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A simple and practical resolution of 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol

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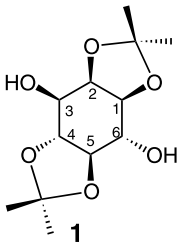
Abstract—An efficient method for the resolution of 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol has been developed. The diketal was converted to diastereomeric 3,6-di-*O*-mandelates by the reaction with (*S*)-*O*-acetylmandeloyl chloride. Both the diastereomers could be separated by sequential crystallization in multi-gram quantities. The enantiomers of the diol were obtained by removal of the chiral auxiliaries. Also the *trans*-isopropylidene was cleaved efficiently to obtain another pair of chiral diols. © 2003 Elsevier Science Ltd. All rights reserved.

In the last two decades we have witnessed a renaissance in the chemistry and biology of inositols due to the involvement of phosphorylated inositols in various biological phenomena such as cellular signal transduction,[1] the anchoring of proteins to the cell membrane,[2] etc. The receptor-controlled breakdown of phosphatidylinositol 4,5-bisphosphate [PI(4,5)P_2] to the second messengers D-*myo*-inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG) is a well-established phenomenon.[3] The cytosol soluble IP_3 mobilizes Ca^{2+} from endoplasmic reticulum, which ultimately leads to a cell response. After this process, by the action of many specific phosphatases and kinases, IP_3 is recycled back to inositol and then to the lipid PIP_2 with the intermediacy of several *myo*-inositol phosphates (IP_n). In addition, many phosphatidylinositol phosphates like PI(3,5)P_2, PI(3,4,5)P_3, PI(4)P, PI(3)P, PI(5)P have recently been isolated from cells. Despite, a clear understanding of the cellular role played by each of these phosphates and PIP_ns are lacking due to the insufficient or impractical access to these derivatives from natural resources. This increased interest in the biological role played by phosphoinositols necessitated better synthetic strategies for their preparation. In addition, the disclosed therapeutic potential[4] of inositol derivatives and the recent use of inositol as the synthon for the synthesis of many natural products[5] have given further reorientation to the *myo*-inositol chemistry. This multi-faceted importance of inositol demands better methods for optical resolution and selective protection–deprotection for this *meso*-cyclohexane hexol.

During the last decade, there have been many methods reported for the selective protection and deprotection of *myo*-inositol hydroxyl groups and also for the effective phosphorylation or glycosylation of these protected derivatives. However the search for efficient methodologies for optical resolution continues. Now the synthetic chemistry using *myo*-inositol has come to the stage where the efficiency of a particular synthetic strategy solely depends on its effective resolution methods. The most commonly used starting materials for the syntheses of phosphoinositols are the diketal derivatives **1** and **2**. The relative reactivity of hydroxyl groups in 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol, **1**, has been studied extensively.[6] It is reported that phosphorylation,[7] acylation,[7,8] silylation,[7,9] alkylation,[10] etc., undergo selectively at the 3-*O*-position. Also it is documented that the *trans*-isopropylidene can be cleaved in presence of the *cis*.[11] These selectivities in this diol project it as a good synthon for many inositol phosphates and lipid derivatives.



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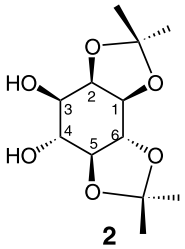

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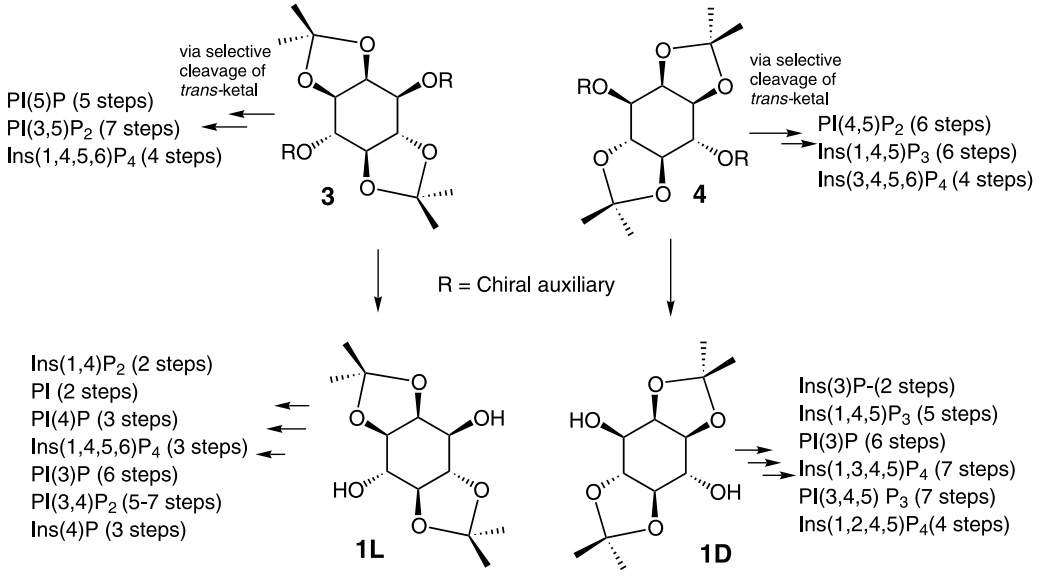
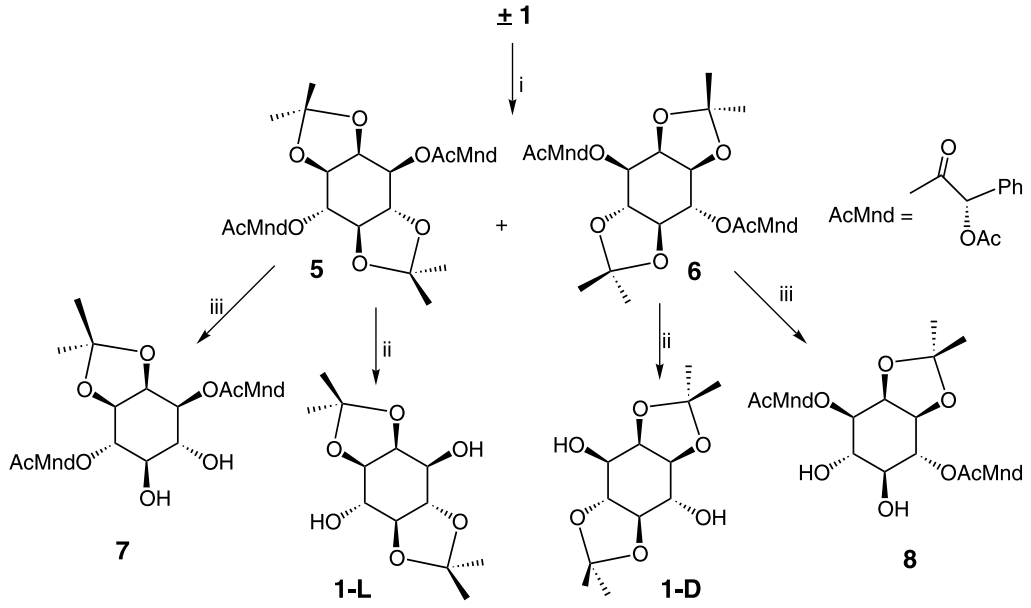
From a careful analysis of the structure it is reasonable to think that diketal **1** is more versatile and appropriate for the synthesis of important phosphoinositols as, unlike in the case of **2**, both the enantiomers of **1** are equally important for the synthesis of different phosphates and PIPs (Scheme 1). These out-weighed importances rendered effective methodologies for the complete (to obtain both the enantiomers in pure form) resolution of this diketal indispensable. Many efforts have been made for the resolution of this diketal by different groups. However, there is no practical method for the resolution of this diketal on a large scale. In some cases, the resolution was carried out after a less yielding initial protection of the 3-OH followed by a tedious column chromatographic[12] or HPLC[9] separation of the diastereomers. Although the resolution of diol **1** has been achieved on small scale, the reported methods involve either tedious chromatographic separation[13] of the bis-camphanates or resulted in the separation of small quantity of only one of the diastereomers.[14] During our ongoing program to provide easy access to many inositol phosphates and their lipid analogues, we required enantiomers of this diketal in multi-gram quantities. Herein we report a simple and practical method for the efficient resolution (to have access to both the enantiomers) of this important intermediate, which does not involve any chromatographic separation.

The diketal **1** was acylated with (*S*)-*O*-acetylmandelic acid chloride[15] in pyridine at 0°C (Scheme 2) to obtain the diacylated derivatives (**5** and **6**) in quantitative yield. Aqueous work-up followed by crystallization from a mixture of ethyl acetate and hexane yielded pure D-3,6-di-*O*-[(*S*)-*O*-acetylmandeloyl]-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol, **6** (46%) as cotton like fluffy crystals {mp 215–217°C, $[\alpha]_D = +64.4$ (*c* 1, CH_2Cl_2)} The ^1H NMR analysis of the concentrated mother liquor revealed that it contains almost pure D-1,4-di-*O*-[(*S*)-*O*-acetylmandeloyl]-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol **5**.[16] Further crystallization of the mother liquor from chloroform–hexane yielded pure **5** in good yield[17] (42%) as dense thick crystals [mp 177°C, $[\alpha]_D = +53.2$ (*c* 1, CH_2Cl_2)]. It is noteworthy that the crystals of **5** showed liquid crystalline property for a small range of temperature with softening at 163–164°C and final melting at 177°C. The chiral auxiliaries could be removed under basic conditions to yield enantiomers of diol **1** in quantitative yields.[18] Also, to check the feasibility of our synthetic strategies (Scheme 1), we proceeded for the *trans*-isopropylidene cleavage in presence of the *cis*. In general, the reported methods for the selective *trans*-ketal cleavage are less yielding (around 60%). Very recently a high yielding method using ion-exchange resin has appeared,[11c] but unfortunately we failed to reproduce their result. After a series of experimentation, we arrived at optimum conditions[19] for the selective cleavage of the *trans*-ketal in presence of the *cis*- by using a limited amount of TFA and water (2 and 1 equiv., respectively) in CH_2Cl_2 to obtain diols **7**[20] and **8**[21] in very good yields (82–87%). Thus we have presented efficient methods for the preparation of four highly advanced intermediates for the synthesis of phosphorylated inositols and other natural products. Although many resolutions of *myo*-inositol derivatives by crystallization have been reported, only one of the diastereomers can be obtained by those methods. In many cases, in order to obtain the other diastereomer, the mother liquor had to be converted back to the alcohol and functionalized with the opposite chiral auxiliary. To the best of our knowledge, this is the first case where both the diastereomers of a *myo*-inositol derivative can be obtained by sequential crystallizations.



Scheme 1. Different phosphoinositols that can be obtained from enantiomers of diketal **1** and its diastereomeric derivatives **3** and **4** by utilizing the known selective reactions. The number in parenthesis indicates the number of transformations required for the synthesis.



Scheme 2. *Reagents and conditions*: (i) (*S*)-(+)-*O*-acetylmandeloyl chloride (2.1 equiv.), pyr, 0°C, 2 h; (ii) *i*-butylamine (5 equiv.), MeOH, reflux, 30 min; (iii) TFA (2 equiv.), H_2O (1 equiv.), CH_2Cl_2, 0°C–rt, 50 min.

In conclusion, we have achieved the optical resolution of an important intermediate for the synthesis of many *myo*-inositol phosphates. The advantage of the method reported here is that it excludes tedious chromatographic separation. Both the enantiomers can be obtained in very good yield on a multi-gram scale. We hope this resolution method will be useful not only for the inositol chemists but also for chemists working on natural product synthesis. Presently we are investigating the synthetic utility of these diols and diester derivatives to achieve phosphoinositols as depicted in Scheme 1 and other derivatives, which will be reported in a full account elsewhere.

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15. DCC-mediated coupling between acid and **1** resulted in racemization to a small extent in our hand. This could be the reason for the separation of only one of the diastereomer (**6**) in low (18%) yield even after column chromatography and multiple crystallizations in the

reported case.[14] Although, DCC method had been used in inositol, it appears that special care (like low temperature) is needed to avoid racemization where as chloride method had been used in inositol successfully (e.g. Garegg, P. J.; Lindberg, B.; Kvarnstrom, I.; Svensson, S. C. T. *Carbohydr. Res.* **1985**, *139*, 209). To make sure that no racemization occurred in our case, the mixture of diastereomers was converted into chromatographically separable diols **7** and **8** and converted to the known **1**-D and **1**-L-1,4,5,6-tetra-*O*-benzoyl-*myo*-inositols respectively both with >99% ee (HPLC, Chiralcel OD).

16. All new compounds were characterized by ^{1}H, ^{13}C NMR and elemental analysis.
17. Separation of **5** and **6**: To a solution of (±) diol **1** (520 mg, 2 mmol) in pyridine (10 mL), a solution of (*S*)-*O*-acetyl mandeloyl chloride (893 mg, 4.2 mmol) in CH_2Cl_2 (5 mL) was added dropwise at 0°C and stirred for 3 h gradually allowing the reaction mixture to attain room temperature. After 3 h, ethyl acetate was added and washed successively with water, dil. HCl, satd solution of $NaHCO_3$ and brine. The organic layer was dried over anhd. Na_2SO_4 and evaporated under reduced pressure to obtain a solid (1.23 g). Compound **6** (563 mg, 46%) could be obtained by crystallization from a mixture of ethyl acetate and hexane (1:3 v/v). The concentrated mother liquor was redissolved in a mixture of $CHCl_3$ (10 mL) and hexane (20 mL) to yield crystals of **5** (514 mg, 42%).
18. **1**-L: mp 160–162°C, $[\alpha]_D^{25}=+22.3$ (*c* 1, CH_3CN). Lit.[12] mp 159–161°C, $[\alpha]_D^{25}=+22$ (*c* 1.08, CH_3CN); **1**-D: mp 159–161°C, $[\alpha]_D^{25}=-21.8$ (*c* 1, CH_3CN).
19. Selective cleavage of *trans* ketal: To a solution of **5** or **6** (612 mg, 1 mmol) in CH_2Cl_2 (5 mL), added water (18 μL, 1 mmol) and TFA (140 μL, 2 mmol) at 0°C and stirred under a nitrogen atmosphere. The reaction was followed by TLC and when the reaction was complete (50 min–1 h), the mixture was dissolved in ethyl acetate, washed with satd $NaHCO_3$ and brine. The organic layer was dried over anhd. Na_2SO_4 and evaporated under reduced pressure. The resulting residue was chromatographed over silica gel (flash, ethyl acetate:benzene 1:3) to obtain the corresponding diol **7** or **8** in the yield range 82–87%.
20. Mp 100–101°C, $[\alpha]_D^{25}=+53$ (*c* 1, CH_2Cl_2).
21. Mp 119–120°C, $[\alpha]_D^{25}=+71$ (*c* 1, CH_2Cl_2).