

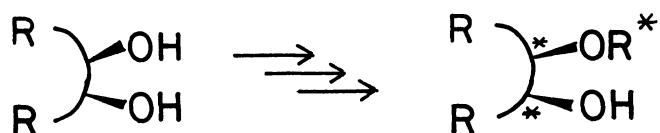
ASYMMETRIC ACYLATION OF meso-1,2-DIOLS WITH
d-KETOPINIC ACID CHLORIDE

Teruaki MUKAIYAMA,* Isao TOMIOKA, and Makoto SHIMIZU

Department of Chemistry, Faculty of Science,
 The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

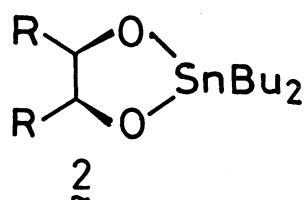
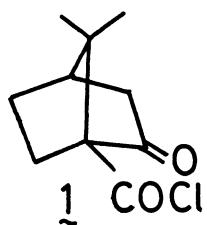
Highly selective asymmetric acylation of meso-1,2-diols has been achieved using d-ketopinic acid chloride as acylating reagent.

Differentiation of two identical functional groups in meso-compounds offers rapid and simple preparation of synthetically useful chiral materials.



For this purpose, enzymatic processes have been utilized as one of the most convenient approaches to chiral lactones,¹⁾ prostagrandin precursors,²⁾ and so on, whilst rather laborious separation of diastereomers has been required for chemical methods.³⁾

Our interest in creating optically active materials from symmetrical molecules⁴⁾ led us to consider asymmetric acylation of meso-1,2-diols with a suitable optically active acid chloride. In principle, acylation of meso-1,2-diols with an optically active acid chloride gives two diastereomers and their separation leads to resolution of two enantiomers. This kind of strategy has been used in the synthesis of some natural product precursors.⁵⁾ However, simple and selective monoacetylation methods with readily available acylation reagents have not been reported.

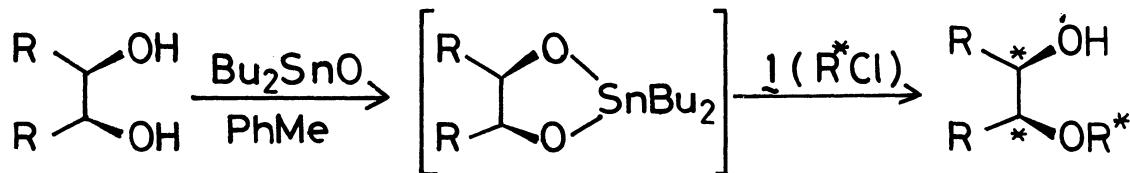


We have now found that acylation with d-ketopinic acid chloride 1 provides differentiation of two hydroxy groups in a highly selective manner.

d-Ketopinic acid chloride 1 was readily prepared from commercially available d-10-camphorsulfonyl chloride by oxidation with potassium permanganate followed by chlorination and has been stored at ambient temperature under an argon atmosphere for two months without noticeable change.⁶⁾

Initial examination by using pyridine and the acid chloride 1 gave a mixture of the diastereomers in a 1:1 ratio together with a small amount of the diacylation product (entry 1 in Table 1). Recent examples of tin(II)⁷⁾ and tin(IV)⁸⁾ alkoxide promoted reactions found in our laboratory led to the consideration that a rigid cyclic tin alkoxide intermediate 2 would provide proper steric bulk around the hydroxy groups and enhance the selectivity.

Indeed, treatment of meso-dimethyl tartrate with dibutyltin oxide followed by acylation with 1 gave the monoacetylation product exclusively in high yield with high diastereomer selectivity (entry 2).



Brief examination of the reaction solvent indicates that toluene or dichloromethane is a solvent of choice. In the cases with cyclic diols studied here the selectivity was not high regardless of reaction conditions. Diphenyltin ether derivatives were not suitable for monoacetylation probably because of the insufficient formation of cyclic tin ethers. The high selectivity particularly in the case of meso-dimethyl tartrate is postulated to be due to the dipole-dipole interaction between 2-keto group of the acid chloride and an ester group of the tartrate.

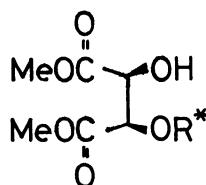
The following example is representative: A mixture of meso-dimethyl tartrate (93.5 mg, 0.525 mmol) and dibutyltin oxide (141.0 mg, 0.566 mmol) in 10 mL of toluene in the presence of molecular sieves 4A (1 g) was heated under reflux for 2 h. To the resulting mixture was added a solution of d-ketopinic acid chloride (141.7 mg, 0.706 mmol) in 2 mL of toluene at 0 °C. After stirring for 1 h at 0 °C, phosphate buffer (15 mL) was added at that temperature. The entire mixture was filtered through Celite and was extracted with chloroform (10 mL x 3). The combined extracts were dried over anhydrous sodium sulfate and concentrated to leave

an oil. Purification by silica gel column chromatography gave the monoacylation product (144.1 mg, 80%) as a colorless oil.⁹⁾

Table 1. Asymmetric Acylation of meso-1,2-Diols with 1.

Entry		Reaction conditions	Yield ^{a)} /%	d.e. ^{b)} /%
1		Pyridine, 0 °C-rt, overnight	39	0 ^{c)}
2		CH ₂ Cl ₂ 0 °C, 0.5 h	80	89 ^{d)}
3		CH ₂ Cl ₂ -78 °C, overnight	65	78
4		PhCH ₃ 0 °C, 1.0 h	80	90
5		THF 0 °C, 1.0 h	79	80
6		CH ₂ Cl ₂ 0 °C-rt, overnight	89	46
7		PhCH ₃ 0 °C, 1.0 h	69 ^{e)}	8
8		PhCH ₃ 0 °C, 1.0 h	79	7
9		PhCH ₃ 0 °C, 1.0 h	90	20

a) All compounds gave satisfactory spectral data. b) Determined by ¹⁹F measurement of its MTPA ester. c) The diastereomers were separated by silica gel column chromatography. d) The absolute configuration was determined to be as follows: by comparison with the optical rotation of 2-O-methyl-L-erythritol.¹⁰⁾ e) The reaction was carried out in the presence of 1 equiv. of DMAP.



In designing optically active 1,2-diol derivatives, the ability of the acylation reagent to differentiate two hydroxy groups is dependent both on the manipulation of diol functionality, e.g., cyclic tin alkoxides, and on designing the structure of the acid chloride. The present study shows that an easily accessible reagent, d-ketopinic acid, coupled with cyclic tin alkoxides opens a simple idea of creating optically active materials from symmetrically substituted molecules. This idea may be further applicable to the differentiation of hydroxy

groups in 1,3-diols.¹¹⁾

References

- 1) H. B. Goodbrand and J. B. Jones, J. Chem. Soc., Chem. Commun., 1977, 469; I. J. Jakovac, G. Ng, K. P. Lok, and J. B. Jones, *ibid.*, 1980, 515.
- 2) T. Tanaka, S. Kurozumi, T. Toru, S. Miura, M. Kobayashi, and S. Ishimoto, *Tetrahedron*, 32, 1713 (1976); S. Miura, S. Kurozumi, T. Toru, T. Tanaka, M. Kobayashi, S. Matsubara, and S. Ishimoto, *ibid.*, 32, 1893 (1976).
- 3) See for example, S. Terashima, M. Nara, and S. Yamada, *Tetrahedron Lett.*, 1978, 1487.
- 4) T. Mukaiyama, H. Yamashita, and M. Asami, *Chem. Lett.*, 1983, 385.
- 5) Ref 3; Y. Nagao, T. Inoue, E. Fujita, S. Terada, and M. Shiro, *J. Org. Chem.*, 48, 132 (1983) and earlier references cited therein.
- 6) H. Paulsen and O. Brauer, *Chem. Ber.*, 110, 331 (1977); R. B. Woodward, J. Gosteli, I. Ernst, R. J. Friary, G. Nestler, H. Raman, R. Sistrin, C. Suter, and J. K. Whitsell, *J. Am. Chem. Soc.*, 95, 6853 (1973).
- 7) T. Mukaiyama, J. Ichikawa, and M. Asami, *Chem. Lett.*, 1983, 293.
- 8) K. Saigo, A. Morikawa, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 49, 1656 (1976); *Chem. Lett.*, 1975, 145; T.-L. Su, R. S. Klein, and J. J. Fox, *J. Org. Chem.*, 47, 1506 (1982); A. Shanzer, *Tetrahedron Lett.*, 21, 221 (1980); S. Sakai, Y. Kiyohara, M. Ogura, and Y. Ishii, *J. Organometal. Chem.*, 72, 93 (1974); I. D. Jenkins, J. P. H. Verheyden, and J. G. Moffatt, *J. Am. Chem. Soc.*, 93, 4323 (1971).
- 9) The following spectra were obtained: IR (neat) 3500, 2970, 1760 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.07 (6H, s), 1.20-2.80 (7H, m), 3.67 (7H, s, including OH proton), 4.60 (1H, d, $J=2.5$ Hz), 5.48 (1H, d, $J=2.5$ Hz); ^{13}C NMR (CDCl_3) δ 210.5, 170.9, 168.2, 166.7, 73.8, 70.8, 67.7, 52.9, 52.6, 49.0, 44.2, 43.7, 26.6, 26.5, 20.8, 19.5.
- 10) The acylation product was transformed into 2-O-methyl-L-erythritol. The stereochemical course of this reaction is thought to be the same in all examples.
- 11) We have met with moderate success in acylation of 2-benzyloxy-1,3-propandiol. (about 70% d.e. was obtained.)

(Received October 1, 1983)