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The Synthesis of Optically Active Pyridyl Alcohols from the Corresponding Racemates by *Catharanthus Roseus* Cell Cultures

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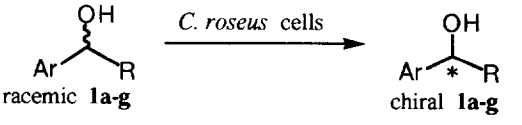
Abstract A novel method for producing optically active pyridyl alcohols **1a-f** from the corresponding racemates was developed. When racemic 3-pyridylphenylmethanol **1b** is reacted with *Catharanthus roseus* cell cultures, (-)-**1b** is obtained in 96% yield with 100 %ee.

α-Pyridyl alcohol derivatives are intermediates of some pharmacological interest,[1-3] and (*S*)-(+)-α-phenyl-2-pyridylmethanol **1c** itself has analgetic and anticonvulsant activities.[4] Kessar *et al.* have synthesized **1c** via metallation of BF_3-pyridine complex, but optically active alcohol **1c** was not obtained from chiral boron compounds.[5] Inoue *et al.* have synthesized (*S*)-**1c** by asymmetric reduction with a chiral polymethylene-bridged bis(NADH) model compound.[6] Recently, we have synthesized optically active α-phenylpyridyl-methanols **1a-c** by reduction of the corresponding ketone **2a-c** with baker's yeast[7] or cell cultures of *Nicotiana tabacum*[8]. The biological methodologies to obtain chiral alcohols are mainly i) the reduction of the corresponding ketones by baker's yeast or other microorganisms, ii) the lipase catalyzed resolution of the racemic alcohols via esterification or hydrolysis iii) microbial oxidation of corresponding racemic alcohols (optical resolution or deracemization of racemates). However, there are few reports for kinetic resolution via oxidation[9-11] or deracemization of racemates[12,13]. In this work, we would like to report a novel method for producing optically active pyridyl alcohols **1a-f** from the corresponding racemates by *C. roseus* cell cultures.



racemic **1a-g** chiral **1a-g**

a ; Ar = 4 - pyridyl ; R = Phenyl
b ; Ar = 3 - pyridyl ; R = Phenyl
c ; Ar = 2 - pyridyl ; R = Phenyl
d ; Ar = 4 - pyridyl ; R = methyl
e ; Ar = 3 - pyridyl ; R = methyl
f ; Ar = 2 - pyridyl ; R = methyl
g ; Ar = phenyl ; R = methyl

When racemic alcohols **1a-f** were subjected to immobilized *C. roseus* cells (ICRC) in B5 medium, 92-

100% of chiral alcohols **1a-f** were obtained as shown in Table I. Only 0-8% of the substrate were oxidized to the corresponding ketone **2a-f**. To our suprise, 93% of racemic **1b** and 100% of **1d** were converted to (-)-**1b** (100% ee) and (*R*)-**1d** (87%ee), respectively.

Table 1. Optically active pyridyl alcohols **1a-f** production from the corresponding racemates **1a-f** by *C. roseus* cells

Substrate	Incubation days	Yield of alcohol (%)	[Ee, %]	(Config.)
1a	17	92	23	(-)
1b	17	93	100	(-)
1c	17	92	19	(*R*)
1d	9	100	87	(*R*)
1e	12	98	11	(*S*)
1f	10	98	0	

Figure 1 illustrates the time course of enantiomeric excesses in the production of (-)-**1b** and (*R*)-**1d** from the corresponding racemic alcohols **1b** and **1d**. The enantiomeric excesses increased with incubation times, reaching maximum values of 100%ee (**1b**, 17days) and 87%ee (**1d**, 9days). The chemical yields were consistent from beginning to end [(-)-**1b** : 92-96%, (*R*)-**1d** : 100%].

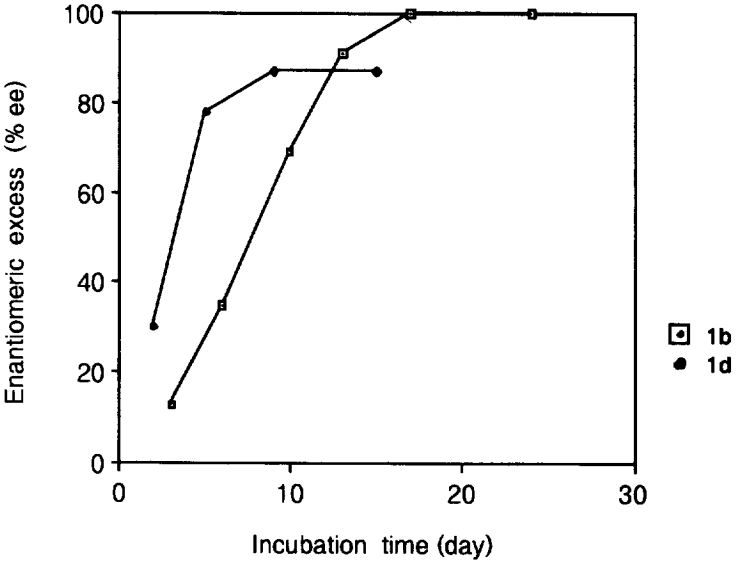
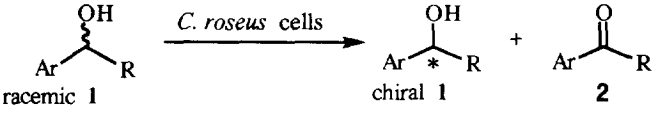


Fig. 1. The time course of enantiomeric excess in the production of (-)-**1b** and (*R*)-**1d** from the corresponding racemate, **1b** and **1d**.

When incubation were continued further, the oxidation of the alcohols **1a-c** occured to afford the corresponding ketones **2a-c** leaving unreacted the (-)-enantiomer of the alcohol **1a-c** as shown in Table II. In

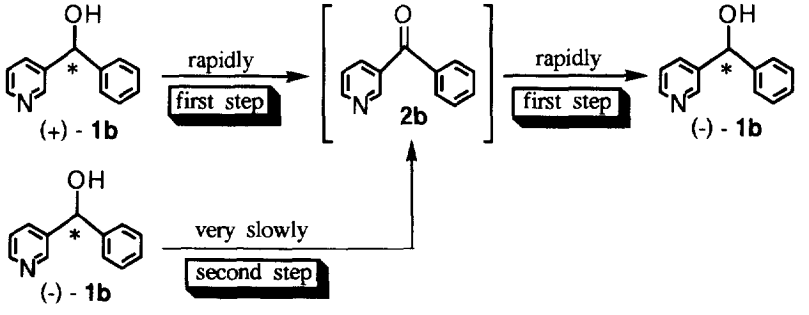
the case of **1c**, the enantiomeric excesses of **1c** were increased with increasing of chemical yield of **2c**, reaching a maximum of 92%ee. In the case of **1g**, the oxidation occured from the beginning of incubation to afford ketone **2g**.

Table. II. Kinetic resolution of racemic alcohols **1a, 1b, 1c, 1g** with *C. roseus* cells via oxidation



Substrate	Time (days)	1 : 2 (ratio %)	% ee of 1	Config.
1a	38	92 : 8	34	(-)
	45	82 : 18	38	(-)
	52	70 : 30	43	(-)
1b	32	80 : 20	100	(-)
	38	67 : 33	100	(-)
	45	61 : 39	100	(-)
	52	55 : 45	100	(-)
1c	24	85 : 15	39	(*R*)
	32	66 : 34	57	(*R*)
	38	52 : 48	73	(*R*)
	45	43 : 57	85	(*R*)
	60	41 : 59	92	(*R*)
1g	2	57 : 43	4	(*S*)
	12	25 : 75	37	(*S*)

Although the mechanism for the deracemization and the successive oxidation are not clear at present, we expect the following mechanism in the case of **1b**. At first, (+)-**1b** is converted to the corresponding ketone, **2b**, which is reduced to (-)-**1b**. As shown in Fig 1, the enantiomeric excesses of **1b** increased with incubation times, but the chemical yields of **1b** were consistently 92-96% from beginning to end. These facts show the oxidation of (+)-**1b** and the successive reduction of the ketone, **2b**, proceeds relatively fast. On the contrary, (-)-**1b** is registant to the oxidation. As shown in Table II, this oxidation requires for a long time. The chemical yield of **2b** began to increase after 32 days.



For a typical experiment, we used suspension-cultured cells which had originally been isolated from *C. roseus*. ICRC were prepared according to the following procedure. Freely suspended *C. roseus* {20g of cells and B5 medium 80 ml} in the stationary phase after 10 days of incubation was mixed with 5% sodium alginate solution (80ml). The resultant mixture was dropped into a 0.6% $CaCl_2$ solution (1000ml) and rinsed with water to give ICRC. ICRC prepared from 7g of cell and 30ml of broth was added to freshly prepared B5 medium (80ml per flask) and was shaken on a rotary shaker (110rpm) in the dark for 2 days at 25°C. A substrate (35mg) was added to the ICRC-B5 medium and the mixture was shaken on a rotary shaker (110 rpm) at 25°C. The incubation mixture was filtered. ICRC was washed with CH_2Cl_2 and the filtrates were combined. The combined mixture was extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$ and subjected to column chromatography. The optical yields of **1a-g** were measured by HPLC using Chiralcel OB (**1a,b,d,f,g**) and Chiralcel OJ (**1c,e**). Absolute configuration of **1c**, **1d**, **1e** and **1g** were determined by comparison of the sign of the specific rotation with reported value [**1c**[14], **1d**[15], **1e**[15] and **1g**[16]].

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