Application of the Quiral Program to the Challenge of Myoinositol Synthesis

Jean-Marc Nuzillard, Aline Banchet, and Arnaud Haudrechy*

Institut de Chimie Moléculaire de Reims, UMR CNRS, Université de Reims, BP 1039, F-51687 REIMS Cedex 2, France

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The Quiral program helps chemists to choose synthetic approaches to myoinositol or its protected derivatives.

The Quiral computer program that we have recently developed[1] analyzes the 3D structure of a target organic molecule to find which sugar(s) can be used as a starting material for its synthesis. The program also proposes schemes for the preparation of rare or unavailable sugars whose chiral centers fit with those of the target molecule.

The idea of computer assisted retrosynthetic analysis emerged several decades ago. The first computer program was proposed by E. J. Corey as early as 1969,[2] according to the guidelines defined by G.-E. Vléduts.[3] This pioneering work was followed by others (Hendrickson,[4] Ugi,[5] and Gasteiger,[6] see also reviews in ref 7). The most successful program was undoubtedly 'Logic and Heuristics Applied to Synthetic Analysis' (LHASA), that was developed at Harvard University by E. J. Corey.[8]

The synthesis of enantiopure molecules remains a challenge in organic synthesis. The main strategies in this field rely either on asymmetric catalysis or on the use of compounds derived from the natural chiral pool. In the latter approach, asymmetric centers from carefully selected starting materials are reused to elaborate those in the target molecules. Among naturally chiral compounds, carbohydrates are of particular importance because they generally present adjacent asymmetric centers that may be "recycled" in target molecules that also contain adjacent asymmetric centers. This approach minimizes the waste of high value carbon atoms. S. Hanessian created the Chiron software which relates a complex structure to simpler chiral precursors, in order to guide chemists in the synthesis of enantiopure molecules.[11] We wrote the Quiral program with the same goal in mind, but so that a chemist may more quickly identify to which sugar(s) a synthetic target is structurally related. We chose to focus on sugars as starting materials and gave ways to identify inversion of configurations (inter-relations between sugar families), keeping in mind the practical feasability.

Myoinositol and its protected derivatives are carbocyclic compounds involved in numerous biological processes. For example, inositol phosphates and phosphatidyl inositols play a crucial role as secondary messengers in intracellular signal transduction.[9] Other natural myoinositol derivatives have been involved in calcium mobilization, chloride secretion, exocytosis, cytoskeletal regulation, insulin stimulation, intracellular trafficking of vesicles, and anchoring of proteins to cell membranes.[10]

* Corresponding author phone: +33 (0)3 26 91 32 36; fax: +33 (0)3 26 91 31 66; e-mail: arnaud.haudrechy@univ-reims.fr.

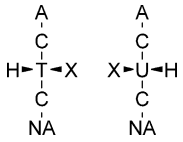

Figure 1. Definition of the T and U configuration of C# atoms, as used by the Quiral program. In aldoses, T and U configurations are like R and S, respectively (a Fischer-type representation was chosen).

Myoinositol is particularly challenging from a stereochemical point of view. It is achiral in its unprotected form as well as when the hydroxy groups in positions 1 and 4 are protected (Scheme 1). Chirality results when any one of the hydroxy groups in positions 2, 3, 5, or 6 are modified. The structural complexity of myoinositol makes it a good candidate to demonstrate how Quiral helps chemists to identify the most adequate starting material in a sugar-based synthetic approach. It does not propose a fully detailed synthetic scheme yet but provides a quick and easy way to define a global strategy.

SOFTWARE DESCRIPTION

In order to be as accurate as possible, a list of definitions is necessary. A $C^{\#}$ atom is a carbon bound to two carbon atoms, a hydrogen atom, and an X atom, X being oxygen, nitrogen, sulfur, or any halogen. A Q-sugar is an aldose molecule that contains from $p = 3-6$ carbon atoms and therefore $n = p - 2$ adjacent $C^{\#}$ atoms. The aldehyde carbon of a Q-sugar is its A-end (anomeric end), and the primary alcohol is the NA-end (nonanomeric end). In order to avoid confusion with conventional R and S labeling, T and U have been introduced to qualify the configuration of the $C^{\#}$ atoms (Figure 1). In Q-sugars, R chiral centers are of the T type, and S chiral centers are of the U type. The configuration of the chiral atoms in a Q-sugar is simply summarized by a list of its "T or U's", arbitrarily starting from the $C^{\#}$ that is bonded to the A-end. With this convention, the reference of D-glucose is "TUTT".

A target molecule contains one or more clusters of adjacent $C^{\#}$ atoms. By definition, a cluster is either linear or monocyclic. A linear cluster has two ends, one qualified as the A-end and the other one qualified as the NA-end, without any consideration of the oxidation state. In a cyclic cluster, two adjacent $C^{\#}$ atoms are arbitrarily transformed into an A-end and an NA-end. When an X atom that is bonded to a $C^{\#}$ is not an oxygen, its configuration is automatically

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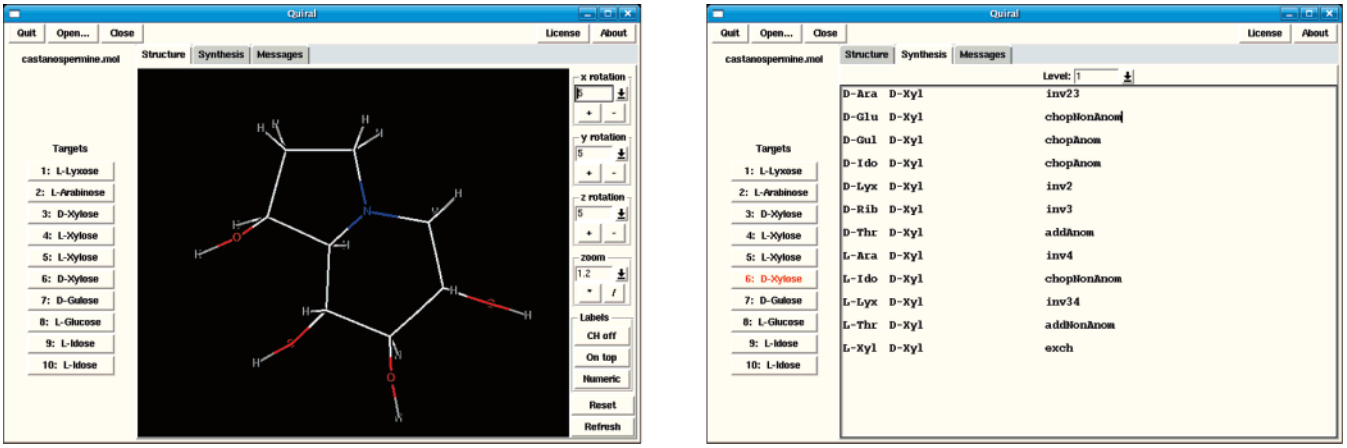
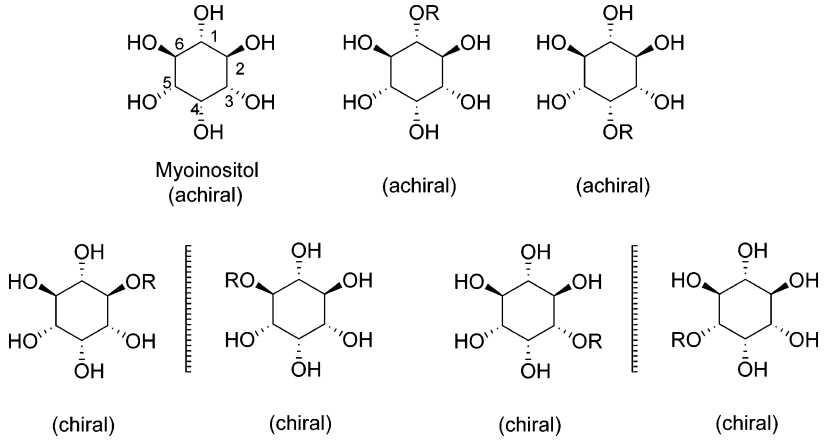


Figure 2. The user interface of the Quiral program: (a) the "Structure" page, once a molecular structure file has been read, and (b) the "Synthesi" page, once a Q-target has been selected.

Scheme 1. Myoinositol and Monoprotected Derivatives



inverted because the introduction of the X atom is assumed to require a substitution reaction that inverts configuration. A Q-target of a target molecule is a Q-sugar whose reference exactly matches the one of a cluster of C# atoms within this target.

A Q-reaction transforms a Q-sugar into another Q-sugar. In a general reaction scheme (Scheme 1), a Q-reactant is transformed into a Q-target, possibly with a Q-subtarget(s) as intermediate(s), to obtain the desired asymmetric configurations in the target. Q-reactants and Q-subtargets are also Q-sugars. A particular Q-target may be very expensive or, more generally, not suitable to start with in a practical synthesis. A Q-scheme is succession of one or more Q-reactions that transforms a Q-reactant in a Q-target. Q-schemes that contain up to three Q-reactions are proposed by Quiral to solve this type of synthetic problem. The list of Q-reactions includes the following: the inversion of a single C# (Mitsunobu reaction, for example), the inversion of two adjacent C#s (epoxide formation and opening), the exchange of the A-end and the NA-end, the cleavage of one of the ends, and the addition of a carbon atom to one of the ends. For the latter reaction, the possible generation of a new C# with either a T or a U configuration is considered.

The Quiral program reads a 3D MDL (http://www.mdli.com, accessed June 6, 2007) MOL file of the target molecule, that is conveniently created by ChemDraw 3D (http://www.cambridgesoft.com, accessed June 6, 2007). Quiral is written in the Perl script language (http://www.perl.com, accessed June 6, 2007), taking advantage of its availability for a wide range of computer operating systems, of its object-oriented programming features, and of the existence of a wide library of software modules (a description that is admittedly also valid for nearly all modern script languages).

The first time Quiral is run on a computer it creates a file named "schemes" that contains all the Q-schemes made of one to three Q-reactions. This file is generated by the "schemes.pl" Perl script only if it does not yet exist. The names and structure of the available sugars is taken from "sugars.txt", while the Q-reactions are coded within the perl module "sugars.pm". A Q-sugar is internally represented either by its "T or U" character string or by its abbreviated chemical name, such as L-Ara for L-arabinose. The latter form is used to represent a Q-reaction in the "reactions.pm" module as a [initial Q-sugar, reaction name, final Q-sugars] triplet. Reaction names are character strings: "inv2", "inv3", "inv4", "inv5" for the inversion of a single C#, "inv23", "inv34", "inv45" for the inversion of two adjacent C#s, "exch" for the exchange of the A-end and of the NA-end, "chopAnom", "chopNonAnom" for the elimination of a chain extremity, and finally "addAnom", "addNonAnom" for chain elongation reactions. A "Reactions" object contains the list of all possible Q-reaction triplets. Such an object is build by the "schemes.pm" module to create a "Schemes" object that allows the connection of any Q-sugar with any other Q-sugar through all Q-schemes made of up to three Q-reactions. A "Schemes" object is created by the "schemes.pl"

Table 1. Myoinositol Analysis Using the Quiral Program[a]

pentoses	occurrences	screenshot identifier	reference
D-arabinose	**1**	1	UTT
L-arabinose	**1**	2	TUU
D-lyxose	1	3	UUT
L-lyxose	1	4	TTU
D-ribose	**1**	5	TTT
L-ribose	1	6	UUU
D-xylose	**3**	7, 8, and 9	TUT
L-xylose	3	10, 11, and 12	UTU
hexoses	occurrences	screenshot identifier	reference
D-allose	0		
L-allose	0		
D-altrose	1	13	UTTT
L-altrose	1	14	TUUU
D-galactose	0		
L-galactose	0		
D-glucose	**1**	15	TUTT
L-glucose	1	16	UTUU
D-gulose	1	17	TTUT
L-gulose	1	18	UUTU
D-idose	2	19 and 20	UTUT
L-idose	2	21 and 22	TUTU
D-mannose	0		
L-mannose	0		
D-talose	1	23	UUUT
L-talose	1	24	TTTU

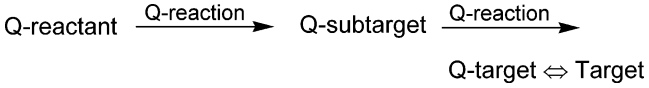
[a] Number of occurrences/screenshot identifier, corresponding to the Supporting Information/Q-sugar reference.

script and then serialized by the "Storable" standard Perl module as the "schemes" binary file. This file is the only link between the strictly chemical part of the Quiral software and the graphical user interface.

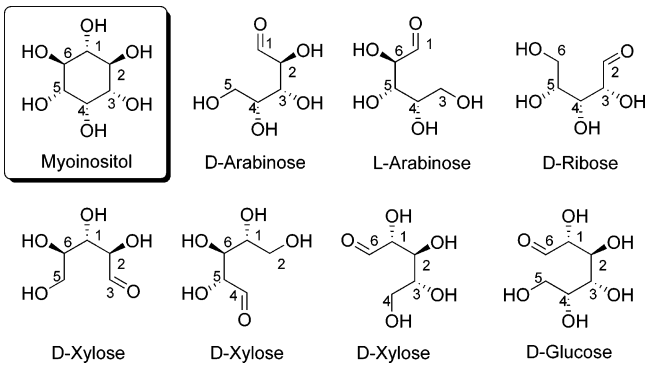
When "quiral.pl" is launched, the interface window appears, composed of three tabbed pages. Each page is dedicated to a particular task: molecular structure drawing, Q-scheme display, and message posting. The latter page shows up first, posts the "About.." message, and invites the user to read the license file. The 3D.mol file of the target molecule for which a retrosynthetic analysis is desired is accessed by the "Open..." button. The selected molecule shows up, as visible in Figure 2a. A.mol file contains atom and bond descriptions that are needed by "molecule.pm" to build a "Molecule" object. The C# atoms are then identified and grouped into clusters. In each cluster, either linear or cyclic, an A-end and an NA-end are defined; the other atoms then receive their "T" or "U" label according to the rule that is illustrated in Figure 1. Definition of the "T or U" value of a C# within a cluster boils down to the calculation of the determinant of a three vector set, to know if it forms a right-handed or a left-handed coordinate system.

The clusters that contain three or more C# atoms are the only ones retained for further analysis. All pentose and hexose Q-sugars, whose structures and names are imported from the "schemes" file, are then searched for within all clusters to define the Q-target set of the molecule. For example, a four-membered linear cluster (C_1 to C_4) matches with 2 pentoses (C_1 to C_3 and C_2 to C_4) and 1 hexose (C_1 to C_4), each being placed in two directions along the cluster (C_3 to C_1, C_4 to C_2, and C_4 to C_1), thus providing a 6 Q-target set. Of course, identical Q-targets may exist, depending on the repartition of the "T or U" within the cluster. Atoms, bonds, and clusters are implemented in Quiral as objects.

Scheme 2. General Scheme for the Creation of Adjacent Asymmetric Centers in a Given Target Molecule



Scheme 3. Myoinositol Relationships with Chosen Carbohydrates

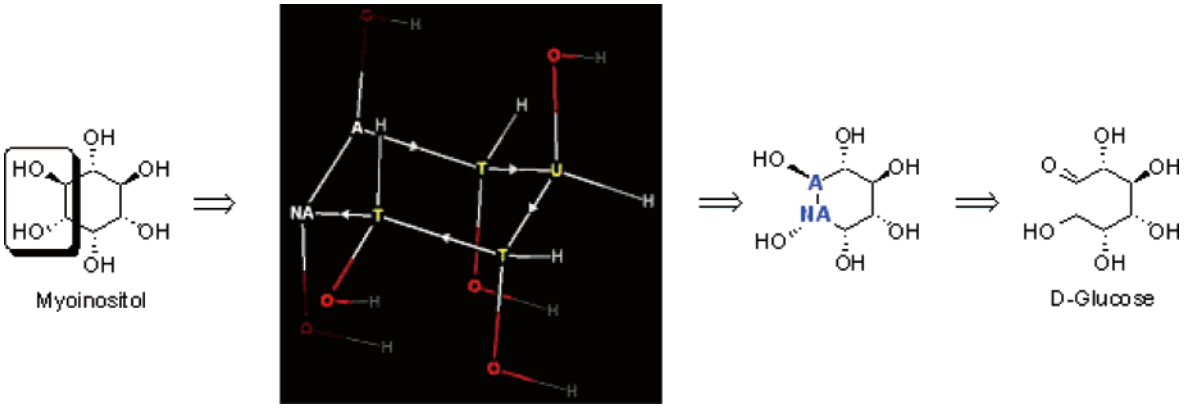


The sets of such objects are also objects, whose addresses are members of the current "Molecule" object.

The "moldro.pm" package contains all that is needed to draw a molecule on screen, seen from various view angles, at different scales and with options that will be detailed hereafter. Coordinate transformation mathematics is delegated to the "mat.pm" module. The "Moldro" class is a subclass of "Molecule", considering that a "Moldro" is a "Molecule" that is able to draw the information it contains. The whole user interface is laid out by "Molshow.pm" when a "Molshow" object is created by the execution of the top level "quiral.pl" script. All drawing operations are performed by the standard Tk module and its astonishingly powerful Canvas widget class.

Molecular rotations are controlled by three widgets, one per rotation axis, and view scaling by a fourth one. Three toggle buttons change the way a molecule is displayed. The "CH on"/"CH off" button hides or shows the H atoms that are bonded to carbon atoms. This can be useful to improve the drawing readability. The "on top"/"in place" button controls the z-ordering of the graphical objects. In the "in place" mode all objects are drawn from the most distant ones to the closest ones, atom labels included. This gives the feeling of depth dimension on screen but may obscure label reading. In the "on top" mode, the labels are drawn after all bonds have been displayed. This sometimes not only results in drawings that look like the famous Escher "Waterfall" painting but also may ease information readability. The "Normal"/"Numeric" button switches between the display of atom labels and atom numbers, as defined in the molecule.mol file. The "Reset button" redraws the molecule in the position it first appeared on screen and that is optimized to occupy a maximum area for a given scaling factor. This effect is obtained by computing the eigenvalues and eigenvectors of the molecule inertia tensor. If I_X, I_Y, and I_Z are the three inertia moments ($I_X \leq I_Y \leq I_Z$), associated with the X, Y, and Z directions, then the molecule is rotated so that the X axis is superimposed with the horizontal screen axis and the Y axis with the vertical screen axis. The "Refresh" button redraws the molecule in its current state and is only useful when the size of the drawing area has been modified by the user.

Scheme 4. Myoinositol Starting from D-Glucose, as Found by Quiral



The list of the molecule Q-targets is placed on the leftmost panel of the interface window. Each Q-target is associated with a button that, when pressed, modifies the way the molecule is drawn and writes information about the molecular synthesis on the "Synthesis" page of the graphical interface, as shown in Figure 2b. A selected Q-target appears in the molecule drawing area as if its atoms were highlighted (the other parts of the molecule are shaded). The A-end and the NA-end labels are made visible, and arrows indicate the way from the former to the latter through chemical bonds. The "T or U's" of each $C^{\#}$ within the selected Q-target are also made visible. The "Synthesis" page provides all Q-schemes that lead to the Q-target. The maximum number of involved Q-reactions (between 1 and 3) is the level parameter that can be adjusted by the user by means of a list widget. The reaction display area is divided in four columns. Each line corresponds to a Q-scheme. It successively indicates the name of the Q-reactant, the name of the Q-target, the Q-subtarget list (empty if the level is 1, a single Q-sugar if the level is 2, a Q-sugar pair if the level is 3), and the list of Q-reactions that constitute the current Q-scheme.

THE CHALLENGE OF MYOINOSITOL SYNTHESIS

In the case of myoinositol, the Quiral program enabled us to choose the carbohydrates that best fit the myoinositol backbone among the 8 pentoses and 16 hexoses (see Table 1 and the Supporting Information).

From these lists as well as from careful consideration of the depicted structures the user is able to select a backbone as the basis for a viable chemical synthesis. The obvious choice of D-arabinose, L-arabinose, D-ribose, D-xylose, and D-glucose as inexpensive starting materials is the first step toward a possible synthetic solution. Scheme 3 shows the stereochemical relationships between these carbohydrates and myoinositol.

Because the myoinositol skeleton is composed of six carbons, starting from a hexose would seem to be the best possible choice, namely D-glucose (Scheme 4). Unfortunately, the desired connection involves a 1,2-*trans*-diol relationship. Key steps such as a pinacol[12] or a metathesis reaction followed by selective osmylation[13a,d,e,g,14] cannot be used.

As a result, the different pentoses chosen in the Quiral answer set should then be considered. Scheme 5 depicts three nonfavorable approaches from D-arabinose, L-arabinose, and D-ribose because of a 1,2-*trans*-diol relationship.

With D-xylose as a starting material, two approaches are favored in which a 1,2-*cis*-diol relationship and a 1,2-syn selective vinylation is the key step (favored with chelating counter cations) as shown in Scheme 6.

MYOINOSITOL AND 3- OR 6-MONOPROTECTED DERIVATIVES

Inspired by these results, we can, for example, propose the following synthesis (Scheme 7).

The D-xylose aldehyde function is first protected with ethanethiol under Lewis acid conditions. After selective protection of the primary alcohol with a trityl group, extensive benzylation of the three resulting free alcohol groups, and deprotection under oxidative conditions, aldehyde **1** could be obtained. 1,2-Syn vinylation and subsequent protection of the generated alcohol is possible with a protected hydroxy group α to the aldehyde which promotes chelation and orients the vinyl attack.[15] Deprotection of the primary alcohol, followed by oxidation and Wittig olefination, would allow the key metathesis ring closure.

This approach can be very useful for the monoprotected derivatives of myoinositol because an accurate choice of the protecting group (R) would direct the final controlled osmylation (depending on steric hindrance, chelating control, etc.), giving access to the individualized 3 and 6 positions.

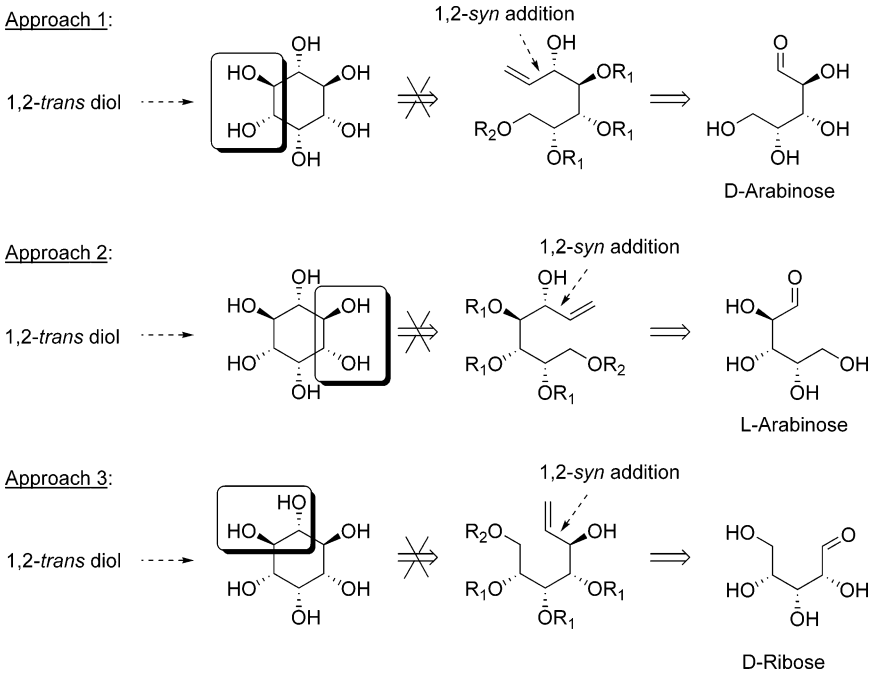
2-MONOPROTECTED DERIVATIVES

The same approach starting from D-xylose can also give access to 2-monoprotected derivatives of myoinositol as schown in Scheme 8. The D-xylose aldehyde function is protected with ethanethiol under Lewis acidic conditions, and after selective external diol protection with an isopropylidene group, selective protection on the position closest to the dithioacetal moiety and benzylation of the resulting free alcohol can furnish the fully protected compound **6**. Acid deprotection of the diol, followed by tritylation of the primary alcohol, benzylation of the secondary one, and finally deprotection under oxidative conditions, would give aldehyde **7**. This compound could then be transformed into the monoprotected derivative **9** using the same series of transformations explained in Scheme 8.

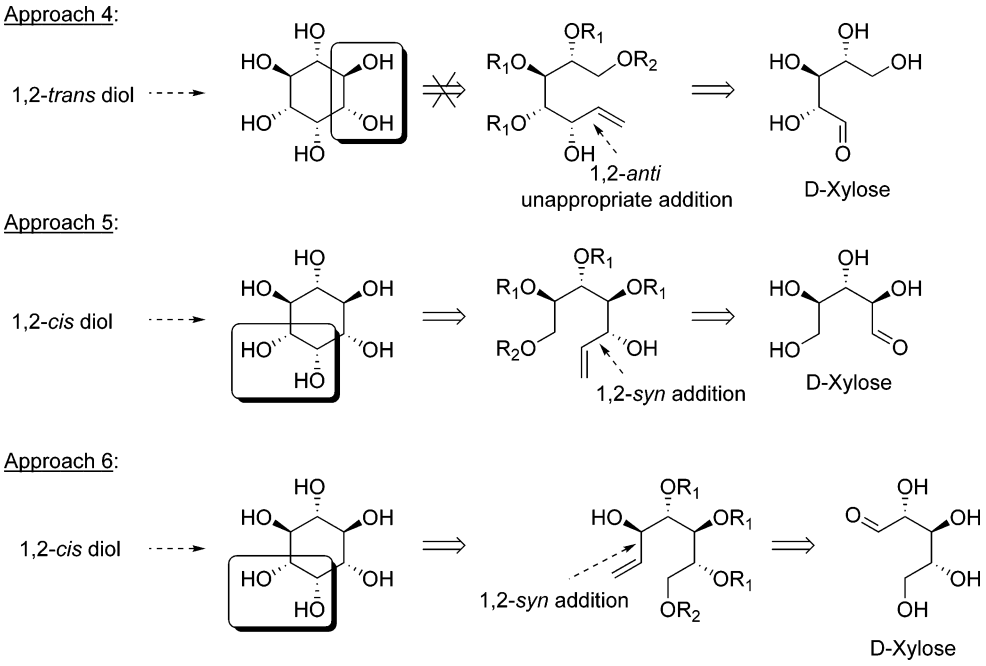
4- AND 5-MONOPROTECTED DERIVATIVES

The monoprotected myoinositol derivative in positions 4 and 5 can only be obtained by selective protection of one of

Scheme 5. Myoinositol Starting from D-Arabinose, L-Arabinose, and D-Ribose



Scheme 6. Myoinositol Starting from D-Xylose



the hydroxy groups resulting from the final osmylation. It is well-known that protection of equatorial alcohols is much easier than axial ones. Thus, to obtain the 5-protected myoinositol, the equatorial alcohol could be selectively protected in the presence of the axial one. To obtain the 4-monoprotected derivative, a series of protection and deprotection steps is necessary.

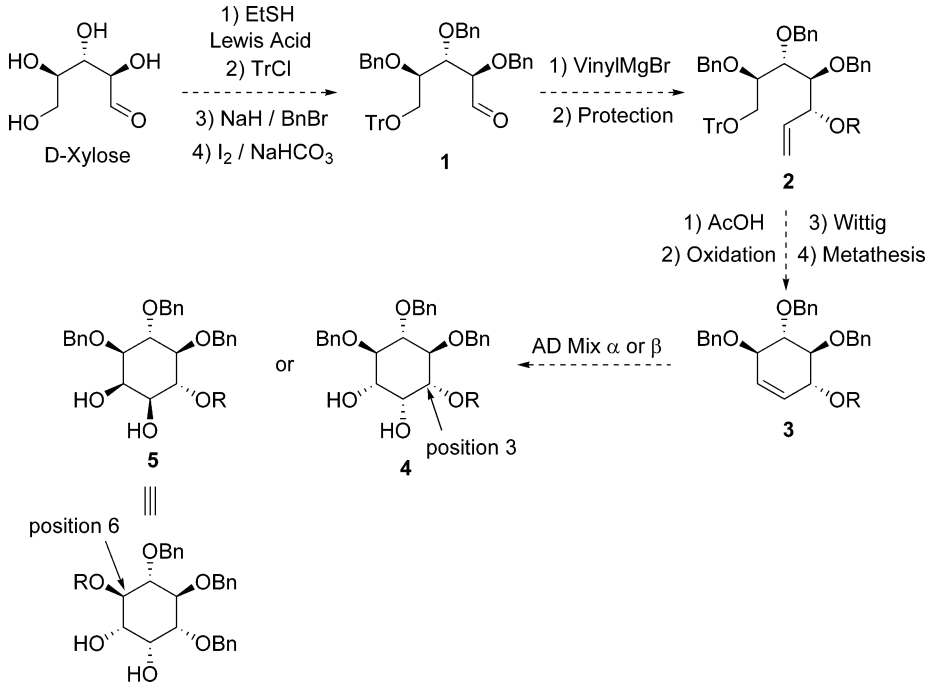
It is interesting to note that this last approach, which we consider as the more versatile and interesting, was developed by d'Alarcao in 1997.[16]

PERSPECTIVES AND CONCLUSION

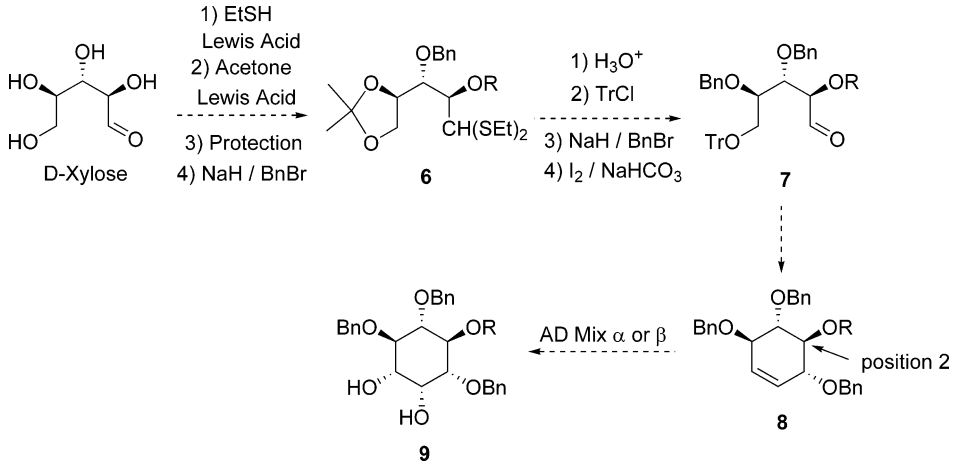
In summary, we have demonstrated how the Quiral program has indicated the most convenient approaches to the synthesis of myoinositol derivatives. We believe that this program is a very useful tool for proposing synthetic strategies for numerous organic compounds if the sugar chiral pool is chosen as the starting point of the synthesis. The total synthesis of bioactive molecules, inspired by the schemes that Quiral suggests, is underway.

Future improvement of the Quiral software will be carried out to widen its capabilities and to make it easier to use. For example, two clusters of chiral centers that are separated by a CH_2 or a CO group could be fused together as it is chemically possible to reduce or to oxidize an alcohol function to form the desired achiral group. A branched (i.e., not linear or simply cyclic) chiral center set should also be considered for analysis. The direct reading of

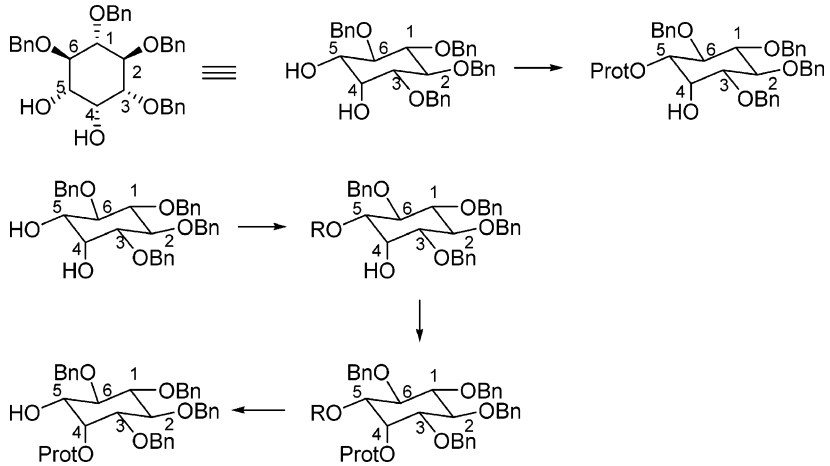
Scheme 7. Possible Synthesis of Myoinositol Derivatives Protected in Positions 3 and 6 Starting from D-Xylose



Scheme 8. Possible Synthesis of Myoinositol Derivatives Protected in Position 2 Starting from D-Xylose



Scheme 9. Protection of Positions 4 and 5



ChemDraw files with stereochemical information on bonds should replace the creation of structures by means of Chem3D. The user interface should also make is easier to rotate the molecule using the mouse pointer and to display reaction schemes in a graphical way, instead of a textual one.

ACKNOWLEDGMENT

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Supporting Information Available: Screenshots corresponding to Table 1 for myoinositol analysis using the Quiral program. This material is available free of charge via the Internet at http://pubs.acs.org.

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