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AN ASYMMETRIC SYNTHESIS OF GLYCEROL DERIVATIVES BY THE ENANTIOSELECTIVE ACYLATION OF PROCHIRAL GLYCEROL

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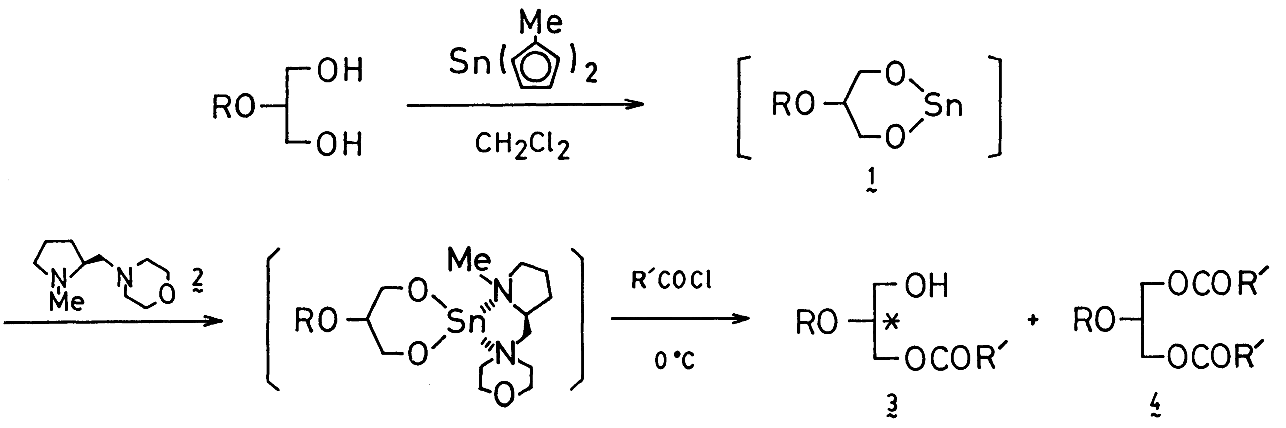
Optically active glycerol derivatives are obtained in up to 84% e.e. by the selective acylation of the tin(II) alkoxides generated from 2-O-arylsulfonylglycerols and 1,1'-dimethylstannocene or (methylcyclopentadienyl)tin(II) chloride by the use of a chiral diamine derived from (*S*)-proline as a ligand.

Optically active glycerol derivatives are of central importance in biochemical field as lipid chemistry[1)] and also have often been used as versatile chiral precursors in enantioselective syntheses of natural products.[2)] Concerning the preparation of chiral glycerol derivatives, many methods have already been published, however, most of these methods are based on the degradation of chiral progenitors of natural origin, such as D-mannitol[3)] and L-ascorbic acid,[4)] and few attempts by asymmetric synthesis have been reported in spite of their utility.[5)]

In the previous paper, we reported a new and efficient method for the acylation of alcohols *via* tin(II) alkoxides generated *in situ* from alcohols and 1,1'-dimethylstannocene.[6)] It was also found in our laboratory that chiral diamines derived from (*S*)-proline are efficient ligands to form chelate complexes with divalent tin compounds and effectively employed in the enantioselective aldol reactions.[7)] These observations prompted us to apply the above mentioned acylation reaction to the asymmetric synthesis of glycerol derivatives, that is, the enantioselective acylation of the two primary hydroxyl groups of prochiral glycerol characterized by the formation of chelate complex between the tin(II) alkoxide and the chiral diamine.

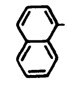
This type of asymmetric synthesis based on the selective transformation between two enantiotopic groups has been well known in enzymatic processes,[8)] and recently some papers have reported on the purely chemical methods.[5,9)] However, few examples have been reported to utilize the coordination of a chiral ligand to give an unsymmetrical environment to a symmetrical molecule,[10)] though these methods are earnestly desired because of their ease of manipulation.

Now, we wish to report an asymmetric synthesis of glycerol derivatives starting from 2-O-protected glycerol as studied in the hope that the selective acylation would be achieved to afford an optically active glycerol derivative (**3**) by the use of a chiral ligand as sketched below.



In the first place, 2-O-benzylglycerol[11] was treated with 1,1'-dimethylstannocene in dichloromethane, and then a chiral diamine, (*S*)-1-methyl-2-(morpholinomethyl)pyrrolidine (2)[7a] and benzoyl chloride were added successively at 0 °C. After stirring for 1 h, usual work-up afforded the desired product, the monobenzoate (3) in 55% yield, though this product was found to be optically inactive. Then, several 2-O-protected glycerols[11] were examined, and the results are summarized in Table 1.

Table 1. The Effect of Protective Group on Optical Purity[a] (R'=Ph)

Entry	Protective group (R)	Yield of 3/%[b]	Yield of 4/%[b]	O.P. of 3/%e.e.
1	$PhCH_2$-	55	15	≈0
2	PhCO-	13[d]	29	≈15[c]
3	*p*-$MeC_6H_4SO_2$-	46	23	48[c][e]
4	 SO_2-	20	36	62[c]

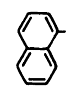
a) Molar ratio of $Sn(MeC_5H_4)_2$: 2-O-protected glycerol : chiral diamine : benzoyl chloride = 1 : 1 : 1 : 1.
b) Isolated yield. All samples gave satisfactory ^1H NMR and IR spectra.
c) Determined by ^{19}F NMR measurement of its MTPA ester.[12]
d) 1,3-Di-O-benzoylglycerol was obtained in 19% yield.
e) The absolute configuration was determined to be 3-O-benzoyl-2-O-tosyl-*sn*-glycerol by the optical rotation of 3.[13]

The optical purity of 3 varied dramatically with the nature of the protective group of the secondary hydroxyl group. As shown in Entries 3 and 4, arylsulfonyl group is found to be very effective in this asymmetric induction.

Next, we examined various acyl chlorides as acylating reagents taking 2-O-tosylglycerol as a model compound, and it was found that benzoyl chloride gave the best result as shown in Table 2.

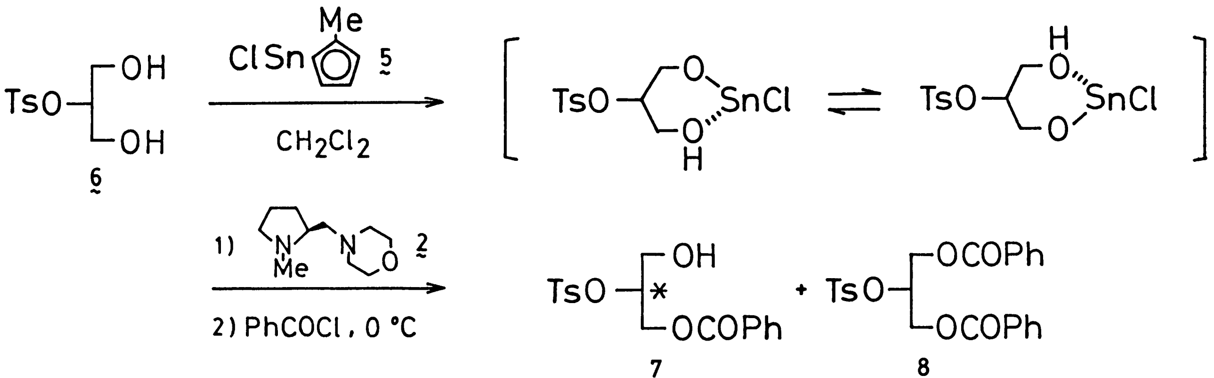
Furthermore, (methylcyclopentadienyl)tin(II) chloride (5)[14] was tried in place of 1,1'-dimethylstannocene in the above mentioned reaction, and it was shown that pronounced changes in both chemical and optical yields were not observed when the reaction was carried out under the same conditions. On the other hand, the

Table 2. The Effect of Acyl Chloride on Optical Purity

Entry	R'COCl	Yield of 3/%[a]	Yield of 4/%[a]	O.P. of 3/%e.e.
1	PhCOCl	46	23	48[b]
2	*o*-ClC_6H_4COCl	50	19	24[b]
3	-COCl	42	24	34[b]
4	PhCH=CHCOCl	87	6	≈0
5	cyclo-$C_6H_{11}COCl$	71	trace	≈0

a) Isolated yield. All samples gave satisfactory ^1H NMR and IR spectra.
b) Determined by ^{19}F NMR measurement of its MTPA ester.

use of excess benzoyl chloride increased the optical purity of 3-O-benzoyl-2-O-tosyl-*sn*-glycerol (7) up to 84% e.e. (see Table 3).



Ts: p-$MeC_6H_4SO_2$-

Table 3. The Effect of Molar Ratio on Optical Purity[a]

Entry	Molar Ratio of 6:PhCOCl	Yield of 7/%[b]	Yield of 8/%[b]	O.P. of 7/%e.e.[c]
1	1 : 1	32	20	43
2	1 : 1.5	32	40	67
3	1 : 2	20	57	84

a) Molar ratio of MeC_5H_4SnCl : 2-O-tosylglycerol : chiral diamine = 1 : 1 : 1.
b) Isolated yield.
c) Determined by ^{19}F NMR measurement of its MTPA ester.

These results suggest that additional kinetic resolution of the monobenzoate (7) initially formed by asymmetric acylation should increase the enantiomeric excess, that is, the minor enantiomer of 7 should be preferentially acylated to give the dibenzoate (8) resulting in enrichment of the major enantiomer of 7. Thus, optically active 3-O-benzoyl-2-O-tosyl-*sn*-glycerol (7) could be obtained in high optical purity by the two-step selective acylation; the first step is an asymmetric acylation of the achiral 2-O-tosylglycerol to the optically active 7, and the second step is the kinetic resolution of 7.

A typical procedure is described for the preparation of 3-O-benzoyl-2-O-tosyl-*sn*-glycerol using (methylcyclopentadienyl)tin(II) chloride; to a dichloromethane solution (4 ml) of (methylcyclopentadienyl)tin(II) chloride[14] (0.48 mmol) was added 2-O-tosylglycerol (117 mg, 0.48 mmol) in dichloromethane (2 ml) at 0 °C under an argon atmosphere. After stirring for 30 min at that temperature, (*S*)-1-methyl-2-(morpholinomethyl)pyrrolidine (88 mg, 0.48 mmol) in 2 ml of dichloromethane was added, and the mixture was stirred for 5 min. Then benzoyl chloride (134 mg, 0.95 mmol) in 2 ml of dichloromethane was added dropwise at 0 °C. The reaction mixture was further stirred for 1 h at the same temperature, then quenched with pH 7 phosphate buffer. The organic layer was extracted with ethyl acetate three times, and the combined extracts were washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, 3-O-benzoyl-2-O-tosyl-*sn*-glycerol (34 mg, 20%) and 1,3-di-O-benzoyl-2-O-tosylglycerol (123 mg, 57%) were isolated by column chromatography on silica gel.

It should be noted that the present enantioselective acylation reaction is the first example of forming glycerol derivatives in rather high optical purity utilizing the non-covalent bonded interaction between the chiral diamine and the symmetrical molecule. Further studies on the kinetic resolution in acylation of racemic glycerol derivatives are now in progress.

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