



Potential of *myo*-inositol as a starting material for natural product synthesis[†]

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Phosphorylated derivatives of *myo*-inositol are involved in various cellular processes and they are crucial for the survival of cells. Discoveries related to these biological aspects revived the interest in the chemistry of inositols, since derivatives and analogs of phosphoinositols were required as molecular tools for the delineation of the *myo*-inositol cycle in eukaryotic cells. Extensive research on the chemistry of inositols in the last 3–4 decades encouraged organic chemists to explore the use of *myo*-inositol, the most abundantly available inositol, as a starting material for the synthesis of natural products. This article is an attempt to review the progress in this area of synthetic chemistry and identify aspects that need to be addressed to increase the potential of *myo*-inositol as a starting material for natural product synthesis.

Keywords: Cyclitol, inositol, natural product, protecting group, total synthesis.

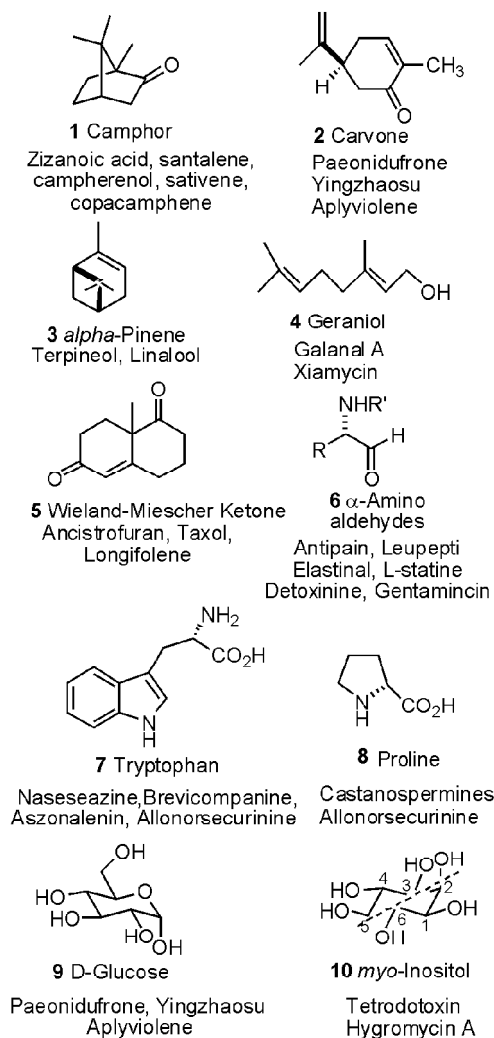
Introduction

Natural product synthesis has been a major area of research in organic chemistry for more than a century. It might not be an exaggeration to state that some of the major developments and discoveries in organic chemistry was a consequence of research related to natural product synthesis. The thrust for sustained research activity in natural product synthesis might have varied over decades, but the interest and efforts towards synthesizing natural products and their analogs does not appear to have declined, although the wisdom of carrying out natural product synthesis (or not) has been debated¹. It is interesting to note that discovery of new reactions and reagents for organic synthesis and research on targeted synthesis of natural products fueled each other. The growth of these areas of research was multi-directional (like the expansion of a balloon) rather than in selected specified directions, and hence contribution of natural product synthesis for the overall development of organic chemistry is perhaps unparalleled, compared to other areas of research in chemistry. Although it is conceivable to arrive at a sequence of reactions for the synthesis of a given natural product from

any available organic compound (not necessarily of petrochemical origin), the choice of a suitable starting material for a natural product synthesis is a major decision in the whole process. The latter is of special significance in the light of recent developments in automated or computer assisted organic synthesis². In principle, a 'good starting material' for the efficient synthesis of a given natural product, is the one that has the molecular structure closest to that of the target natural product. The 'closeness' in the structures of the starting material and the targeted product, could be in terms of the carbon skeleton, functional groups, or stereochemical disposition of atoms or groups of atoms or a combination of all these (which could over ride greater 'closeness' of any one of these factors considered alone). As expected, due to lack of universal agreement of what is 'close' or 'not close' different organic chemists approach the synthesis of a natural product by different routes and from different starting materials. Nevertheless, selection of the starting material remains a crucial decision for achieving efficient synthesis of natural products and their analogs. The current article is an attempt to examine the scope or potential of *myo*-inositol

[†]Review.

(10) as a primary source for the synthesis of natural products. We have included as many references as possible that deal with the synthesis of natural products from *myo*-inositol (10), however the referencing is not exhaustive. Some of the organic compounds that have been used for the synthesis of natural products are shown in Scheme 1.



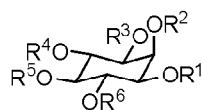
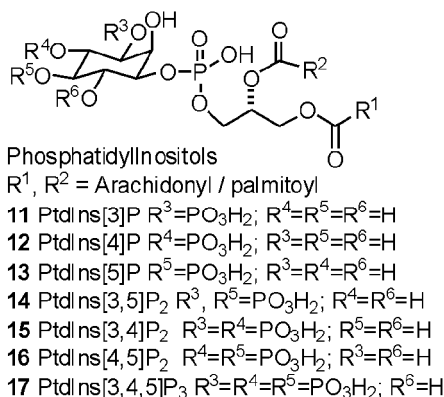
Scheme 1. Selected organic compounds 1-10 that have been used for the total synthesis of natural products (listed below each structure). Conventional numbering of the carbon atoms of *myo*-inositol (10) is shown; the mirror plane passes through C2 and C5.

myo-Inositol (10) is a *meso*-isomer of 1,2,3,4,5,6-hexahydroxy cyclohexane. All the secondary hydroxyl groups have the equatorial orientation except the C2-OH (i.e. axial), with respect to the carbocyclic ring. The volume of research

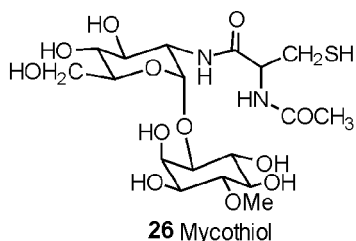
related to the chemistry of *myo*-inositol (10) formed only an insignificant portion of the published chemistry literature till about thirty to forty years ago³. The early studies on *myo*-inositol (10) and its isomers pertained mostly to the isolation and establishment of the molecular structure of naturally occurring derivatives, largely from plant sources. Although *myo*-inositol (10) derivatives are abundant in plants and ubiquitous in animal cells, it does not occur in the free-state in nature. Phytic acid (*myo*-inositol hexakisphosphate) which is present in large quantities in plants is the source of commercial *myo*-inositol (10). Industrially, *myo*-inositol (10) is obtained by the hydrolysis of phytic acid and it is about 5–10 times more expensive than D-glucose. Hence large quantities of *myo*-inositol (10) can be procured at reasonably low cost for research purposes. Isomers of *myo*-inositol (10, eight are known)⁴ on the other hand are 500 to 1000 times more expensive than *myo*-inositol (10) and are not available in large quantities. Accordingly, the published research related to the chemistry of inositols was biased towards *myo*-inositol (10). As expected there were attempts to convert abundantly available *myo*-inositol (10) to its isomers and their derivatives⁵. However *myo*-inositol (10) and its chemistry remained mostly a curiosity for most of the researchers. During the three decades of 1970s-1990s, biologists and biochemists realized that certain phosphorylated *myo*-inositol derivatives (Scheme 2, phosphoinositols, which include inositol phosphates IP_s – 18-25; their lipid derivatives-phosphatidylinositols 11-17 – PIs; inositol pyrophosphates – IPPs) played crucial roles in cellular processes.

Involvement of phosphoinositols and their glycosylated derivatives (glycosylphosphoinositols – GPI) in various cellular processes (signal transduction, calcium mobilization, anchoring of proteins to cell membranes, virulence factor of certain parasites, allosteric effectors of human hemoglobin, regulators of cellular energy metabolism, metastatic growth)⁷ fueled research related to the chemistry of inositols, in general and *myo*-inositol (10), in particular. This is reflected in the number of published papers related to *myo*-inositol (10) and its derivatives (Fig. 1).

The increased visibility of *myo*-inositol (10) in the literature resulted in an increase of synthetic efforts by chemists towards developing novel methods for the synthesis of naturally occurring phosphoinositols and their derivatives/analogs^{4,6b,8}, as well as to explore the use of *myo*-inositol (10) for the synthesis of other interesting natural products⁹.



- Inositol phosphates
18 Ins(1)P $R^1=PO_3H_2; R^2=R^3=R^4=R^5=R^6=H$
19 Ins(1,4)P₂ $R^1=R^4=PO_3H_2; R^2=R^3=R^5=R^6=H$
20 Ins(4,5)P₂ $R^1=R^2=R^3=R^6=H; R^4=R^5=PO_3H_2$
21 Ins(1,4,5)P₃ $R^1=R^4=R^5=PO_3H_2; R^2=R^3=R^6=H$
22 Ins(1,3,4)P₃ $R^1=R^3=R^4=PO_3H_2; R^2=R^5=R^6=H$
23 Ins(1,3,4,5)P₄ $R^1=R^3=R^4=R^5=PO_3H_2; R^2=R^6=H$
24 Ins(1,3,4,5,6)P₅ $R^1=R^3=R^4=R^5=R^6=PO_3H_2; R^2=H$
25 Ins(1,2,3,4,5,6)P₆ $R^1=R^2=R^3=R^4=R^5=R^6=PO_3H_2$



Scheme 2. Naturally occurring IPs, PIs and a glycosylamino inositol **26**⁶.

Attempts were also made to use the *myo*-inositol (**10**) scaffold for applications in materials chemistry¹⁰. On the other hand, synthesis of the carbocyclic framework of inositols from other molecules (such as benzene, glucose, tartaric acid, etc.) was investigated¹¹. All in all, the delineation of the chemistry of inositols was revived, which led to an upsurge in interest in the synthesis of inositols, their derivatives/analogs and natural products containing the inositol or cyclitol (cyclohexanes containing at least three hydroxyl groups) moieties.

Synthesis of natural phosphoinositols from *myo*-inositol (**10**)

Although phosphoinositols and GPIs are ubiquitous in eukaryotic cells, they occur in small quantities and require

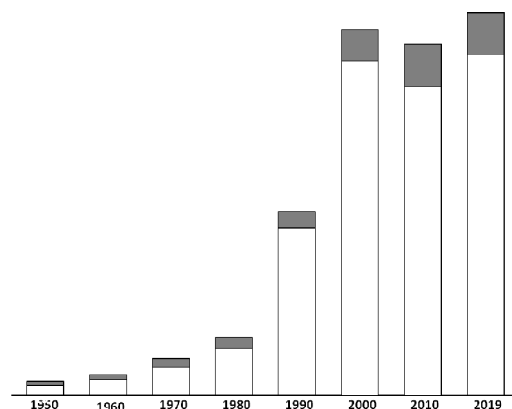
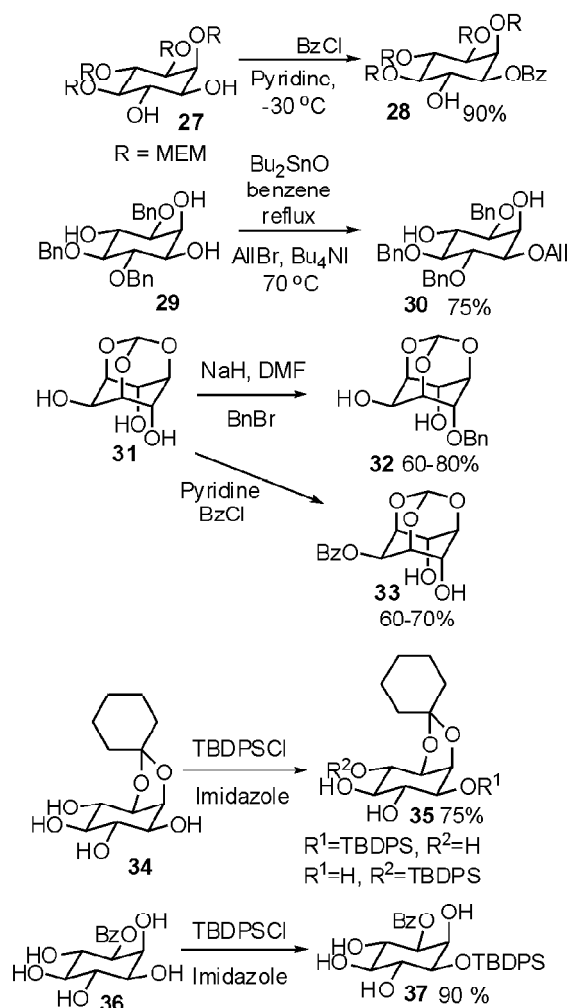


Fig. 1. Each bar represents the total number of papers related to inositols, published in the decade ending with the year shown on X-axis. The shaded region on top of each bar represents the portion of papers published in synthetic chemistry journals. The total number of published papers (and the number of published papers in synthetic chemistry) were 788 (22); 1715 (67); 2744 (198); 3879 (222); 14482 (425); 30173 (1487); 27639 (1598); 30498 (1569) respectively for each decade. This figure is illustrative; number of published papers may not be exact.

elaborate isolation and purification procedures to obtain in pure state. Furthermore, phosphate groups are prone for migration between hydroxyl groups of *myo*-inositol (**10**) and hydrolysis during isolation. Hence total synthesis of phosphoinositols is essential to obtain structurally well defined phosphoinositols in sufficient quantities necessary for biological experiments (to understand the role of phosphoinositols in various cellular processes). Basically, synthesis of phosphoinositols from *myo*-inositol (**10**) requires (i) the preparation of a suitably (partially) *O*-protected *myo*-inositol derivative; (ii) phosphorylation of the hydroxyl groups in the (partially) *O*-protected *myo*-inositol derivative; (iii) de-protection of all the protecting groups to obtain the required phosphoinositol. It is crucial to choose regio-selective methods of protection of *myo*-inositol hydroxyl groups so as to mainly generate the required isomer and de-protection methods so as not to disturb the phosphates and carbon-carbon double bonds present in natural phospholipids. These aspects have been reviewed^{4, 6b, 8}. Some of the regio-selective reactions of *myo*-inositol (**10**) and its derivatives are shown in Scheme 3. A compilation of the reactions of *myo*-inositol (**10**) and its partially protected derivatives revealed that the reactivity of the six hydroxyl groups are in the order $C1 \approx C3 > C4 \approx C6 > C5 > C2$ ⁴.

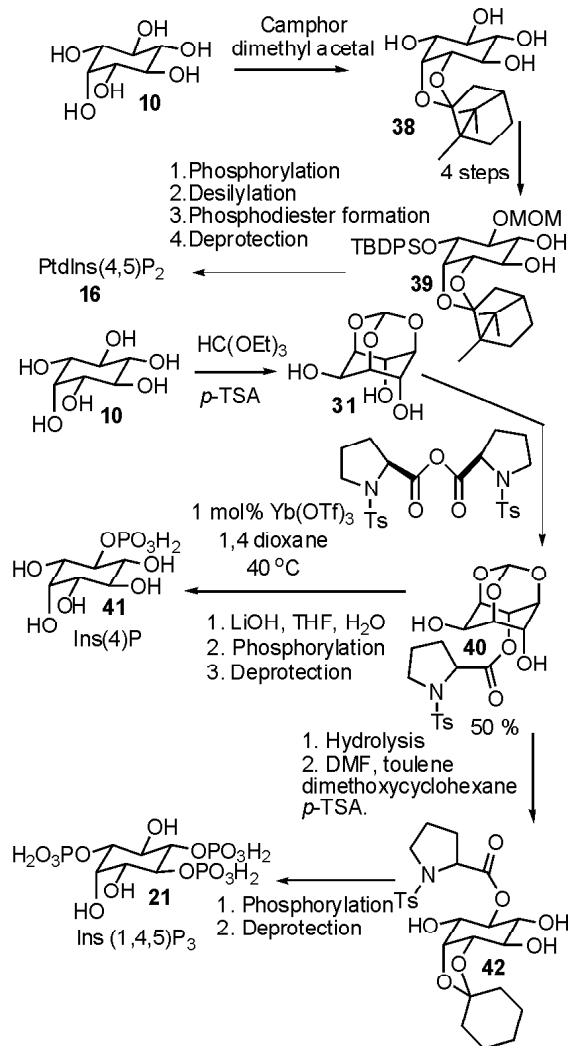
For the synthesis of phospholipid derivatives of *myo*-inositol (**10**), one needs to introduce phosphatidic acid as well as



Scheme 3. Selected examples of regio-selective methods for the protection of *myo*-inositol hydroxyl groups. A comparison of similar reactions reported in the literature revealed the order of reactivity mentioned above¹².

the required number of phosphates, while for the synthesis of GPIs, in addition, introduction of sugar units in the required configuration (α or β) is essential. These demand orthogonal protection of the hydroxyl groups of inositol as well as other sugar moieties. For the synthesis of chiral phosphoinositols, preparation of optically active *myo*-inositol derivatives is essential. This could be achieved either by conventional resolution of racemic *myo*-inositol derivatives or by asymmetric catalysis¹³. Clearly achieving all these (without compromising the yield) is a formidable task. Fortunately, due to the progress in chemistry related to inositols in the last 2–3 decades, current state of art allows the synthesis of phosphoinositols fairly routinely. However, the efforts required

(in terms of labor, cost and time) in obtaining phosphoinositols from *myo*-inositol (**10**) is quite high. Illustrative examples for the synthesis of phosphoinositols which reveal the aspects discussed above are shown in the Scheme 4.

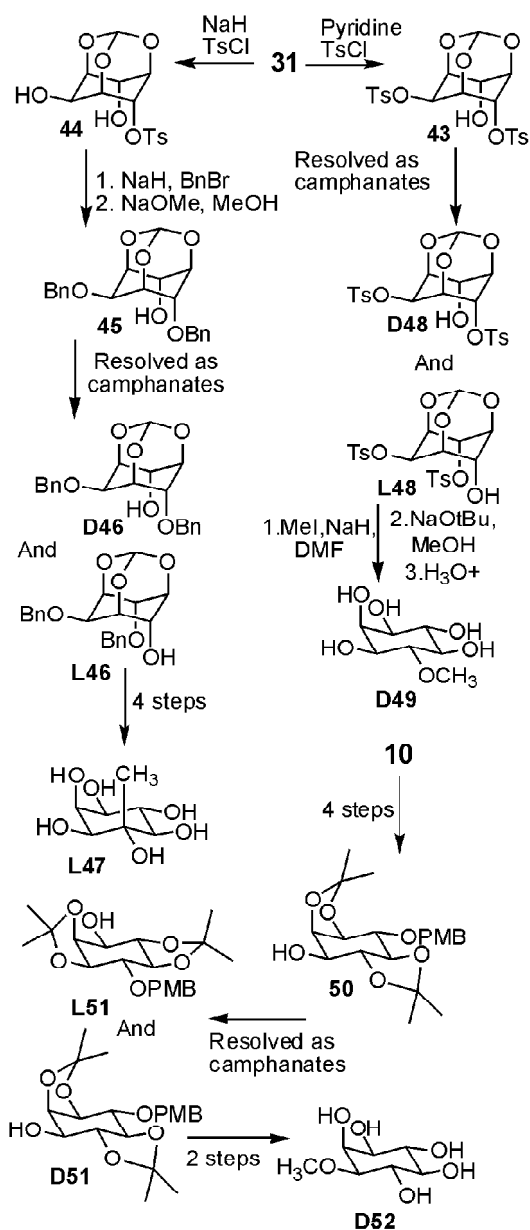


Scheme 4. Synthesis of naturally occurring IPs and a PI from *myo*-inositol (**10**) reveal the extensive protection – de-protection sequences necessary in the course of the synthesis^{5d,14}.

Synthesis of natural cyclitols from *myo*-inositol (**10**)

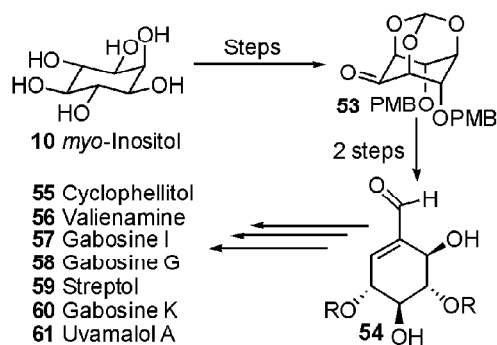
Synthesis of naturally occurring cyclitols from *myo*-inositol (**10**) is somewhat similar to the synthesis of phosphoinositols in that extensive orthogonal protection – de-protection steps could be involved. Usually, a suitably protected *myo*-inositol derivative is required, to be able to carry out the necessary functional group transformations.

As expected the carbocyclic ring remains more or less unaltered, at the end of the synthesis. The key to carrying out an efficient synthesis of these naturally occurring cyclitols is to be able to carry out selective reactions on the hydroxyl groups of *myo*-inositol that adhere to stereochemical requirements of the targeted end product. This is illustrated with the synthesis of ononitol (**D49**), laminitol (**L47**) and



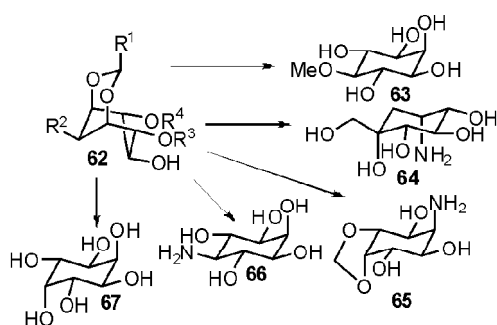
Scheme 5. Synthesis of ononitol (**D49**), laminitol (**L47**) and bornesitol (**D52**) from *myo*-inositol (**10**)^{15,16} reveal extensive protection – de-protection sequences needed to synthesize cyclitols and their derivatives from *myo*-inositol (**10**).

bornesitol (**D52**). Some of these synthetic schemes utilized the protection of three of the *myo*-inositol hydroxyl groups as the orthoesters, examples of which are shown in Scheme 5. Ononitol (**D49**) and laminitol (**L47**) were synthesized using the orthoformate **31** as an early intermediate. Synthesis of **L47** required the introduction of a methyl group on the inositol ring, which was realized by Swern oxidation of **L46** followed by Grignard reaction with methylmagnesium iodide. All the protecting groups were removed subsequently to obtain **L47**. Synthesis of **D49** on the other hand only required introduction of an *O*-methyl group in **L48** followed by deprotection. Synthesis of **D52** involved the use of acetal protecting groups followed by classical resolution and *O*-methylation at the C1-hydroxyl group. The advantage of using *myo*-inositol orthoesters is that three of the six hydroxyl groups (1,3,5-hydroxyl groups) can be blocked in a single step. *myo*-inositol orthoesters can be obtained as single products from *myo*-inositol (**10**) and due to inversion of the *myo*-inositol ring, the three hydroxyl groups (2,4,6-hydroxyl groups) in *myo*-inositol orthoesters can be selectively protected¹⁷. Since these orthoesters are analogs of adamantane, they have very rigid molecular frame, which can be exploited to carry out selective and unusual reactions. For instance, tosylates could be used for the protection of *myo*-inositol orthoester hydroxyl groups (Scheme 5), which is not ordinarily possible for normal alcohols^{15,18–20}. Sureshan and co-workers utilized *myo*-inositol orthoformate derivative **53** for the synthesis of several cyclitols and valienamine (Scheme 6)²¹. The key intermediate, cyclohexene derivative **54**, was obtained from an inositol orthoester derived enol ether.



Scheme 6. Synthesis of cyclitols using *myo*-inositol orthoformate derivatives as key intermediates. See reference 21 for detailed synthetic sequences.

Yet another advantage of using *myo*-inositol orthoesters as early intermediates is that the three protected 1,3,5-hydroxyl groups can be released sequentially by reductive cleavage. Reduction of one of the orthoester C-O bond generates 1,3-acetal of *myo*-inositol (**62**), which cannot be obtained by direct acetalization of *myo*-inositol (**10**). These bicyclic *myo*-inositol 1,3-acetal molecules are not as rigid as their precursor orthoesters and hence the two rings could exist in different conformations^{22–24}. This opened up novel and efficient routes for the synthesis of sequoyitol (**63**)²⁵, racemic valioline (**64**)²⁶ and aminoinositol (**65**) of hygromycin A (Scheme 7)^{9b}.



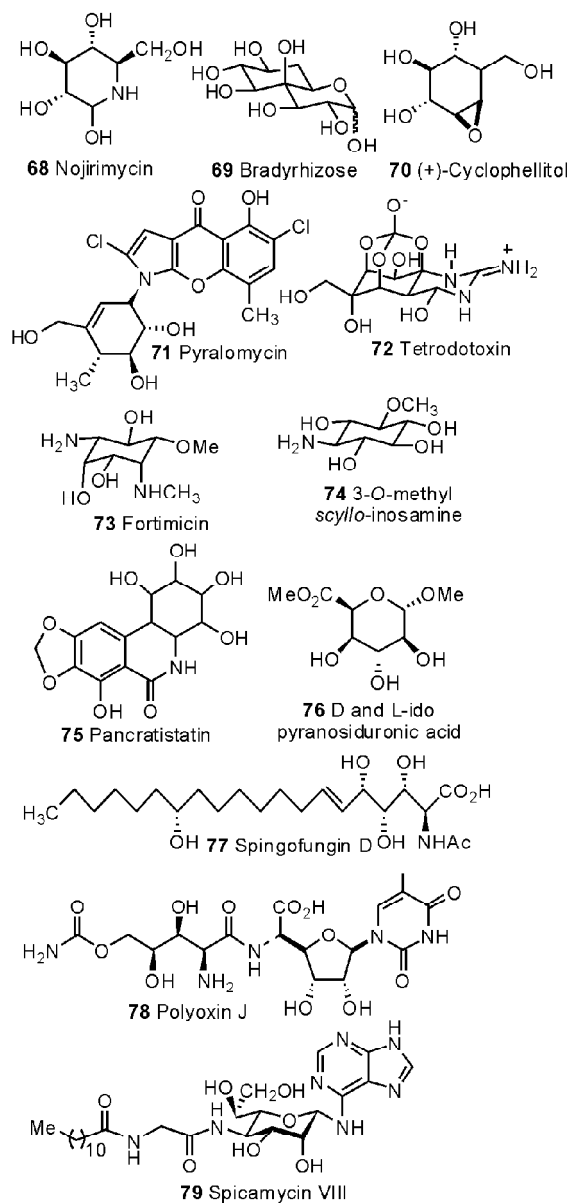
Scheme 7. Synthesis of cyclitols using *myo*-inositol 1,3-acetals as key intermediates. R¹ = H, C₆H₅; R², R³, R⁴ = protecting groups. See reference 22 for a review on synthetic utility of 1,3-acetals.

An interesting aspect of the synthesis of sequoyitol (**64**) was that the benzyl ethers could be cleaved using palladium hydroxide (in methanol), without the use of hydrogen. Later it was found that palladium hydroxide in alcohols (methanol, ethanol or *iso*-propanol) could also be used to cleave allyl ethers as well, in one step²⁷. Several other natural products which can be classified as cyclitols or their derivatives have been synthesized from *myo*-inositol (**10**)²⁸. Synthesis of cyclitols is of significance due to their importance in our diet and health benefits attributed to several cyclitol derivatives. For example, (a) intake of *myo*-inositol (**10**) and D-*chiro*-inositol is thought to benefit women with polycystic ovary syndrome (PCOS)²⁹; (b) D-pinitol is known to be involved in the regulation of cell proliferation, apoptosis, and angiogenesis and hence has shown promise of being an inhibitor of cancer growth³⁰; (c) aminocyclitols form part of several antibiotics and some also function as glycosidase inhibitors and are intermediates during the biosynthesis of streptomycin³¹. Due

to these reasons cyclitols and their derivatives have potential to function as drugs and drug precursors and have implications for medicinal chemistry^{11(a)}.

Synthesis of assorted natural products from *myo*-inositol (**10**)

myo-Inositol has been used for the synthesis of several natural products wherein the carbocyclic ring was transformed to other carbon skeletons (Scheme 8). These include nojirimycin (**68**), bradyrhizose (**69**), cyclophellitol (**70**),



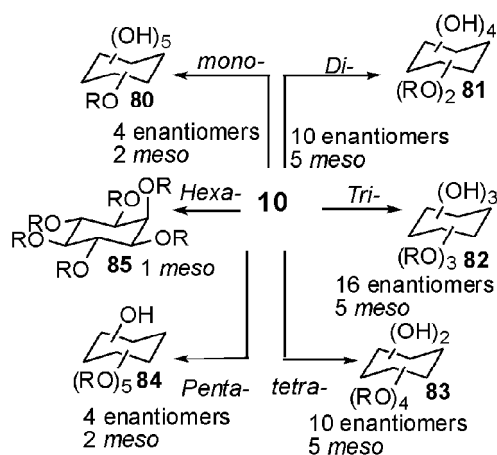
Scheme 8. Assorted natural products synthesized from *myo*-inositol (**10**).

pyralomycin (**71**), tetrodotoxin (**72**), fortimicin (**73**), iduronic acid derivatives (**76**), sphingofungin D (**77**), polyoxin J (**78**) and spicamycin (**79**)^{9(a),32}.

During the synthesis of many of these natural products, the carbocyclic ring of *myo*-inositol was either cleaved to obtain a linear polyol (as in **78**) or converted to a lactone via Baeyer-Villiger oxidation (as in the synthesis of **68**, **76**, **77**, **78**). Tetrodotoxin(**72**) was built on the *myo*-inositol orthoformate scaffold, while the intermediate for pancratistatin (**75**) was synthesized using *myo*-inositol acetals as early intermediates. Each of these syntheses is an elegant demonstration of the use of *myo*-inositol (**10**) and involved novel chemistry.

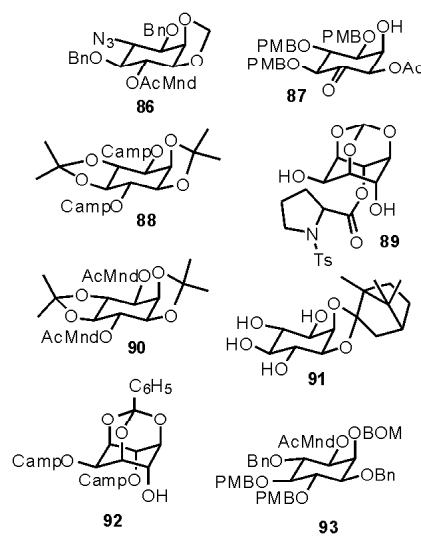
Summary and outlook for the future

From the foregoing it is clear that natural products synthesized from *myo*-inositol (**10**) were either symmetric, or racemic or required intervention by an optically active molecular entity (for resolution/asymmetric catalysis/enzymatic catalysis), to obtain an enantiomeric end product. This is due to the inherent *meso*-configuration of *myo*-inositol (**10**), which demands introduction of chirality at some point in the synthetic scheme. Also the presence of six secondary hydroxyl groups with subtle differences in reactivity often results in the formation of a mixture of products (Scheme 9), necessitating elaborate and labor-intensive separation and purification procedures and contributes to reduction in the overall yield of the end product^{24,33}.



Scheme 9. Number of isomers generated (total 64) on *O*-substitution of *myo*-inositol hydroxyl groups, for a given *O*-substituent. The molecular complexity increases many fold when *O*-substituents are different.

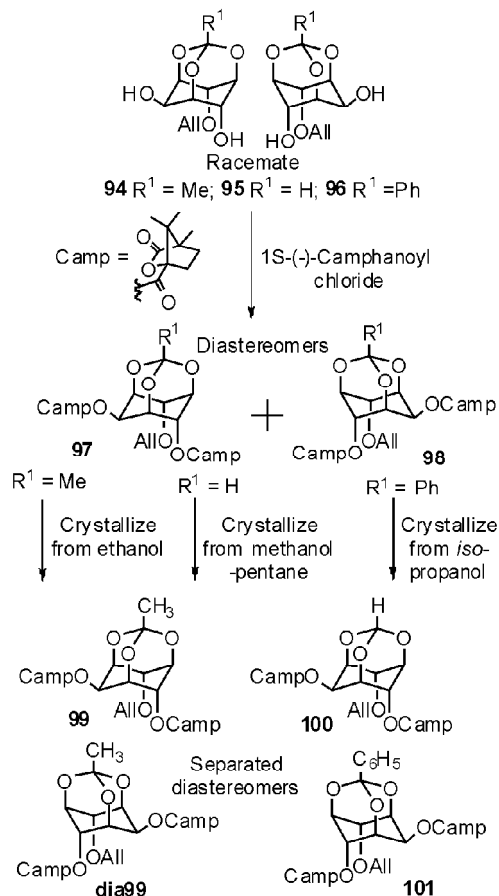
However, well documented chemistry of inositols in the recent past, use of *myo*-inositol orthoesters and 1,3-acetals aid in improving the overall yield of the products^{4,5c,8,11b,24,33}. Although classical resolution of synthetic intermediates or the use of asymmetric catalysis does provide enantiomeric end products, the current methods are quite specific for the synthesis of one or at best few natural products (Scheme 10).



Scheme 10. Enantiomeric *myo*-inositol derivatives used in natural product synthesis^{5d,9b,11c,14,34} (Camp = camphanoyl, AcMnd = acetyl mandelate).

Hence, availability of versatile chiral *myo*-inositol derivatives which have the potential to be used for the synthesis of a variety of natural products could enhance the use of *myo*-inositol (**10**) as a starting material for natural product synthesis. With this in view, we recently developed methods for the synthesis of enantiomeric 4-*O*-allyl and 6-*O*-allyl-*myo*-inositol orthoesters. The diastereomeric precursors to these allyl ethers could be obtained from *myo*-inositol (**10**) in several grams quantities without the use of chromatographic separation methods (Scheme 11)³⁵. We are also attempting to develop methods for the synthesis of enantiomeric inositol derivatives without the use of chiral molecular entities³⁶.

Chemistry of inositols has grown into a very active field of research over the last few decades, with implications in the areas of synthetic organic chemistry, biological chemistry and medicinal chemistry. Synthetic progress in this area of research indicate that *myo*-inositol (**10**) has the potential and shows promise of being a starting material for the syn-



Scheme 11. Resolution of racemic 4-O-allyl-myo-inositol orthoesters by crystallization on 5–20 gram scale. See reference 36 for details.

thesis of natural products due to its availability, ubiquitous occurrence of its derivatives in nature, presence of six hydroxyl groups which are amenable for transformation to other functional groups, presence of a conformationally stable carbocyclic ring and well developed chemistry which allows the preparation of any required derivative. Hence we believe that the future efforts must be directed towards desymmetrization of myo-inositol (**10**) and its enantiomeric scaffolding, which could allow the synthesis of a lot more chiral end products and make myo-inositol (**10**) the preferred starting material for the synthesis of a variety of natural products.

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