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1-Ethoxyvinyl 2-furoate, an efficient acyl donor for the lipase-catalyzed enantioselective desymmetrization of prochiral 2,2-disubstituted propane-1,3-diols and meso-1,2-diols†

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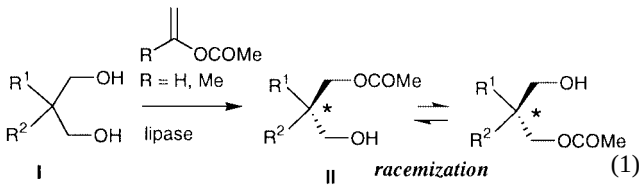
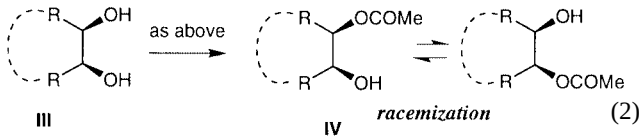
A novel acyl donor, 1-ethoxyvinyl 2-furoate, was found to produce the title reactions with high enantiotopic selectivity, high reactivity and stability of the products under various conditions.

The enzymatic transesterification of alcohols with acyl donors in organic solvents has become a widely applicable protocol to provide a variety of optically active compounds.[1] However, its application to the enantioselective desymmetrization of prochiral 2,2-disubstituted propane-1,3-diols (**I**) has rarely been reported, despite the promising potential of this approach as a powerful alternative to the well-investigated chemical syntheses of compounds bearing an optically active quaternary carbon center.[2] Recently, Fadel and Arzel reported the first practical enzymatic desymmetrization of **I** using well-known acyl donors, *i.e.* vinyl acetate and isopropenyl acetate. The reactions, however, suffered from low reactivity (it usually took several days or more to consume **I**), and racemization of the products **II** *via* acyl group migration was often observed [eqn. (1)].[3] Easy racemization of the products **IV** has also been an



(1)

annoying problem for the desymmetrization of the *meso*-1,2-diols (**III**) [eqn. (2)].[4,5] Therefore, to solve these problems



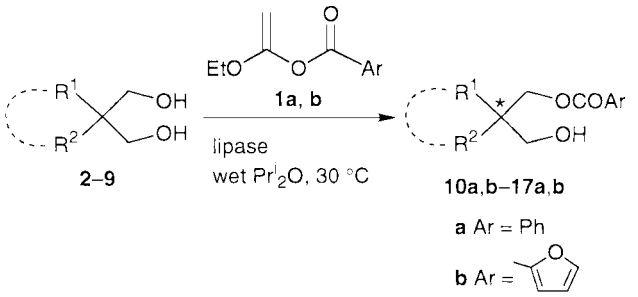
(2)

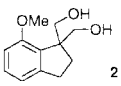
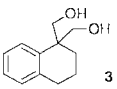
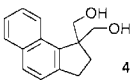
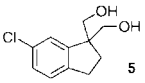
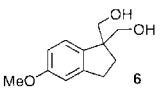
the development of an effective acyl donor which fulfills the criteria of high enantiotopic selectivity, high reactivity,[6] and production of stable products under various conditions is an urgent matter.

Very recently, we reported that 1-ethoxyvinyl acetate is similar-to-more reactive than vinyl acetate in the common enzymatic transesterifications[7] and we developed 1-ethoxyvinyl benzoate (**1a**) as an effective reagent for the desymmetrization of **I**.[8] However, this method is still unsatisfactory for sterically congested 1,3-diols in terms of the reaction time and the enantiotopic selectivity. The finding for **1a** encouraged us to find a more prominent ethoxyvinyl aromatic ester.[9] In this communication, we present 1-ethoxyvinyl 2-furoate (**1b**) as an effective reagent applicable to both diols **I** and **III**.

In the preliminary evaluation of 19 aroyl reagents **1** on the desymmetrization of the congested diol **2** under identical reaction conditions (the reaction was quenched when **2** was consumed), we observed that the 2-furoate (**1b**) was the best reagent in both reactivity and enantiotopic selectivity (Table 1, run 1). Some other reagents (**1**, Ar = *p*-tolyl, *p*-bromophenyl, 5-bromo-2-furyl, 2-thienyl) were fairly effective in producing the corresponding mono esters (75–86% ee, 46–60% isolated yields), and the rest were moderate (Ar = 2-naphthyl, *p*-

Table 1 Desymmetrization of various 1,3-diols using **1a**,**b**[a]



			Using **1b**			
Run	Diol	Lipase[b]		*t*/h	Ee (%)[c]	Yield (%)
1	 2	MY	**10b**	5	81	69
2		MY	**10b**	8[d]	90	38 (98)[e]
3	 3	MY	**11b**	5	61	84
4	 4	MY	**12b**	5	79	93
5		MY	**12b**	48[d]	91	78 (98)[e]
6	 5	MY	**13b**	5	85	71
7	 6	MY	**14b**	5	92	35
8	 7 R = Me	CRL	**15b**	5	>99	66
9	8 R = Et	CRL	**16b**	2	89	87
10	9 R = allyl	CRL	**17b**	2	82	72

[a] The reaction was run using **1b** (3.0 equiv. for runs 1–7 or 1.5 equiv. for runs 8–10) and was quenched when the diol was consumed, unless otherwise noted. Results of the similar reaction using **1a**[8]: **2**, 100 h, 71% ee, 82%; **3**, 170 h, 46% ee, 74%; **4**, 170 h, 73% ee, 53%; **5**, 100 h, 74% ee, 74%. [b] MY (from *Candida rugosa*, Meito), CRL (from *Candida rugosa*, Sigma Type VII) immobilized on Hyflo Super Cell. [c] Determined by HPLC using Daicel Chiralcel OD (hexane–PriOH). [d] Prolonged reaction. [e] In parentheses, the yield in consideration of the recovered diol is shown.

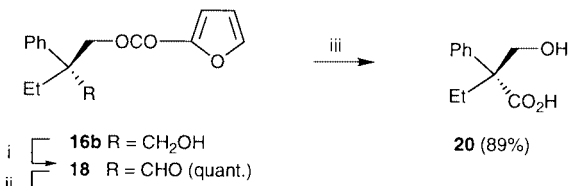
† Electronic supplementary information (ESI) available: preparation of 1-ethoxyvinyl 2-furoate. See http://www.rsc.org/suppdata/cc/b0/b003871g/

methoxyphenyl, *p*-nitrophenyl, 3-methyl-2-furyl, 3-furyl; 50–80% ee, 22–41% isolated yields) or poorly reactive (Ar = *o*-tolyl, 1-naphthyl, 1-anthryl, 1-methylpyrrol-2-yl, 4-pyridyl, 3-pyridyl, 3-quinolyl, benzofuran-2-yl, 1-methylindol-2-yl).[10] Therefore, the desymmetrization of various types of 2,2-disubstituted 1,3-diols (**3–9**) was performed using **1b** (Table 1). These results disclosed the eminent performance of **1b** as follows.

First, the reactions using **1b** were generally completed within 5 h. This is quite remarkable because all of the other aroyl donors required at least 1 day and generally more than 4 days to consume the diols. Second, the optical and the chemical yields of the products **10b**–**17b** were generally high and better than those obtained using the other aroyl reagents. Particularly, the product **15b** was obtained with > 99% ee. Third, the stability of the furoate **10b**–**17b** under acidic conditions was very much improved as noted from the following example. Thus, **16b** was inert to racemization in an acidic medium [0.1 equiv. of camphorsulfonic acid (4×10^{-4} M) in CH_2Cl_2] at room temperature after 1 d, whereas the same treatment of the corresponding benzoate resulted in gradual racemization ($t_{1/2}$ = 18 h).[8] All of these products were easily isolated by standard column chromatography on SiO_2, and the optical purity did not decrease during the chromatography.

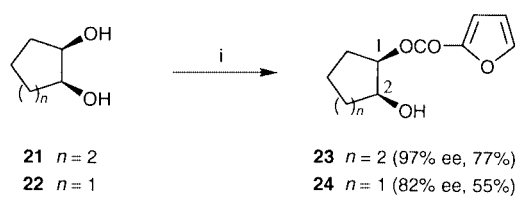
In addition, an improvement in the optical purity of the products was observed by prolonging the reaction time beyond the complete mono acylation of the substrates due to kinetic amplification (*e.g.* runs 2 and 5). Because the only side-products, *i.e.* the diesters, were quantitatively hydrolyzed to the starting diols, this method provides products with high optical purity without any loss in chemical yield.

The furoate moiety was preserved under oxidizing conditions. Neither a decrease in optical purity nor decomposition of the furan ring was observed after treatment of **16b** (88% ee) with the Dess–Martin periodinane, and the corresponding aldehyde **18** was quantitatively obtained with 87% ee as determined using a chiral HPLC column. Further treatment of **18** with $NaClO_2$ followed by methanolysis gave the known carboxylic acid (*R*)-**20** {$[\alpha]_D^{22}$ +13.4 (*c* 0.8, $CHCl_3$), lit.[11] $[\alpha]_D^{20}$ −16.5 (*c* 1.0, $CHCl_3$) for 97% ee of the (*S*)-form}. Therefore, the absolute configuration of **16b** was determined to be *S* (Scheme 1).



Scheme 1 *Reagents and conditions*: i, Dess–Martin periodinane, CH_2Cl_2, 0 °C → room temperature, 30 min; ii, $NaClO_2$, NaH_2PO_4, Bu^{t}OH–H_2O, room temperature, 10 min; iii, NaOMe, MeOH, 0 °C → room temperature, 1 h.

The reaction of the *meso*-1,2-diol **21** with **1b** using CHIRAZYME® L-9 (from *Mucor miehei*, Roche Diagnostics) provided the monofuroate (1*R*,2*S*)-**23** (97% ee, 77% yield) (Scheme 2). The optical purity did not change during purification by the standard column chromatography on SiO_2. Similarly, the desymmetrization of **22** gave (1*R*,2*S*)-**24** (82% ee, 55% yield).†[12,13]



Scheme 2 *Reagents and conditions*: i, **1b** (2.5 equiv.), CHIRAZYME® L-9, Bu^{t}OMe, 45 °C, 2 d.

In conclusion, the above-mentioned procedure using **1b** features the following advantages. (1) **1b** is readily prepared from commercially available ethoxyacetylene and 2-furoic acid in high yield and may be stored in a refrigerator for more than six months. (2) The products are obtained in high optical and chemical yields. If necessary, the only side-products, diesters, can be converted to the starting diols. (3) The products are sufficiently stable under various conditions and can serve as the key synthetic intermediates for optically active compounds having a quaternary carbon center at the benzylic position. Moreover, the high reactivity and high enantiotopic selectivity of **1b** are outstanding among a large number of acyl donors and offer an interesting topic from the mechanistic point of view.

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10 All these reagents were prepared according to the reported method (Y. Kita, H. Maeda, K. Omori, T. Okuno and Y. Tamura, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2999) by the addition of commercial carboxylic acids to ethoxyacetylene in ⩾80% yields in most cases.

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12 *Typical procedure for the enzymatic desymmetrization of the 1,3-diols using **1b***. Commercially available Pr$^i_2$O was distilled as usual, and 0.1% of water was added. After vigorous stirring at room temp. for 20 min, the mixture was allowed to settle. The upper layer (3.0 cm^3) was placed in a resealable test tube, to which were successively added **1b** (0.60 mmol), the 1,3-diol (0.20 mmol), and lipase MY (125 mg). The flask was sealed, and the reaction mixture was stirred at 30 °C during the time given in Table 1 and filtered through a Celite® pad. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography on SiO_2 (hexane–EtOAc) to give the monoester and the diester. *Optical rotations of the products*: **10b**, 90% ee, $[\alpha]_D^{28}$ −37.0 (*c* 0.99, $CHCl_3$); **11b**, 61% ee, $[\alpha]_D^{23}$ +10.5 (*c* 0.95, $CHCl_3$); **12b**, 91% ee, $[\alpha]_D^{28}$ −16.5 (*c* 0.68, $CHCl_3$); **13b**, 85% ee, $[\alpha]_D^{23}$ +18.6 (*c* 1.4, $CHCl_3$); **14b**, 92% ee, $[\alpha]_D^{23}$ +30.8 (*c* 0.96, $CHCl_3$); **15b**, > 99% ee, $[\alpha]_D^{20}$ −4.9 (*c* 0.86, $CHCl_3$); **16b**, 89 ee, $[\alpha]_D^{20}$ −10.3 (*c* 0.93, $CHCl_3$); **17b**, 82 ee, $[\alpha]_D^{20}$ −19.3 (*c* 0.54, $CHCl_3$); **23**, 97% ee, $[\alpha]_D^{19}$ −3.0 (*c* 0.7, $CHCl_3$); **24**, 82% ee, $[\alpha]_D^{19}$ −1.9 (*c* 1.1, $CHCl_3$).

13 The absolute configurations of the products, (*S*)-**15b**, (*S*)-**17b**, (1*R*,2*S*)-**23** and (1*R*,2*S*)-**24**, were deduced by comparison of specific rotations of these or their derivatives with those of authentic samples. The details will be presented in a forthcoming full paper. The absolute configuration of the others (**10b**–**14b**) have not been established yet.