (1H, t, $J_{4,4} = J_{4,5}$ = 9.8 Hz, H-4$_E$), 3.21 (1H, t, $J_{4,4} = J_{4,5}$ = 8.0 Hz, H-4$_Z$, oxaz), 2.30, 2.28, 2.08, 2.06, 2.03, 2.01 (10 × 3H, s, CH_3 acetates); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.3, 170.1, 170.0, 169.8, 169.3 (C═O), 169.1, 168.1 (N−*C*═O), 151.5, 150.8, 136.5, 135.7, 128.1, 122.1, 121.2 (C-arom), 89.7 (C-2$_Z$), 88.4 (C-2$_E$), 76.6 (C-5$_E$), 76.4 (C-5$_Z$), 69.1, 69.0 (C-2′$_Z$ and C-2′$_E$), 68.6, 68.4 (C-1′$_Z$ and C-1′$_E$), 68.1, 68.0 (C-3′$_Z$ and C-3′$_E$), 61.5 (C-4′$_Z$ and C-4′$_E$), 47.4 (C-4$_E$), 46.5 (C-4$_Z$), 23.2 (CH_3, Ac−N of the *E* isomer), 22.8 (CH_3, Ac−N of the Z isomer), 21.1, 20.8, 20.7, 20.6, 20.4 (CH_3, acetates). Anal. Calcd for $C_{25}H_{31}NO_{12}$ (537.51): C, 55.86; H, 5.81; N, 2.61. Found: C, 55.37; H, 5.84; N, 2.49.

Synthesis of Polyhydroxyalkyl Oxazolidines. To a solution of the corresponding oxazolidine (0.98 mmol) in methanol (16 mL) was added a saturated solution of ammonia in methanol (16 mL). The transformation was monitored by thin layer chromatography (benzene−methanol 9:1) and then the mixture was filtered off and evaporated to dryness at a temperature below 30 °C. The title compound is obtained as a solid.

(2*R*,5*S*)-3-Acetyl-2-(4-hydroxyphenyl)-5-(D-*arabino*-tetritol-1-yl)oxazolidine (42*E*,*Z*): 98%; recrystallized from ethanol had mp 233−234 °C; $[\alpha]25_{578}$ −37.0 (*c* 0.5, pyridine); IR (KBr) ν_{max} 3500−3100 (OH), 1612 (C═O), 1518 (aryl), 1234 (C−N), 1079, 1038 cm^{-1} (C−O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (2H, bs, OH-arom), 7.30 (1H, bs, H-arom), 7.21 (1H, d, J = 8.0 Hz, H-arom), 7.19 (1H, d, J = 8.4 Hz, H-arom), 6.78 (1H, d, J = 8.0 Hz, H-arom), 6.70 (1H, d, J = 8.4 Hz, H-arom), 5.96 (1H, s, H-2$_E$), 5.88 (1H, s, H-2$_Z$), 4.71 (2H, m, OH-1$_Z$ and OH-1$_E$), 4.53 (2H, m, OH), 4.37 (2H, m, OH), 4.14 (1H, dt, $J_{4A,5}$ = 10.0 Hz, $J_{5,1'} = J_{4B,5}$ = 6.4 Hz, H-5$_Z$), 4.06 (2H, m, $J_{5,1'} = J_{4B,5}$ = 6.8 Hz, H-4$_E$ and H-5$_Z$), 3.90 (1H, dd, $J_{4,4}$ = 9.6 Hz, $J_{4,5}$ = 5.6 Hz, H-4$_Z$), 3.78 (2H, m, H-1′$_Z$ and H-1′$_E$), 3.59 (2H, m, H-4′$_Z$ and H-4′$_E$), 3.49 (2H, m, H-3′$_Z$ and H-3′$_E$), 3.39 (2H, m, H-4″$_Z$ and H-4″$_E$), 3.23 (2H, m, H-2′$_Z$ and H-2′$_E$), 3.13 (2H, t, $J_{4,4} = J_{4,5}$ = 9.6 Hz, H-4$_E$ and H-4$_Z$, oxaz), 2.00 (3H, s, CH_3, *Z*), 1.58 (3H, s, CH_3, *E*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 167.5 (C═O), 158.5, 157.8, 131.0, 130.51, 129.3, 128.8, 115.7, 115.0 (C-arom), 89.8 (C-2$_E$), 89.3 (C-2$_Z$), 80.4 (C-5$_Z$), 79.8 (C-5$_E$), 71.7, 71.6, 71.4, 71.3, 71.2, 70.9 (C-1′$_Z$ and C-1′$_E$ and C-2′$_Z$ and C-2′$_E$, C-3′$_Z$ and C-3′$_E$), 63.8 (C-4$_Z$ and C-4$_E$), 48.4

(C-4′$_E$), 47.4 (C-4′$_Z$), 23.7, 22.9 (4 CH_3). Anal. Calcd for $C_{15}H_{21}NO_7$ (327.33): C, 55.04, H, 6.47, N, 4.28. Found: C, 54.93, H, 6.39, N, 4.18.

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Supporting Information Available: General methods, syntheses, and structural characterization for compounds **8**−**20**, **22**, **23**, **25**−**33**, and **43**−**50**, NMR spectra for all new compounds, variable-temperature experiments for compounds **25**, **27**, **28**, and **32**, Cartesian coordinates of compounds **25**, **27**, **28**, and **32**, and crystallographic data for compound **33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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