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Tetrahedron: *Asymmetry* 15 (2004) 1193–1198

An efficient route to optically active inositol derivatives via the resolution of *myo*-inositol 1,3,5-orthoformate: a short synthesis of D-*myo*-inositol-4-phosphate

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Received 9 February 2004; accepted 20 February 2004

Abstract—An efficient method for the resolution of *myo*-inositol 1,3,5-orthoformate has been developed. The triol, **1** was converted to diastereomers via reaction with (*S*)-*O*-acetylmandeloyl chloride. Conditions were optimized for a diastereomeric ratio of 7:3. Both the diastereomers could be separated by column chromatography. The absolute configurations of the diastereomers were determined by converting the less polar diastereomer to the known L-2,4-di-*O*-benzyl-*myo*-inositol. The utility of the resolved derivatives is illustrated by a short and efficient synthesis of D-*myo*-inositol-4-phosphate in four steps from *myo*-inositol.

1. Introduction

Recently, there have been significant advances in the chemistry and biology of *myo*-inositol and its derivatives due to their important biological roles.[1] The realization that phosphatidylinositol phospholipase C (PIPLC) mediates hydrolysis of phosphatidylinositol 4,5-bisphosphate [PI(4,5)P_2] to the second messengers D-*myo*-inositol 1,4,5-trisphosphate [Ins(1,4,5)P_3] and diacylglycerol (DAG), has augmented the pace of research in this field. Many phosphoinositols are involved in the *myo*-inositol cycle, through which Ins(1,4,5)P_3 recycles back to the lipid PI(4,5)P_2. Additionally, many other phosphatidylinositol phosphates (PIP*n*s) have recently been found in living cells. However a clear understanding of the biological significance of these phosphoinositols has been lacking mainly due to difficulties in isolating these derivatives from natural resources. As the isolation of these phosphorylated derivatives from natural sources is impracticable, biological studies rely on the efficient synthesis of these phosphoinositol derivatives. On the other hand, the judicious design and synthesis of structurally modified natural substrates of different enzymes as prospective effectors or inhibitors is also one of the major focuses of inositol chemistry. The increased interest in the biology of phosphoinositols has necessitated better synthetic strategies for their preparation. Furthermore, the disclosed therapeutic potential[2] of inositol derivatives and the recent use of inositol as a synthon for the synthesis of many natural products[3] have given further impact to the *myo*-inositol chemistry. This multi-faceted importance of inositol demands better methods for resolution and selective protection–deprotection[4] for this *meso* cyclohexane hexol.

The most commonly used intermediates for the syntheses of phosphoinositols are the orthoformate **1** and diketal derivatives **2** and **3** (Fig. 1). Following Kishi's first report,[5] the efforts of different groups to improve the yield of triol **1** has culminated in various excellent methods[6] for the isolation of triol **1** in very good yields. Such a high yield (90%) of triol, **1** from *myo*-inositol unlike diketals **2** and **3** (around 25% as a mixture of four or more components) promote **1** as the preferred starting material for various phosphoinositol syntheses. A good distinction can also be made between the reactivities of the three hydroxyl groups [C-2-OH and C-4-OH (C-6-OH)] of this triol. For instance, methods for the selective protection of (a) only the C-4 (or C-6) hydroxyl group,[7] (b) only the C-2 hydroxyl group,[5,7b,8] (c) C-2 and C-4 (or C-6) hydroxyl groups[9] simultaneously, and (d) C-4 and C-6 hydroxyl groups[7c,10] simultaneously, in **1** have been developed. Thus by choosing the appropriate reagent, any required protection of the three hydroxyl groups can be achieved. Acidic deprotection of the

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doi:10.1016/j.tetasy.2004.02.020

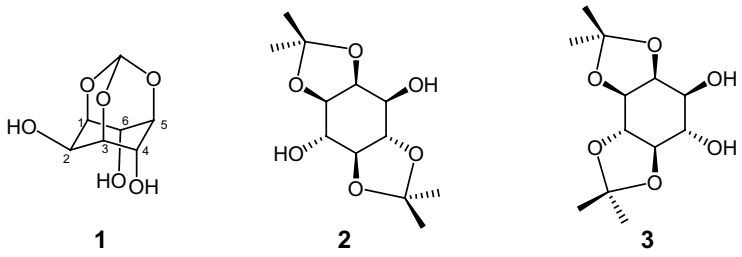


Figure 1.

orthoester functionality of fully protected orthoesters provides the 1,3,5-*meso* triol, which has been exploited as a starting material for the synthesis of D-*myo*-inositol-1-phosphate via enantioselective phosphorylation with synthetic polypeptide catalysts.[11] Also, different selectivities are reported for the partial deprotection of the orthoester functionality (to form acetals or ketals) in fully protected orthoester derivatives. Treatment of a fully protected orthoester derivative with DIBALH gave access to the C-5 hydroxyl group[12] while treatment with $AlMe_3$ gave access to the C-1(3)-hydroxyl group.[10b,12b,13] Treatment with 1 equiv of Grignard reagent gave access to the C-1(3)-hydroxyl group while the use of excess reagent provided the symmetrical diol (C-1 and C-3 OH).[14] Thus access to any single or combination of hydroxyl groups is possible with orthoesters unlike in the case of diketals (Fig. 2). Due to this possible modulation of protecting groups, orthoesters of *myo*-inositol are gaining more preference over the traditional diketals. Another added advantage is the possible absolute enantioselectivity (or diastereoselectivity) during resolution, as the triol is a *meso* derivative.

Despite this importance of triol **1** over diketal derivatives **2** and **3**, the exploration of resolution methods for this triol has not kept pace with its diketal counterparts. Efforts toward enzymatic resolution have been reported[15] to give no enantioselectivity, presumably because of the faster acyl migration between C-6 and C-4-OH due to their diaxial disposition and spatial proximity. Riley et al.[9b] resolved orthoformate, **1** via chromatographic separation of its diastereomeric biscamphanates. During our ongoing studies to provide easy access to many inositol phosphates and their lipid analogues, we required enantiomerically pure orthoester derivatives. We herein report the resolution of triol **1** as its di-*O*-acetylmandelate derivatives. To illustrate the utility and advantages of this method, an efficient synthesis of D-*myo*-inositol-4-phosphate is also described.

2. Results and discussion

The acylation of triol **1** with 2.1 equiv of (*S*)-*O*-acetylmandelic acid chloride in pyridine at 0 °C (Scheme 1) followed by work-up and chromatographic separation (3% acetone in CH_2Cl_2) yielded two unsymmetrical diacylated derivatives, **12** and **13**, with one of them being enriched.

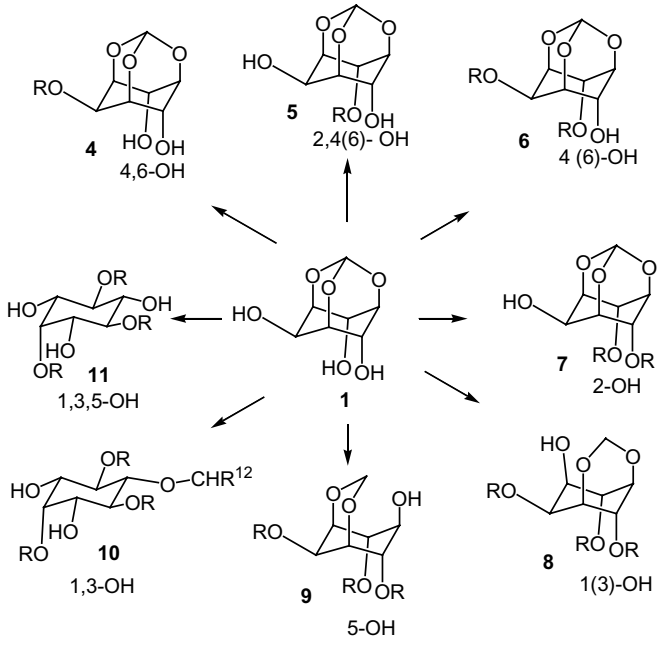
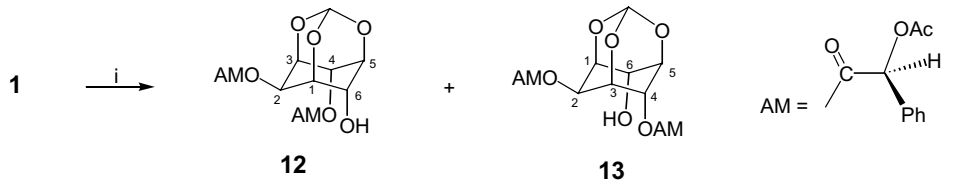


Figure 2.



Scheme 1. Reagents and conditions: (i) (*S*)-(+)-*O*-acetylmandeloyl chloride (2.1 equiv), py, 0 °C, 2 h.

The less polar diastereomer, **12** {mp 72 °C, $[\alpha]_D = +60$ (*c* 1, $CHCl_3$)}, was isolated in 59% as a white solid while the more polar diastereomer, **13** {$[\alpha]_D = +65.7$ (*c* 1, $CHCl_3$)} was isolated in 26% as a gum. Since we obtained a diastereomeric ratio of 7:3, we tried different conditions (Table 1) to see whether we could optimize the diastereomeric ratio (kinetic resolution). Lowering of reaction temperature yielded a mixture of **12** and **13** in a 1:1 ratio. At room temperature (15 °C), the ratio could be slightly improved upon at the cost of chemical yield due to charring. The exact reason for this variation of diastereomeric ratio with temperature is not clear. However acyl migration at higher temperatures may be responsible for the difference in diastereomeric ratio. DCC mediated coupling of (*S*)-*O*-acetylmandelic acid (2 equiv) with triol **1** (1 equiv) gave a 1:1 mixture of diesters **12** and **13** along with other products. The use of (*S*)-*O*-*tert*-butyldimethylsilylmandeloyl chloride[16] as the chiral auxiliary also resulted in the formation of 1:1 mixture (based on ^1H NMR) of diastereomers inseparable by chromatography. Hence entry 1 was taken as the optimum condition.

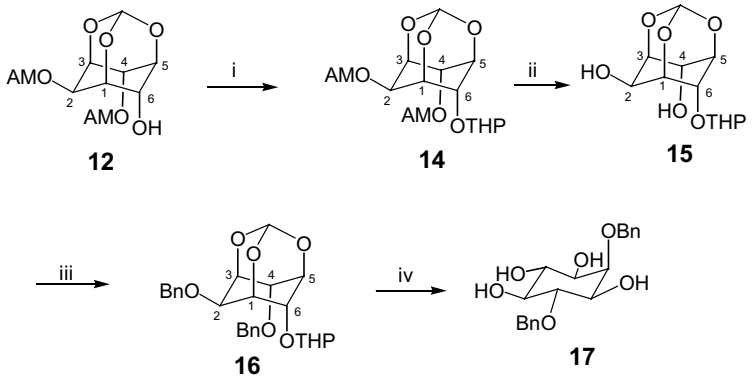
The absolute configurations of diastereomers **12** and **13** were determined by converting the less polar diastereomer **12** to the known[6a] L-2,4-di-*O*-benzyl-*myo*-inositol (Scheme 2). Thus the free hydroxyl group in **12** was protected as the THP ether to give **14** (92%). The chiral auxiliaries were removed by aminolysis and the resulting diol **15** converted to the dibenzyl ether **16** under standard conditions. Finally, the acid labile THP and orthoformate functionalities were removed via treatment with TFA and water to give L-2,4-di-*O*-benzyl-*myo*-inositol **17** {$[\alpha]_D = -28.9$ (*c* 1, EtOH); lit.[6a] $[\alpha]_D = -29.2$ (*c* 1, EtOH)}. Thus the less polar diastereomer **12** was assigned to be L-2,4-di-*O*-[(*S*)-*O*-acetylmandeloyl]-*myo*-inositol 1,3,5-orthoformate. Similarly, the more polar diastereomer **13** was assigned as D-2,4-di-*O*-[(*S*)-*O*-acetylmandeloyl]-*myo*-inositol 1,3,5-orthoformate.

To check the feasibility of this method, we synthesized D-*myo*-inositol-4-phosphate from diester **12** (Scheme 3). Thus the free hydroxyl group in **12** was phosphorylated using dibenzyl *N*,*N*-diisopropylphosphoramidite following Fraser-Reid's[17] protocol to give diester phosphate **18** {$[\alpha]_D = +45$ (*c* 1, $CHCl_3$)} in good yield (87%) as a gum. The benzyl, orthoformate, and acyl functionalities were removed successively, and the phosphate isolated as its bis-cyclohexylammonium salt in 37% yield from *myo*-inositol in four steps against a reported[18] yield of 0.99% in seven steps.

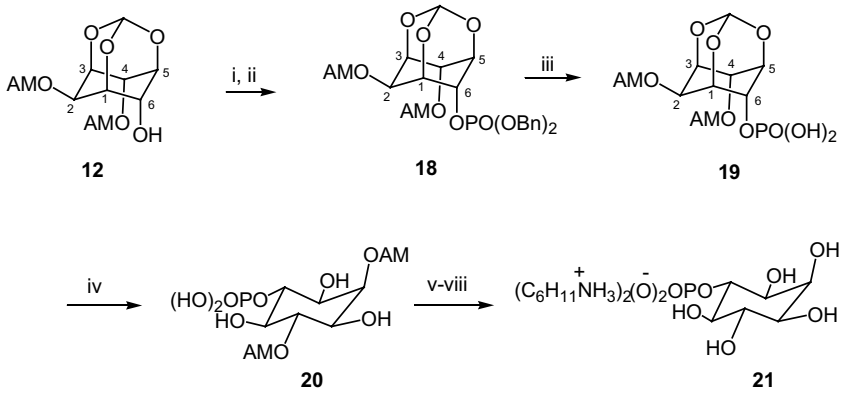
Table 1

Entry no	Conditions	Chemical yield (%)	Ratio **12**:**13**
1	(*S*)-*O*-Acetylmandeloyl chloride, py, CH_2Cl_2, 0 °C	85	70:30
2	(*S*)-*O*-Acetylmandeloyl chloride, py, CH_2Cl_2, −42 °C	79	50:50
3	(*S*)-*O*-Acetylmandeloyl chloride, py, CH_2Cl_2, 15 °C	60	74:26
4	(*S*)-*O*-Acetylmandelic acid, DCC, DMAP, CH_2Cl_2, 0 °C	69	50:50
5	(*S*)-*O*-TBDMS-mandeloyl chloride, py, CH_2Cl_2, 0 °C	70	50:50[a]

[a] This ratio is of corresponding derivatives with *O*-TBDMS-mandeloyl group.



Scheme 2. Reagents and conditions: (i) 3,4-dihydro-2H-pyran, PPTS, CH_2Cl_2, rt, 6 h, 92%; (ii) isobutylamine, MeOH, rt, 6 h, 91%; (iii) BnBr, NaH, DMF, rt, 10 min, 91%; (iv) TFA–H_2O (4:1 v/v), rt, 24 h, 97%.



Scheme 3. Reagents and conditions: (i) $(BnO)_2PN(i\text{-}Pr)_2$, tetrazole, CH_2Cl_2, −42 °C; (ii) *m*-CPBA, −78 °C, 90%; (iii) H_2, 5% Pd/C, EtOAc; (iv) TFA–H_2O, rt, 12 h; (v) 1 M LiOH, THF, rt, 12 h; (vi) H^+, extract with CH_2Cl_2; (vii) DIAION SK1BH (H^+ form) resin; (viii) $C_6H_{11}NH_2$, rt, 10 min.

3. Conclusion

In conclusion, we have achieved the optical resolution of an important intermediate for the synthesis of many *myo*-inositol phosphates and other derivatives. The utility of this method has been illustrated by an efficient synthesis of D-*myo*-inositol-4-phosphate. The enriched distribution of one of the diastereomers is advantageous since any required diastereoselectivity can be achieved by using the appropriate (*R*)- or (*S*)-mandelic acid derivatives. Since *meso* triol can be obtained in very high yield from inositol when compared to diketals, this method offers access to optically active derivatives in an economical way. The UV activity of the products (advantageous for chromatographic separation) and the low cost of mandelic acid (both *R* and *S*) are added advantages of using acetylmandelic acid over camphanic acid. The high yield of triol from inositol, enriched formation of one of the diastereomers by using a relatively cheaper chiral auxiliary and the different known selective reactions of orthoester derivatives offers efficient access to many optically active inositol derivatives in an economical way. We hope this resolution method will be useful not only for inositol chemists but also to a wider cross section of organic chemists as inositols are increasingly being used as synthons for many natural products,[3] metal complexing agents,[19] gelators,[20] catalysts,[21] supramolecular assemblies,[22] chiral auxiliary,[23] etc. Presently we are investigating to explore the synthetic manipulation of these resolved derivatives to achieve different phosphoinositols and other derivatives, which will be reported elsewhere.

4. Experimental

4.1. General

All experiments were conducted under nitrogen atmosphere. Melting points were determined with a Yanaco Micro Melting Point Apparatus and are uncorrected. Flash column chromatography was performed using silica gel (Fuji Silysia, Silica gel BW-300). ^1H, ^{31}P, and ^{13}C NMR spectra were recorded on a Bruker-DPX-400 instrument. Chemical shifts (δ_H values relative to tetramethylsilane, δ_C values relative to $CDCl_3$, and δ_P values relative to H_3PO_4) and coupling constants (*J* values) are given in ppm and Hz, respectively. Optical rotations were recorded in a JASCO P-1010 Polarimeter. Elemental analyses were carried out on a YANACO MT-5 elemental analyzer. Usual work-up refers to the evaporation of the reaction solvent, followed by dissolving the residue in ethyl acetate and washing successively with water, dil-HCl, satd $NaHCO_3$ solution, and brine.

4.2. Resolution of *myo*-inositol 1,3,5-orthoformate

To a solution of triol **1** (190 mg, 1 mmol) in pyridine (5 mL) at 0 °C, was added a solution of (*S*)-*O*-acetylmandeloyl chloride (446 mg, 2.1 mmol) in dichloromethane (5 mL) dropwise over a period of 10 min. After 1 h, the temperature was gradually raised to room temperature and continued stirring for another 3 h. The solvents were evaporated off and the residue dissolved in ethyl acetate and taken into a separating funnel, washed successively with water, cold dil-HCl, satd $NaHCO_3$ solution, and brine, dried over anhydrous sodium sulfate, evaporated under reduced pressure to give a gummy residue, and chromatographed over silica gel with 3% acetone in dichloromethane as the eluent. The less polar diastereomer, L-2,4-di-*O*-[(*S*)-*O*-acetylmandeloyl]-*myo*-inositol 1,3,5-orthoformate **12** (320 mg, 59%) was obtained as a colorless powder. Mp 72 °C; $[\alpha]_D = +60$ (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.24 (s, 3H), 4.03 (m, 1H), 4.30 (m, 1H), 4.35 (m, 1H), 4.40 (m, 1H), 5.22 (s, 1H), 5.49 (s, 1H), 5.56 (m, 1H), 5.96 (s, 1H), 6.02 (s, 1H), 7.38–7.48 (m, 8H), 7.54–7.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 63.7, 66.6, 67.8, 68.7, 68.9, 70.8, 74.5, 102.5, 127.4, 128.7, 128.8, 129.3, 129.4, 132.7, 133.0, 167.1, 168.3, 170.4, 170.6; Anal. Calcd for $C_{27}H_{26}O_{12}$: C, 59.78; H, 4.83. Found: C, 59.61; H, 4.90. Further elution yielded the, D-2,4-di-*O*-[(*S*)-*O*-acetylmandeloyl]-*myo*-inositol 1,3,5-orthoformate **13** (141 mg, 26%) as a colorless gum. $[\alpha]_D = +65.7$ (*c* 2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 3H), 2.22 (s, 3H), 2.92 (d, 4.4 Hz, OH), 4.04 (dt, 1.6 Hz, 3.6 Hz, 1H), 4.33 (dt, 4.0 Hz, 2.0 Hz, 1H), 4.46 (ddd,

5.4 Hz, 3.2 Hz, 1.6 Hz, 1H), 4.61 (m, 1H), 5.23 (m, 1H), 5.41 (ddd, 4.0 Hz, 1.6 Hz, 1H), 5.48 (d, 1.6 Hz, 1H, HCO_3), 5.72 (s, 1H), 5.99 (s, 1H), 7.30–7.46 (m, 8H), 7.50–7.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 64.0, 66.8, 67.5, 68.4, 69.2, 70.7, 74.5, 74.8, 102.7, 127.37, 127.42, 128.7, 129.0, 129.3, 129.7, 131.9, 133.0, 167.3, 168.1, 170.4, 171.2; MS (FAB+) m/z (%): 543 [$(M+H)^+$, 100].

4.3. Determination of the absolute configuration

Compound **12** (50 mg, 0.09 mmol) was dissolved in dichloromethane (1 mL) and then pyridinium *para*-toluene sulfonate (PPTS, 10 mg) and 3,4-dihydro-2H-pyran (37 μL, 0.4 mmol) added and stirred at room temperature for 6 h. Usual work-up followed by column chromatography yielded the THP ether **14** as a mixture of diastereomers (53 mg, 92%). The chiral auxiliaries were removed by refluxing **14** with isobutylamine (0.5 mL) in methanol (2 mL) for 6 h. Evaporation followed by column chromatography afforded diol **15** (21 mg, 91%), which (20 mg, 0.07 mmol) was benzylated with benzyl bromide (44 μL, 0.37 mmol) in the presence of NaH (10 mg, 0.42 mmol) in DMF (1 mL) at room temperature for 10 min. Usual work-up followed by chromatographic separation yielded dibenzyl ether **16** (30 mg, 91%). Dibenzyl ether **16** (30 mg) was stirred with TFA–H_2O (4:1 v/v, 1 mL) at ambient temperature for 24 h, evaporated to dryness and washed with hexane to give tetrol **17** (23 mg, 97%). $[\alpha]_D = -28.9$ (*c* 1, EtOH); lit.[6a] $[\alpha]_D = -29.2$ (*c* 1, EtOH); ^1H NMR (400 MHz, CD_3OD) δ 3.33 (m, 1H), 3.46 (dd, 9.9 Hz, 2.5 Hz, 1H), 3.61 (dd, 9.8 Hz, 2.5 Hz, 1H), 3.69 (dd, 10.0 Hz, 9.6 Hz, 1H), 3.73 (t, 9.5 Hz, 1H), 3.93 (t, 2.5 Hz, 1H, H-2), 4.85–4.94 (m, 4H, benzylic), 7.25–7.36 (m, 6H, Ar–H), 7.45–7.48 (m, 4H, Ar–H).

4.4. D-*myo*-Inositol-4-phosphate

Compound **12** (240 mg, 0.44 mmol) and tetrazole (70.1 mg, 1 mmol) were dissolved in dichloromethane (5 mL) and cooled to −42 °C. Dibenzyl *N*,*N*-diisopropyl phosphoramidite (227.7 mg, 0.66 mmol) was then added and stirred for 3 h and then for another half an hour at room temperature, while following the reaction by TLC. It was then cooled to −78 °C, *m*-CPBA (172.5 mg, 1 mmol) added and stirred for 1 h and then at room temperature for another half an hour. Usual work-up followed by chromatographic separation yielded phosphate **18** as a gum (350 mg, 87%). $[\alpha]_D = +45$ (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.22 (s, 3H), 4.00 (ddd, 1.6 Hz, 2.0 Hz, 4.0 Hz, H-5), 4.03 (ddd, 1.6 Hz, 3.6 Hz, 5.2 Hz, H-3), 4.37 (ddd, 1.6 Hz, 2.0 Hz, 4.0 Hz, H-1), 4.84–4.89 (m, H-4), 4.92–5.11 (m, 4H, benzylic), 5.20 (dd, 2.0 Hz, 3.6 Hz, H-2), 5.43 (d, 1.0 Hz, 1H, HCO_3), 5.48 (dt, 1.6 Hz, 4.0 Hz), 5.75 [s, 1H, PhC*H*(OAC)], 6.02 [s, 1H, PhC*H*(OAC)], 7.22–7.55 (m, 20H, Ar–H); ^{31}P NMR (400 MHz, CDCl3) δ −0.99; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 20.6, 63.4, 67.1, 67.2, 68.0, 68.3, 69.1, 69.2, 69.79, 69.84, 69.9, 70.0, 70.1, 74.3, 74.4, 102.6, 127.5, 128.0, 128.1, 128.2, 128.6, 128.77, 128.8, 129.3, 132.9, 133.2, 135.1, 135.2, 167.8, 167.9, 170.1, 170.3. Phosphate **18** (108 mg, 0.13 mmol) was dissolved in ethyl acetate (3 mL) and stirred with 5% Pd/C (11 mg) under hydrogen atmosphere (balloon) at room temperature for 12 h. The solid materials were filtered off, washed several times with ethyl acetate and methanol, and the combined washings and filtrate concentrated. The residue was dissolved in TFA (3 mL) and a drop of water then added and stirred at ambient temperature overnight. The solvents were evaporated and the residue thus obtained dissolved in THF (1 mL) and stirred with a 1 M solution of LiOH (1 mL) for 6 h. THF was evaporated, the aqueous solution acidified with dilute HCl and the organic acid (mandelic acid) residues extracted with CH_2Cl_2 (7 × 5 mL). The aqueous layer was concentrated and stirred with an ion exchange resin (DIAION SK1BH H^+ form) for 1 h. The filtrate was treated with cyclohexylamine (excess) for 3 h and evaporated to dryness. The residue thus obtained was dissolved in the minimum amount of distilled water and lyophilized with acetone to afford a white precipitate of bis-cyclohexylammonium salt **21** of D-*myo*-inositol-4-phosphate {50 mg, 81%, $[\alpha]_D = +2$ (*c* 2, H_2O)}, lit.[18] $[\alpha]_D = +1.3$ (*c* 5, H_2O)]}. It was found that the $[\alpha]_D$ values varied with pH of the solution. At neutral pH an $[\alpha]_D = +2$ was observed and at a pH of around 10 (by adding cyclohexylamine), the value increased to +9. Such a dependence of $[\alpha]_D$ on pH of the solution has been observed previously in this laboratory.[24]

Acknowledgements

We thank JSPS for a postdoctoral fellowship (K.M.S.) and Grant-in-Aid (No. 02170). We also thank Venture Business Laboratory and Advanced Instrumentation Center for Chemical Analysis, Ehime University for NMR and elemental analysis, respectively.

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