Pergamon

Tetrahedron Letters 42 (2001) 3331–3333

TETRAHEDRON LETTERS

A practical chemoenzymatic synthesis of a key intermediate of antifungal agents

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Received 1 February 2001; revised 2 March 2001; accepted 9 March 2001

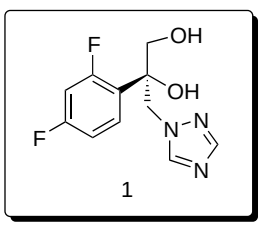
Abstract—A novel synthesis of an azole antifungal building block, the optically active diol, is described. The key step involves an enantioselective hydrolysis of a prochiral diester by a lipase.

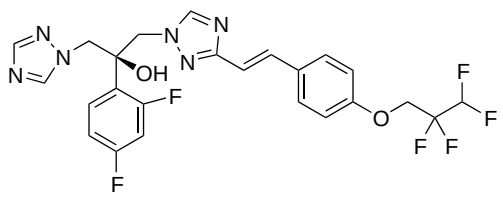
The search for systemic fungal infections continues to be important because of the growing population of immunocompromised patients.[1] There is, therefore, a need for more effective antifungal agents. Two new antifungal agents, ZD0870[2] and Sch45450,[3] show potent broad-spectrum antifungal activities compared to other clinically used antifungal agents. Because these compounds contain chiral centers comprised of a difluorobenzene and a triazole group, an optically active diol (**1**) is a useful common intermediate for their synthesis.[3–5]

Four synthetic methods have been reported to give **1**. Optically active epoxy alcohol (**2**) as a precursor of **1** was prepared via optical resolution by hydrolysis using a porcine pancreatic lipase (PPL)[3] or via Sharpless–Katuski epoxidation for the corresponding allylic alcohol.[4] Optically active **1** was prepared via Sharpless asymmetric dihydroxylation for the corresponding allylic alcohol[3] or via optical resolution by esterification using PPL.[6] The theoretical maximum yield of optical resolution is 50%. Some special reagents are required to prepare the substrates and the catalyst for the asymmetric reaction and thus, application of the reaction for large scale preparation is difficult.

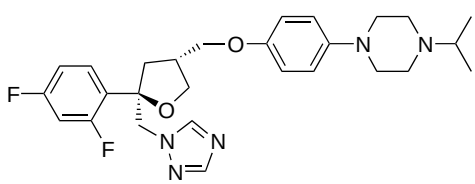
With a view to plant-scale preparation of the optically active diol (**1**) using cheap and readily available materials, we studied a novel approach for enantioselective preparation of **1** by using an enzymatic stereoselective hydrolysis of prochiral diesters (**4a**–**e**) as a key reaction (Scheme 1). The prochiral substrate was prepared by condensing a difluorobenzene group and a C3 unit using an organometallic technique. Optically active diols (**5a**–**e**) were smoothly converted to **1** without racemization.

The substrates of stereoselective hydrolysis, **4a**–**e**, were prepared as follows. A smooth halogen–metal exchange was realized by the treatment of 1-bromo-2,4-difluorobenzene with *n*-butyl lithium in ethyl ether. The resulting aryllithium was trapped by dichloroacetone (**6**) to give the adduct (**3**) in good yield. The adduct was a mixture of 2,4-difluoro and 2,6-difluorobenzene derivatives when THF was used as a solvent. Also, **3** was prepared by treating the Grignard reagent of the





ZD0870



Sch45450

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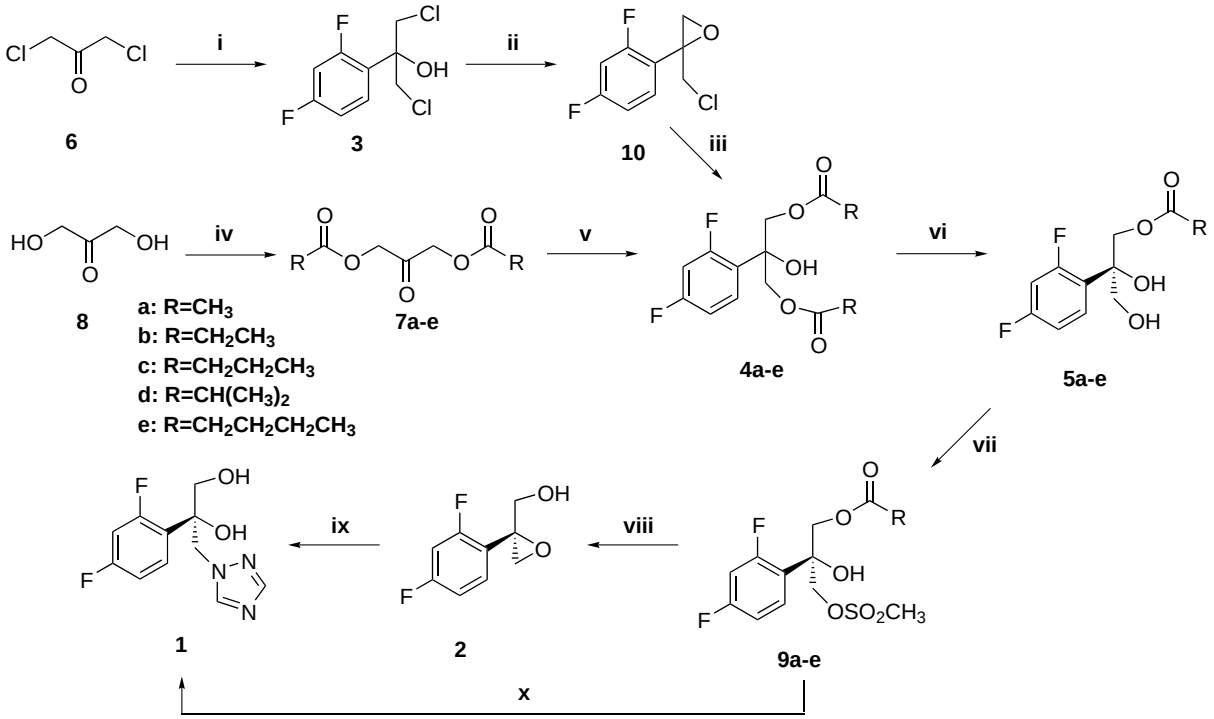

Scheme 1. Reagents and conditions: (i) *n*-butyl lithium, 1-bromo-2,4-difluorobromobenzene, −78°C, **6** (64% from **6**); (ii) 20% KOH, toluene, rt (50%); (iii) AcOK, AcOH, reflux (87%, to **4a**); (iv) **8**, pyridine, DMAP, acid anhydride, rt (84%); (v) magnesium, 1-bromo-2,4-difluorobromobenzene, −10°C, **4** (86% from **7**); (vi) lipase D, acetate buffer, methylcyclohexane, 15°C (90%); (vii) MsCl, pyridine, AcOEt, 30°C (94%); (viii) 20% KOH, toluene, rt (88%); (ix) 1,2,4-triazole, K_2CO_3, THF, reflux (40%); (x) 1,2,4-triazole, Na_2CO_3, MeOH, reflux (83%).

Table 1. Enzymatic hydrolysis of diesters **4a**–**e** by lipase D[a]

Substrate	Product (%)[b]			
	Diester	Monoester		Triol
4	**4**	**5**	% ee	
a	27	71	79	2
b	28	69	91	3
c	14	81	97	5
d	26	73	98	1
e	11	71	97	18

[a] Each reaction mixture, comprising 10 mg of substrate, 10 mg of enzyme in 1 ml of 50 mM acetate buffer (pH 5.0) and 1 ml of hexane, was stirred at 30°C for 18 h. The mixture was extracted with ethyl acetate and the organic layer was analyzed with HPLC.

[b] The yield and the enantiomeric excess of **5a**–**e** were determined by HPLC analysis using a Chiralpak AD (4.6×250 mm) column (Daicel Chemicals, Tokyo, Japan) with a hexane/ethanol = 9/1 (vol/vol) as a mobile phase, flow rate; 1 ml/min, ambient temperature, and detected at 254 nm.

aryl bromide in THF. Dichoroalcohol (**3**) was converted to diester (**4a**) in two steps. Alternatively, **4a**–**e** were prepared by treating the Grignard reagent with the corresponding diesters (**7a**–**e**) which were easily prepared from **8**, in about 85% yield.[7]

The key hydrolysis was examined by commercially available enzymes. Among the lipases tested, lipase D from *Rhizopus delemer*[8] gave the desired (*R*)-monoester (**5a**). The stereoselective hydrolysis of a series of diesters (**4a**–**e**) by lipase D is summarized in Table 1. Probably 1,3-rearrangement of the acetyl group caused the low enantioselectivity for diacetate (**4a**). By selecting a proper diester, the monoester was prepared in good yield and stereoselectivity as high as 97–98% ee.[9]

The following procedures for the target compound (**1**) were performed without loss of optical activity. Optically active (*R*)-monoester (**5d**) was mesylated and subsequently converted to epoxide (**2**) in good yield. 1,2,4-Triazole and **2** were reacted to give **1** in 40% yield. One-pot reaction to give **1** from **9d** was possible and a higher yield was obtained than in the two-step reaction.[10] Finally, optically pure (*S*)-**1** was obtained by recrystallization.[11]

In summary, we have achieved the enantiomeric preparation of the key intermediate of chiral azole antifungal agents by a chemoenzymatic process in only five steps from inexpensive and readily available starting materials. The chiral monoesters prepared by lipase hydrolysis may be applicable to the synthesis of a variety of chiral pharmaceuticals.

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7. Typical procedure: a solution of 1-bromo-2,4-difluorobenzene (96.5 g, 0.5 mol) in THF (450 ml) was added to magnesium (12.8 g, 0.53 mol) at 18°C over 3 hours. After stirring at 5°C for 1 hour, it was slowly poured into a solution of **7d** (103 g, 0.45 mol) in THF (150 ml) below 15°C over 1 hour. After stirring at 5°C for 1 hour, the reaction was stopped by the addition of a 1.2 M HCl solution (500 ml) below 5°C and the mixture was extracted with ethyl acetate (500 ml×2). The organic layer was washed with brine and concentrated to give **4d** as an oil. The crude **4d** was distilled to give a pure **4d** (bp: 114–119°C/0.5–0.6 mmHg). ^{1}H NMR ($CDCl_3$) δ (ppm) 7.73–7.65 (1H, m), 6.95–6.88 (1H, t), 6.85–6.77 (1H, m), 4.54–4.45 (4H, q), 3.90 (1H, s), 2.55–2.47 (2H, m), 1.10–1.03 (12H, m). IR (film) ν_{max} (cm^{-1}) 3468, 1720, 1618, 1500, 968, 850. Calcd for $C_{17}H_{22}F_2O_5$: C, 59.3; H, 6.4. Found: C, 59.1; H, 6.5.
8. Lipase D was purchased from Amano Enzyme Inc., Nagoya, Japan.
9. Preparative-scale procedure: diester (**4d**) (93.5 g, 0.27 mol), lipase D (0.94 g), water (842 ml) and methylcyclohexane (94 ml) were stirred at 15°C for 18 hours. The pH of the reaction mixture was kept at 5.5 with 10 M NaOH. The resulting mixture was extracted with ethyl acetate (200 ml×2) and the organic layer was washed with saturated sodium hydrogencarbonate and brine. The organic layer was dried over anhydrous sodium carbonate and concentrated to give **5d** (66.6 g) with 90% yield and 96.7% ee. $[\alpha]_D^{25} = -7.04$ ($c = 1.00$, MeOH). ^{1}H NMR ($CDCl_3$) δ (ppm) 7.69–7.66 (1H, m), 6.91–6.87 (1H, m), 6.78–6.77 (1H, m), 4.54–4.45 (3H, m), 3.97–3.78 (2H, dd), 2.49–2.42 (1H, m), 1.01–0.99 (6H, m). IR (film) ν_{max} (cm^{-1}) 3400, 1738, 1600, 1500, 968, 850. Calcd for $C_{13}H_{16}F_2O_4$: C, 56.9; H, 5.9. Found: C, 56.8; H, 5.9.
10. Procedure: 1,2,4-triazole (5.8 g, 0.085 mol) and sodium carbonate (13.4 g, 0.127 mol) were added to a solution of **9d** (14.89 g, 0.042 mol) in methanol (300 ml) and the suspension was refluxed for 15 hours under an atmosphere of argon. After cooling and filtration, methanol was removed from the filtrate in vacuo. Water (50 ml) was added to the residue and extracted with ethyl acetate (100 ml). After evaporation, the resulting crystalline solid was recrystallized from acetonitrile to give optically pure **1** (8.22 g) with 60% yield. $[\alpha]_D^{25} = -72.9$ ($c = 1$, MeOH), the reported value for (*S*)-isomer was $[\alpha]_D^{25} = -60$ ($c = 1$, THF).[3]
11. The enantiomeric excess of **1** was determined by HPLC as described in Table 1. Detection was 210 nm.