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EASY ACCESS OF OPTICALLY ACTIVE *MYO*-INOSITOL DERIVATIVES BY ENANTIOSELECTIVE ACYLATION USING A TARTARIC ACID MONOESTER

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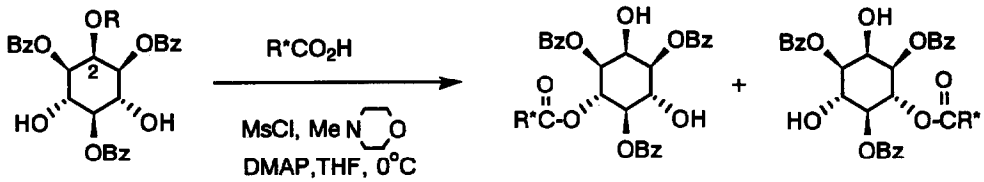
Abstract: An L- or D-tartaric acid monoester is shown to be an excellent chiral auxiliary for asymmetric esterification of *myo*-inositol derivatives and one of the resultant esters with high optical purity is utilized for a short-step and practical synthesis of D-*myo*-inositol 1,3,4,5-tetrakis(phosphate).

Recent explosive investigation in the field of inositol chemistry has resulted in remarkable progress especially in the synthesis of inositol phosphates[1] which are involved as metabolites in a newly discovered intracellular signal transduction system.[2] In order to get optically active intermediates for the synthesis of inositol phosphates, some new methods have been reported recently[3] in addition to old ones.[4] Most of them are based on separation of 1 : 1 mixture of two diastereomers formed from the corresponding racemate and a chiral auxiliary. The others involve a chiral column chromatography[3e] and utilization of chiral starting materials such as glucurono-6,3-lactone[3b] and quebrachitol.[3h,4a] This time we have examined a different methodology which involves enantioselective acylation of inositol derivatives. Such an asymmetric acylation of general alcohols has been known for a long time.[5] But its enantioselectivity was generally low except for Mukaiyama's reports[6] and the synthetic use of this strategy has not been taken into consideration while an enzymatic transformation provides a useful tool for a chiral ester synthesis.[7] In this communication, we describe a highly enantioselective esterification of inositols using a tartaric acid derivative as a chiral acid.

We reported recently benzoylation of *myo*-inositol to give 1,3,4,5-tetra-O-benzoyl-*myo*-inositol **8a** and it has proved to be the useful synthetic intermediate for D-*myo*-inositol 1,3,4,5-tetrakis(phosphate) **6**[8] whose role in the signalling system has been actively investigated. The benzoylation (2.5 equiv BzCl, Pyridine, 90 °C) formed also 1,3,5-tri-O-benzoyl-*myo*-inositol **1**, a *meso* compound and it was readily isolated in 15% yield by silica gel column chromatography. If a chiral acyl group was enantioselectively introduced on one of two identical equatorial hydroxyl groups keeping the axial and stericaly hindered hydroxyl at C-2 intact in prochiral **1**, we can obtain an optically active 1,3,4,5-tetraacyl derivative **3** which is structurally identical with tetrabenzoate **8a** and derive it to optically active **6**. Along this line, symmetrical tribenzoate **1** was acylated with various chiral carboxylic acids and related compounds such as (-)-menthoxyacetyl chloride, ketopinic acid chloride,

Scheme 1



1: R=H
2: R=Ac

D-3 L-3

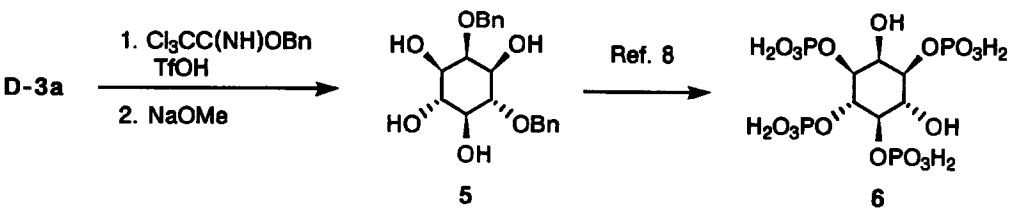
	R^*CO_2H	Ratio D-3 : L-3		Optical purity, % de
(D)- D-4	a:R-R= $(CH_2)_5$, R'=Me	98	2	96
	b:R-R= $(CH_2)_5$, R'=Et	97	3	94
	c:R=Me, R'=Me	94	6	88
(L)- L-4	d:R-R=  , R'=Et	2	98	96
	e:R=Bz, R'=Et	38	62*	24

*The absolute configuration was not determined.

(-)-menthy chlorocarbonate, and (+)-O-acetylmandelic acid to afford the corresponding mono-substitution products 3. Diastereomeric ratio in each reaction was low generally (up to 68:32 for the carbonate), but exceptionally tartaric acid derivative gave excellent results. Thus, treatment of equimolar amount of 1 with methyl hydrogen 2,3-O-cyclohexylidene-D-tartrate **D-4a** in the presence of methanesulfonyl chloride (1.1 equiv), N-methylmorpholine (2.5 equiv), and a catalytic amount of DMAP in THF at 0 °C afforded diastereomeric monotartrates 3 in 57% yield. The ratio of diastereomers was estimated by means of chromatography using a chiral stationary phase column (Chiralcel OD™)[9] and surprisingly almost complete selection (96% de) was recorded (Scheme 1). The isopropylidene tartaric acid monomethyl ester **D-4c** exhibited slightly lower selectivity (88% de) than the cyclohexylidene. In the case employing cyclohexylidene-L-tartrate **L-4d**, the opposite diastereomer L-3 was predominantly formed in 96% optical yield. Contrary to these results using dioxolane derivatives, enantioselectivity in the reaction using noncyclic 2,3-di-O-benzoyl tartaric acid monomethyl ester **L-4e** decreased remarkably to 24% de. Chemical yield in each esterification was generally moderate and was not optimized. In a similar manner, symmetrical 2-acetyl derivative 2 was treated with D-tartaric acid **D-4a** to afford monoacylated diastereomers in 53% yield with high enantioselectivity (95 : 5). This result shows the hydroxyl group at C-2 in 1 dose not play an important role in the esterification described above.

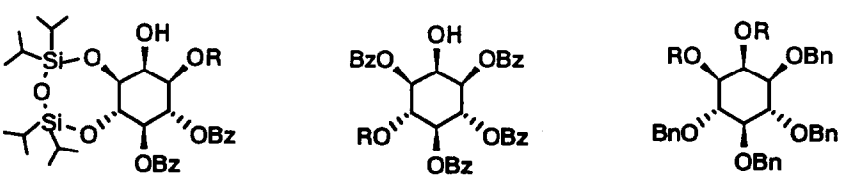
The absolute configuration of the predominant product was confirmed by transformation of inositol 4-tartrate 3a with 96% optical purity to known D-2,6-di-O-benzyl-*myo*-inositol 5[3f,10,11] by benzylation ($Cl_3CC(NH)OBn$/ TfOH) followed by removal (NaOMe) of acyl functions (Scheme 2). Furthermore, fortunately the 2,6-dibenzyl ether 5, mp 146-7 °C, $[\alpha]_D$ -29.2°(c 0.65, EtOH) was found to become optically pure by one recrystallization from dichloromethane as judged from a chiral column chromatography using Chiralcel OD™ and optical rotation. Thus, *meso*-tribenzoate 1 could be converted easily to optically pure 5. Chiral[3f,10,11] and racemic[12] 5 were utilized for the synthesis of inositol 1,3,4,5-tetrakis(phosphate) 6 by several groups and our recent report[8] showed an efficient phosphorylation of racemic 5 using N,N-diethyl *o*-xylene phosphoramidite as a new phosphitylating agent.[13] Consequently, a short-step and practical synthesis of 6 with natural and unnatural configurations has now been achieved formally.

Scheme 2



The ability of tartrate to recognize enantiotopic molecules was tested briefly by kinetic resolution of some inositol derivatives using methy 2,3-cyclohexylidene-D-tartrate D-4a. Thus, two molar equivalent of racemic diols 7a and 8b were treated with the tartrate as above respectively and diastereomeric mixtures 7b and 8b with high optical purities were obtained in 60% each chemical yield based on the acid used (Scheme 3). Since the recovered tetrabenzoate consisted of D-8a and its enantiomer L-8a in a 25 : 75 ratio as analyzed by HPLC using Chiralcel OD™,[8] D-8b with the absolute configuration illustrated in the scheme was apparent to be formed preferencially. Treatment of 0.8 molar equivalent of DL-9a with D-4a gave an 84 : 16 ratio[14] of D-9b and L-9b in 19%

Scheme 3



D-b/L-b: ***83 : 17**** ***86 : 14*** ***84 : 16***

a: R=H, b: R=Tartrate (D-4a) residue
*The absolute configuration was not determined.

yield together with 37% of a mixture of 1- and 2-acylinositols (the latter was predominant) and 7% of the recovered diol (**D-9a/L-9a**, 99 : 1) where yields were calcurated based on the diol used. On the other hand, when 1.7 molar equivalent of **9a** was used the starting diol with high homogeneity (**D-9a/L-9a**, 84 : 16) was recovered in 36% yield accompanied with 46% of monoacyl derivatives and recrystallization of the diol only once from methanol gave optically pure **D-9a** which is a useful chiral intermediate.

In summary, it has now been found that 2,3-O-cyclohexylidene D- and L-tartaric acid monomethyl and monoethyl esters have proved to be useful chiral agents for obtaining an optially active inositol derivatives. Application of the present system to general alcohols and other nucleophiles such as amines and thiols is now under progress.

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14. The ratio was determined by analysis of the hydrolysis product **9a** of the reaction mixture **9b** using the chiral column chromatography.

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