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HIGHLY EFFICIENT ASYMMETRIC SYNTHESIS OF (S)-2,2-DIMETHYL-1,3-DIOXOLANE-4-METHANOL FROM GLYCEROL

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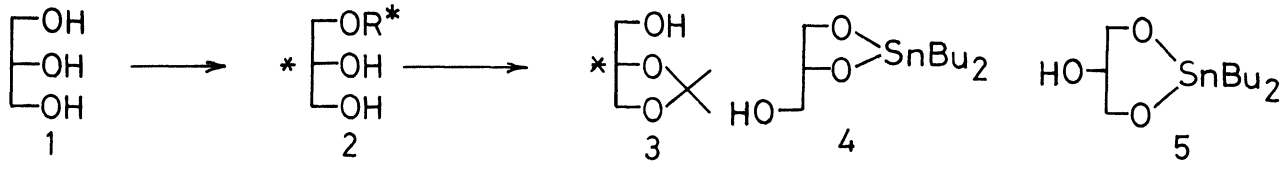
(S)-2,2-Dimethyl-1,3-dioxolane-4-methanol was prepared from glycerol in high yield with high optical purity by simple procedure. The procedure involves acylation of cyclic tin(IV) alkoxide with an optical active acid chloride in the crucial step.

(S)-2,2-Dimethyl-1,3-dioxolane-4-methanol (3) constitutes a very versatile class of building blocks and has been utilized extensively for the synthesis of various natural products,[1] including lipids,[2] carbohydrates,[3] nucleotides.[4] However, this useful material has usually been prepared from a natural source, bis(acetonide) of mannitol via oxidative cleavage followed by reduction.[5]

Our continuing effort on creating optically active compounds from symmetrically substituted molecules led us to investigate a selective mono-acylation method for meso-1,2-diols and we have already pointed out that the use of a rigid cyclic tin(IV) alkoxide intermediate is crucial for this kind of strategy.[6]

It is a more difficult but worthwhile challenge to devise a method to convert achiral glycerol (1) to optically active glycerol acetonide (3) by simple procedure through easy operations. We have now found a simple solution to this approach and wish to describe herein an efficient method for conversion of glycerol to (S)-2,2-dimethyl-1,3-dioxolane-4-methanol.



1 2 3 4 5

One of the most difficult questions on this strategy is how to differenciate three hydroxy groups of glycerol. If the formation of five-membered cyclic tin(IV) alkoxide (4) predominates over the six membered analogue (5), the primary alkoxy group is expected to be more reactive towards acylation reagent. Furthermore, the five membered metalocycle (4) is, presumably, thermodynamically more stable[7] and it would be reasonable to assume that one enantiomer of 4 may react more rapidly with a suitable optically active acid halide than the other.

Based on the above hypothesis, we treated glycerol with dibutyltin oxide, followed by the treatment with an optically active acid chloride (6) and two diastereomers in a 63 : 37 ratio were isolated (see, entry 2 of Table 1).

After screening various acylating reagents, (-)-camphanic acid chloride (6f) [8] was found to give the best result, where rigid cyclic structure was shown to be effective. Results are summarized in Table 1.

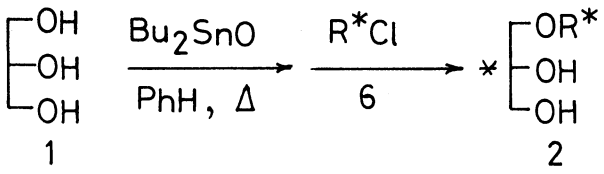
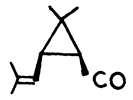
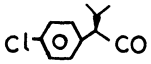
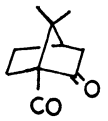
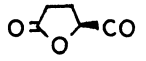
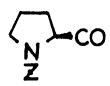
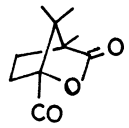


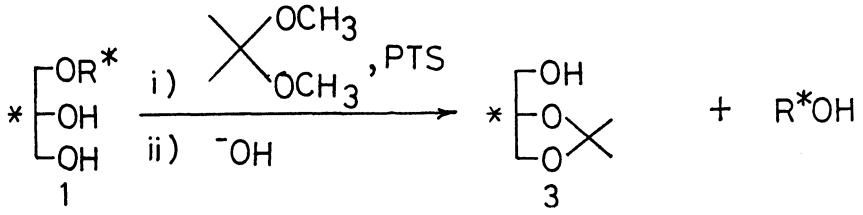
Table 1. Asymmetric Acylation of Glycerol.

Entry	Acid chloride 6	1/6	Reaction conditions		Yield[a]/%	d.e.[b]/%
1	 a	2.0	CH_2Cl_2	0°C, 1 h	72	10
2	 b	1.1	Toluene	-78°C, 1 h	42[d]	25
3		2.0	Toluene	-78°C, 1 h	81	35
4	 c	1.1	Toluene	0°C, 1 h	31[d]	20
5		1.1	CH_2Cl_2	0°C, 1 h	50[d]	20
6		1.1	CH_2Cl_2	-78°C, 20 h	45[d]	35
7		3.0	CH_2Cl_2	-45°C, 12 h	61	37
8		3.0	CH_2Cl_2	-78°C, 24 h	55	45
9	 d	2.0	CH_2Cl_2	-78°C, 5 h	72	50
10		3.0	CH_2Cl_2	-78°C, 5 h	70	55
11	 c) e	3.0	CH_2Cl_2	-90°C, 10 h	73	70
12		5.0	CH_2Cl_2	-90°C, 10 h	75	75
13		5.0	Toluene	-90°C, 10 h	40	60
14	 f	5.0	THF	-90°C, 10 h	55	45
15		5.0	CH_2Cl_2	-78°C, 5 h	80	80
16		5.0	CH_2Cl_2	-90°C, 10 h[e]	77	85
17		5.0	CH_2Cl_2 -THF	-100°C, 10 h[e]	78	90
18[f]		3.0	Pyridine	0°C, 5 h	72	0

a) Based on acid chloride (6) and all compounds gave satisfactory spectral data. b) Determined by ^{1}H-NMR of acetate of 3 using chiral shift reagent Eu(hfc)$_3$ and/or optical rotation.[9] c) Z = benzyloxycarbonyl d) 1,2- or 1,3-diacylated glycerol was obtained as by-product (8-18% yield). e) Added slowly during 5 h. f) In the absence of dibutyltin oxide.

As pointed out in the previous communication, manipulation of triol functionality as its cyclic tin(IV) alkoxide proved to be necessary for minimizing the amount of di or tri-acylated products and at the same time enhanced diastereomeric excess (see, entries 7-18). Molar ratio of 1 vs. 6 was very important to increase the selectivities and lowering acylation reaction temperature also increase the degree of diastereomeric excess. Satisfactory results were obtained when 3-5 equiv.

of glycerol was used[10] and the acylation reaction was carried out with slow addition of (-)-camphanic acid in dichloromethane at -100 °C during 5 h.



Transformation of the acylated product (2) to (S)-2,2-dimethyl-1,3-dioxolane-4-methanol (3) was readily performed through standard sequence in good overall yield.

Typical example was described as follows. A mixture of glycerol (230 mg, 2.5 mmol) and dibutyltin oxide (625 mg, 2.5 mmol) in 20 ml of toluene in the presence of molecular sieves 4A (2.0 g) were heated under reflux for 2 h. Toluene was removed in vaccuo, and dichloromethane (16 ml) and dry THF (4 ml) were added. To the resulting mixture was added a solution of (-)-camphanic acid chloride (108 mg, 0.5 mmol) in 2.0 ml of dichloromethane at -100 °C for 5 h. After stirring for 5 h at -100 °C, the reaction mixture was added to phosphate buffer (pH 7.1) at that temperature. The entire mixture was filtered through Celite and extracted with chloroform (20 ml x 2). The combined extracts were dried over anhydrous sodium sulfate and concentrated. Purification by silica gel column chromatography gave the monoacylation product (175 mg, 78%) as a chlorless oil.

A mixture of the monoacylation product (100 mg, 0.367 mmol) and 2,2-dimethoxypropane (77 mg, 0.734 mmol) in 7 ml of dry ether in the presence of a catalytic amount of p-toluenesulfonic acid (5 mg) was stirred at room temperature for 2 h. Then sat. aqueous sodium bicarbonate was added to the reaction mixture, which was subsequently extracted with ether (20 ml x 2). The combined extracts were dried over anhydrous sodium sulfate and concentrated. The residue was practically pure acetonide (105 mg, 92%), which was hydrolyzed with 0.5 M KOH-mthanol/H_2O (5:1; v/v) at 0 °C for 1 h and then room temperature for 5 h. The reaction mixture was concentrated by reduced pressure and extracted with ether (20 ml x 2). The combined extracts were dried over anhydrous sodium sulfate and concentrated.[11] The crude material was purified by alumina gel column chromatography to give 3 (48 mg, 73% yield from 2).

In addition to the synthetic utility of (S)-2,2-dimethyl-1,3-dioxolane-4-methanol, the strategy shown here demonstrates the usefulness of non-enzymatic process in producing optically pure substances from achiral symmetrical molecules, which is an intriguing challenge among us. Although the versatility of this kind of diastereomer selection was disclosed specifically with glycerol at this stage, the other polyols involving symmetrically substituted aminoalcohols may be equally employable.

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9) The absolute configulation was determined to be (S) by comparison with the known sample.

10) This result implies kinetic resolution of 4.

11) The chiral carboxyric acid was recovered in 80% yield after saponification. The recovered material was optically pure enough (95% o. p.) for another run.

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