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Lipase-catalyzed enantioselective desymmetrization of prochiral 3,3-bis(hydroxymethyl)oxindoles

Shuji Akai, Toshiaki Tsujino, Tadaatsu Naka, Kouichi Tanimoto and Yasuyuki Kita*

Graduate School of Pharmaceutical Sciences, Osaka University 1-6, Yamadaoka, Suita, Osaka 565-0871, Japan

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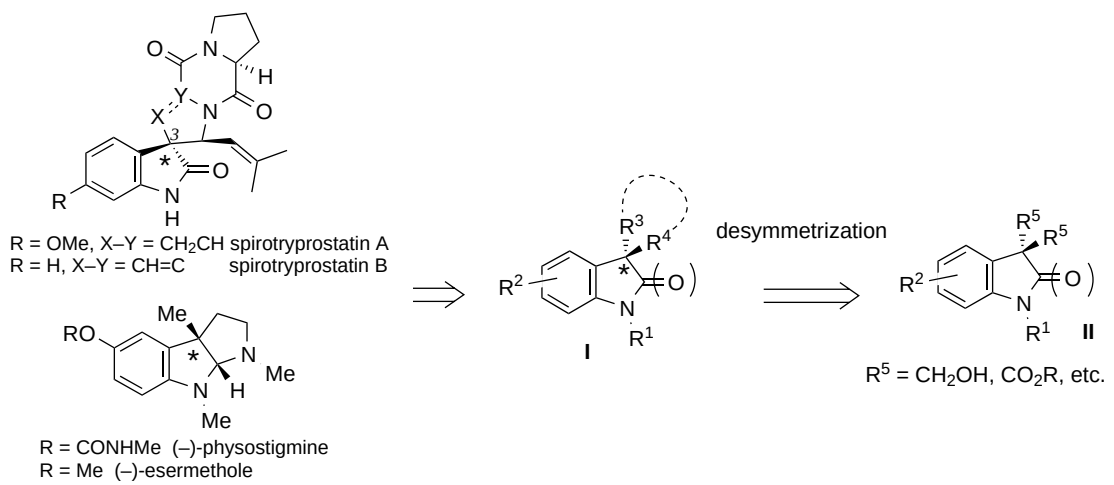
Abstract—Oxindoles **3b–d** (91–98% ee) having a chiral quaternary carbon center at the C-3 position were prepared from readily available oxindoles **5a–c** in 50–64% overall yields, in which an enantioselective desymmetrization of prochiral 1,3-diols **2b–d** using a *Candida rugosa* lipase (Meito OF) and 1-ethoxyvinyl 2-furoate **1** was employed as the key step.

Many biologically important indole alkaloids such as spirotryprostatins A and B, (−)-physostigmine, and (−)-esermethole, have a common structure; viz., indoline **I** with a chiral, nonracemic quaternary carbon center at the C-3 position.[1–3] Effective construction of the chiral quaternary carbon has been one of the pivotal issues for their asymmetric total synthesis, for which a variety of methodologies have been developed based on the enantio- or diastereoselective carbon–carbon bond formation at the C-3 position.[4] On the other hand, neither chemical nor biocatalytic enantioselective desymmetrization of the prochiral substrates **II** having two identical carbon substituents at the C-3 position has been reported. Especially an effective enzymatic desymmetrization of a diol **II** ($R^5 = CH_2OH$) must provide a useful alternative for the preparation of optically active **I** having the advantages of the easy, safe operation and the divergent derivatization to either enantiomer as have often been emphasized in many successful enzymatic reactions[5] (Scheme 1).

Very recently, the first attempt on the desymmetrization of **II** ($R^5 = CH_2OH$) was reported; however, the reaction did not proceed.[6] Alternatively, the authors have



Scheme 1.

Keywords: lipase-catalyzed desymmetrization; prochiral 1,3-diol; oxindole; quaternary carbon center.

* Corresponding author. Tel.: (+81) 6-6879-8225; fax: (+81) 6-6879-8229; e-mail: kita@phs.osaka-u.ac.jp

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achieved the desymmetrization by an enantioselective hydrolysis of a prochiral diester **II** ($R^5 = CH_2OCOEt$) to give the product with 95% ee in 38% yield after 5 days. We present herein a highly effective desymmetrization of the diols **2** using a prominent acyl donor, 1-ethoxyvinyl 2-furoate **1**.[7] The products **3** were obtained with 91–98% ee in 68–79% yields. The presented desymmetrization method is quite useful in terms of the short step and the good overall yield from readily available oxindoles **5a–c**.

The majority of the natural indole alkaloids are classified as either compounds having no substituent at the C-4 through C-7 positions of the indole skeleton or those having an oxygen substituent at the C-5 or C-6 position. Aiming at production of chiral synthons useful for total synthesis of these natural products, the substrates **2a–d** were subjected to the desymmetrization. However, we encountered a serious problem when we applied the reaction conditions [*Candida rugosa* lipase (Meito MY), wet iPr_2O] used in our previous work[7a] to **2a**. Thus, the very poor solubility of **2a** in iPr_2O became an obstacle to its fast esterification and resulted in enhancement of the further esterification of the soluble product **3a** to provide the diester **4a** exclusively. Although **2a** was soluble in polar solvents such as THF, dioxane and acetonitrile, the lipase MY-catalyzed reaction did not proceed. After investigation of the solvent system and the lipase, the use of a *Candida rugosa* lipase (Meito OF) in a mixed solvent (iPr_2O–THF) was found to be effective.[8] Some different ratios of these two solvents were examined in each case of **2a–d**, and the best results were summarized in Table 1. The ratio of iPr_2O to THF around 5:1 was usually the best choice, and the *N*-Boc derivatives **2b–d** were found to be suitable substrates (entries 2–4). In the case of **2c**, use of iPr_2O alone gave a better result than the mixed solvent providing **3c** (98% ee, 77% yield) within 3 h (entry 3). Optically pure **3d** (>99% ee) was obtained by single recrystallization of **3d** (91% ee) from benzene.[9]

The diols **2a–d** were readily prepared from commercial **5a** or the known oxindoles **5b**[4a] and **5c**[10] in good yields (Scheme 2).[11–13] The presented method is useful, because **3b** and **3c** (97–98% ee), for instance, were obtained in three steps in 50–53% overall yields from **5a** and **5b**, respectively.

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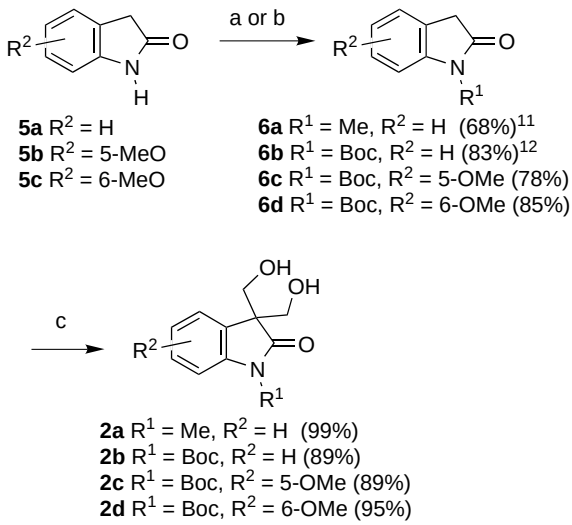
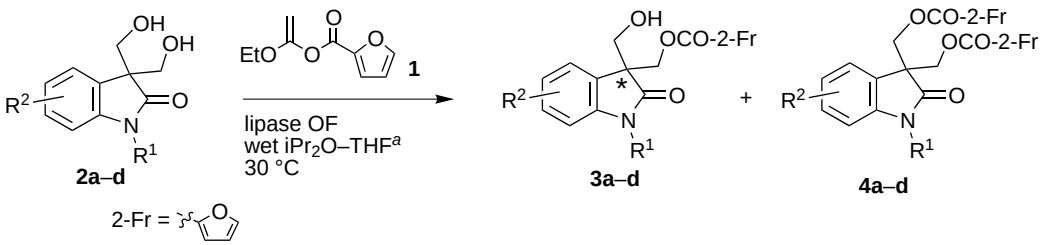


Scheme 2. (a) NaH, Me_2SO_4, xylene, reflux; (b) $(Boc)_2O$, $NaHCO_3$, THF, 45°C–reflux; (c) aq. 37% HCHO, Na_2CO_3, dioxane, room temp.–40°C. Boc = *t*-butoxycarbonyl.

Table 1. Lipase OF-catalyzed desymmetrization of **2** using **1**



Entry	2	R^1	R^2	Ratio of iPr_2O–THF	Reaction Time (h)[b]	3	Ee (%)[c]	Yield (%)[d]	Mp (°C)	$[\alpha]_D^{27}$ ($c = 1.0$, $CHCl_3$)
1	**2a**	Me	H	5:1	20	**3a**	79	60	Oil	+63.3
2	**2b**	Boc	H	5:1	20	**3b**	97	68	125–126	+56.3
3	**2c**	Boc	5-OMe	100:0	3	**3c**	98	77	140–140.5	+49.8
4	**2d**	Boc	6-OMe	5:1	19	**3d**	91	79	136–136.5	+69.6[e]

[a] Water (0.1%) was added to a mixture of iPr_2O and THF. [b] The reaction was quenched when **2** was consumed. [c] Determined by HPLC using Daicel CHIRALCEL OD (hexane–*i*PrOH). [d] Isolated by column chromatography on SiO_2. The rest of the product was the corresponding **4** in each case. [e] For **3d** (>99% ee) after recrystallization.

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8. The following lipases were examined in a 1:1 mixture of iPr$_2$O and THF at 30°C: The reaction using Meito OF gave **3a** (33% ee) after 7 days, whereas *Candida rugosa* lipases (Meito MY, Amano AY, and Novo L3), *Candida antarctica* lipase (Novo L2), *Mucor miehei* lipase (Novo L9), *Pseudomonas aeruginosa* lipase (Toyobo LIP), *Pseudomonas* sp. lipase (Amano AK), *Pseudomonas cepacia* lipases (Amano AH and PS), porcine pancreas (Amano), and pig liver esterase (Amano) were not reactive. Use of a 1:1 mixture of iPr$_2$O and either dioxane or acetonitrile resulted in very poor selectivity and reactivity.
9. *A typical procedure for the desymmetrization of* ***2***: In a resealable tube, a solution of **2b** (150 mg, 0.50 mmol) and **1** (280 mg, 1.50 mmol) in a 5:1:0.006 mixture of iPr$_2$O–THF–H$_2$O (100 mL) was placed, and lipase OF (275 mg) was added to it. The tube was sealed and the reaction mixture was stirred at 30°C for 20 h. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on SiO$_2$ (hexane–EtOAc, 3:1→2:1) to give **3b** (134 mg, 68%). The optical purity was determined to be 97% ee by HPLC using Daicel CHIRALCEL OD (hexane–iPrOH, 90:10; flow rate 1.0 mL/min; 10°C). All new compounds (**2a–d**, **3a–d**, and **6c–d**) were fully characterized by spectroscopic means and combustion analysis.
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