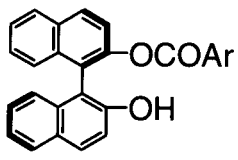
KINETIC RESOLUTION OF 5-HYDROXY-2,3,4,5-TETRAHYDRO-BENZAZEPINES WITH CHIRAL 1,1'-BI-2-NAPHTHOL DERIVED ACYLATING AGENTS

Jun Matsubara, Kenji Otsubo*, Yoshikazu Kawano, Kazuyoshi Kitano, Tadaaki Ohtani, Hiroshi Yamashita, Seiji Morita, and Minoru Uchida

Tokushima Research Institute, Otsuka Pharmaceutical Co., Ltd., Kagasuno 463-10, Kawauchi-cho, Tokushima 771-0192, Japan

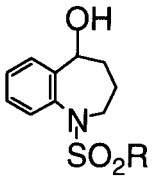
Abstract - (*R*)-2'-Hydroxy-1,1'-binaphthalene-2-yl benzoate (**1a**) was found to be an efficient asymmetric acylating agent for a secondary alcohol, 5-hydroxy-2,3,4,5-tetrahydro-1-(*p*-toluenesulfonyl)-1*H*-benzazepine (**2a**), which is a key intermediate for preparing a metabolite of the vasopressin V_2 receptor antagonist, OPC-31260 (**4**).

Kinetic resolution of racemic secondary alcohols through enzymatic acylation[1] is one of the most effective method for obtaining chiral nonracemic alcohols and has been applied to organic syntheses. Recently, several nonenzymatic versions of this reaction using chiral nucleophilic catalysts[2] and also stoichiometric amounts of chiral acylating agents[3] have been developed, however, many steps are required to prepare most of these reagents. As a result, we have been interested in exploring more convenient and practical reagents. The axially chiral esters[4] ((*R*)-**1**), derived from commercially available (*R*)-1,1'-bi-2-naphthol and appropriate carboxylic acids in one step, might be suitable acyl-donor candidates possessing a phenolic leaving group. Herein, we wish to report the results of the utility of chiral acylating agents such as (*R*)-**1**



(*R*)-**1**

	Ar
a	phenyl
b	2-tolyl
c	2-naphthyl
d	4-trifluoromethylphenyl
e	2-pyridyl
f	3-pyridyl
g	4-pyridyl



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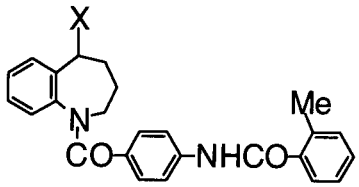
	R
a	4-tolyl
b	phenyl
c	4-methoxyphenyl
d	4-bromophenyl
e	methyl



3; X = OH
4; X = NMe_2

for the kinetic resolution of racemic secondary alcohols[5] (**2**) which have been used as key intermediates for preparing each enantiomer of a metabolite[6] (**3**) of the vasopressin V_2 receptor antagonist, OPC-31260[7] (**4**), and its analogs.

Initially, the reaction of the secondary alcohol, 5-hydroxy-2,3,4,5-tetrahydro-1-(*p*-toluenesulfonyl)-1*H*-benzazepine (**2a**), as a model substrate with chiral acylating agents ((*R*)-**1**) was examined to evaluate the effect of the ester structure of them (Table 1). Thus, **2a** was treated with 0.8 equiv. of (*R*)-**1** and 1.8 equiv. of MeMgBr (dichloromethane or THF, -78 °C), the entire reaction mixture was allowed to stand at room

Table 1. Enantioselective acylations of racemic secodary alcohol (**2a**) with chiral esters ((*R*)-**1a**-(*R*)-**1g**).

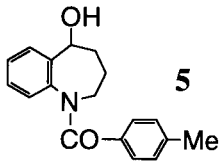
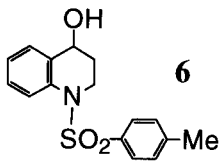
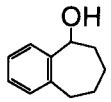
entry	chiral ester	solvent	conversion (%) [a]	optical purity of acylated product (%ee) [b]	*s* [c]
1	(*R*)-**1a**	CH_2Cl_2	22	76	9.0
2	(*R*)-**1a**	THF	26	65	5.9
3	(*R*)-**1b**	CH_2Cl_2	34	54	4.3
4	(*R*)-**1c**	CH_2Cl_2	3	69	5.6
5	(*R*)-**1c**	THF	31	68	7.1
6	(*R*)-**1d**	CH_2Cl_2	37	57	5.0
7	(*R*)-**1e**	CH_2Cl_2	40	0	1.0
8	(*R*)-**1f**	CH_2Cl_2	39	57	5.1
9	(*R*)-**1g**	CH_2Cl_2	43	37	2.8

a) Isolated yield. *b)* Determined by HPLC analysis (Chiralcel OJ). *c)* Calculated from the conversion and ee of the acylated product: Ref. 1a.

temperature with stirring for 48 hours. Acylation of the (*S*)-alcohol preferably proceeded in each instance except for entry 7. While the conversion yields were generally moderate, the reaction rate was accelerated in the case employing the acylating agents with an electron withdrawing function (entries 6-9). The use of the bulkier esters gave no improvement in enantioselectivity (entries 3 and 4). Performing the reaction in THF as the solvent gave comparable results (entries 2 and 5). Next, using the chiral acylating agent ((*R*)-**1a**) and the established conditions defined above, the kinetic resolution of the analogous secondary alcohols to **2a** was examined. These results are summarized in Table 2. The absolute configurations of the resulting esters of entries 1-5 were confirmed after hydrolysis into the starting alcohols by comparison of their HPLC retention time using a chiral column with those of (*S*)-**2b**~(*S*)-**2e** and (*S*)-**5** derived from the corresponding (*S*)-*N*-unsubstituted derivative.[6] It is likely that the enantioselectivity of the reaction is not affected by the electron donating ability of the phenylsulfonyl moiety of the substrates (entries 1-3). From a comparison of the selectivities during the acylation of various *N*-substituted 5-hydroxybenzazepines, it is apparent that the sulfonamide moiety exerts a significant effect on the selectivity (entries 4 and 5). On the other hand, the selectivity in each case of the 6-membered ring system and 7-membered carbocyclic system as the substrate

was low (entries 6 and 7). Although the detailed mechanism is not yet clear, the transition-state model as

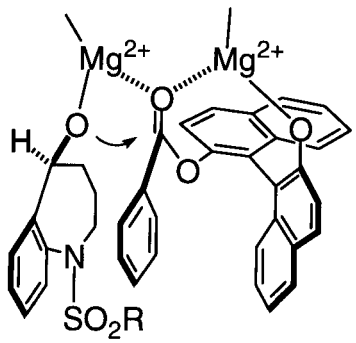
Table 2. Asymmetric acylations of secondary alcohols with (*R*)-**1a**.

entry	secondary alcohol	time (h)	conversion (%) [a]	optical purity of acylated product (%ee) [b]	*s*	config.
1	**2b**	48	24	75	8.8	*S*
2	**2c**	48	22	66	5.8	*S*
3	**2d**	48	28	66	6.3	*S*
4	**2e**	48	24	54	3.9	*S*
5	 **5**	96	7	28	1.8	*R*
6	 **6**	96	17	44	2.8	— [c]
7	 **7**	48	26	16	1.5	*S* [d]

a) Isolated yield. *b)* Determined by HPLC analysis on chiral column. *c)* Unknown. *d)* Ref. 8.

depicted in Figure 1 is assumed. The magnesium coordinates with the ester carbonyl and the oxyanion of the naphthyl ring to form a cyclic intermediate,[9] where the axially dissymmetric binaphthyl group dictates the orientation of the approach to the secondary hydroxyl group from the less hindered face of the reagent. Subsequently, it is likely that the additional π-π interaction between the benzoyl π-system of the reagent and the aromatic ring of the secondary alcohol would draw a distinction between the approaching each enantiomer. No reasonable explanation for the reversal of the stereoselectivity in the reaction starting from **5** as well as the low optical yields in the case of Table 2, entries 6 and 7, is available at the moment.

Figure 1. Possible mechanistic explanation for the observed enantioselectivity during asymmetric acylation with (*R*)-**1a**.



In conclusion, the present study demonstrates a simple and convenient preparation of optically active *N*-sulfonylated 5-hydroxy-2,3,4,5-tetrahydrobenzazepines with a high degree of ee. Since both enantiomers of the acylating agents (**1**) are easily accessible, current efforts are focused on additional studies of the utility of **1** for the kinetic resolution of other racemic compounds.

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3. a) D. A. Evans, J. C. Anderson, and M. K. Taylor, *Tetrahedron Lett.*, 1993, **34**, 5563; b) S. Yamada and T. Ohe, *ibid.*, 1996, **37**, 6777; c) E. Vedejs and X. Chen, *J. Am. Chem. Soc.*, 1996, **118**, 1809.
4. (*R*)-**1a** ($[\alpha]^{24}_{D}$ +51.0° (c 1.0, MeOH)) was prepared from (*R*)-1,1'-bi-2-naphthol (1.0 mmol) with benzoic acid (1.1 mmol) in the presence of WSC (1.5 mmol) and DMAP (0.1 mmol) in dichloromethane (25 ml) at rt for 15 h in 99 % yield. (*R*)-**1b**-**1g** were prepared from (*R*)-1,1'-bi-2-naphthol with the corresponding carboxylic acids as described for (*R*)-**1a**. (*R*)-**1b** (63 % yield, $[\alpha]^{24}_{D}$ +31.0° (c 1.0, MeOH)); (*R*)-**1c** (83 % yield, $[\alpha]^{24}_{D}$ +67.0° (c 1.0, MeOH)); (*R*)-**1d** (83 % yield, $[\alpha]^{24}_{D}$ +37.6° (c 1.0, MeOH)); (*R*)-**1e** (75 % yield, $[\alpha]^{24}_{D}$ +34.0° (c 0.1, MeOH)); (*R*)-**1f** (91 % yield, $[\alpha]^{24}_{D}$ +34.7° (c 1.0, MeOH)); (*R*)-**1g** (91 % yield, $[\alpha]^{24}_{D}$ +27.5° (c 1.0, MeOH)). For an alternative procedure of (*R*)-**1a** and (*R*)-**1c** see: S. M. Azad, S. M. W. Bennett, S. M. Brown, J. Green, E. Sinn, C. M. Topping, and S. Woodward, *J. Chem. Soc., Perkin Trans. 1*, 1997, 687.
5. Representative preparation of racemic alcohols: To a solution of 5-oxo-2,3,4,5-tetrahydro-1*H*-benzazepine (1.0 mmol) in pyridine (1.2 ml) was added *p*-toluenesulfonylchloride (1.1 mmol) at 0 ℃ and stirred for 4 h. The product was extracted with dichloromethane followed by dried over anhydrous $MgSO_4$. The solvent removed under reduced pressure to give a white solid. This was dissolved in tetrahydrofuran and treated by $NaBH_4$ (1.1 mmol) at 0 ℃. The resulting solution was stirred for 4 h. The usual work-up procedure left an oily residue, which was purified by column chromatography (hexane/ethyl acetate, 4:1) over silica gel to give **2a** as a white solid in 90 % yield. This procedure was used to prepare the other alcohols (**2b**-**2e**).
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