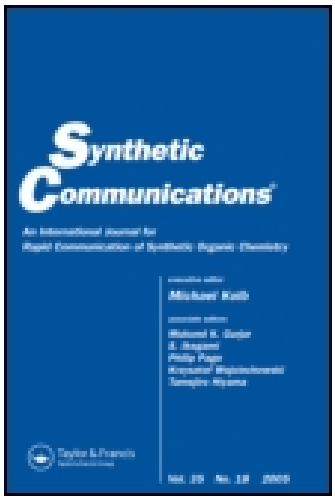

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AN EFFICIENT METHOD FOR THE RESOLUTION OF KEY INTERMEDIATE TO D-BIOTIN VIA CHIRAL AMINES

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AN EFFICIENT METHOD FOR THE RESOLUTION OF KEY INTERMEDIATE TO D-BIOTIN VIA CHIRAL AMINES

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ABSTRACT

An efficient method for the resolution of key intermediate to D-biotin in high chemical and optical yields is reported.

D-biotin, referred to as vitamin H or coenzyme R, was widely distributed in animals and plants. More of its functions had been recognized and these findings had led to a timeless challenge for total synthesis of it.[1]

Enantiomerically pure alcohol 4-hydroxythieno[3,4-d]imidazole-2-one (+)-**2** was an important intermediate in independent routes to D-biotin.[2,3] In the formal report,[4,5] it was prepared by resolution via the corresponding diastereomeric ethers, but the process was not very good for the material 4-chloroethieno[3,4-d]imidazole-2-one (±)-**1** was not stable when exposed to the air or light, the most efficient chiral auxiliary, (*S*)-(+)-mandelic acid, was more expensive and the final yield was not high when repeated.

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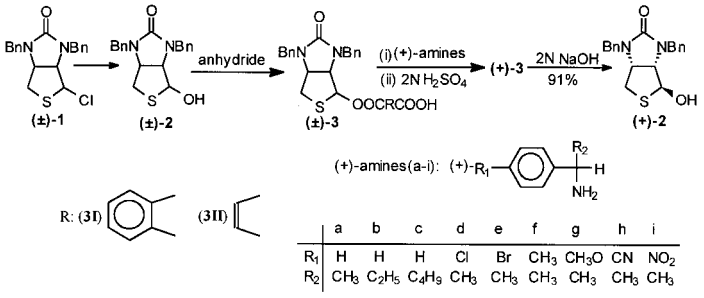
In this paper, for the preparation of enantiomerically pure alcohol (+)-**2**, required the following steps (see scheme): (a) reaction of anhydride with racemic alcohol (±)-**2** in pyridine leading to the corresponding racemic ester (±)-**3**, (b) resolution of ester (±)-**3** by salt formation with (+)-amines in methanol, ethanol or 2-propanol and recrystallization from the same solvent, (c) recovery of the enantiomerically pure ester (+)-**3** as a dark red oil from the salt by ethyl acetate–2 N H_2SO_4 extraction, and (d) hydrolysis of the ester (+)-**3** in base solution to afford alcohol (+)-**2**. Chiral GC analysis of ester (+)-**3**, previously methylated by diazomethane, indicated enantiomeric excesses higher than 90%, the results were summarized in the table.

In conclusion, comparing to the literature method, the procedure had following advantages: high chemical and optical yields, cheap chiral



Scheme.

Table. Results for the Preparation of Ester (+)-**3**

			Yield[a] (%)		e.e. (%)	
Entry	Amine	Solvent	3**I**[b]	3**II**[c]	3**I**[b]	3**II**[c]
1	a	methanol	38.2	36.7	94	96
2	b	methanol	41.6	38.6	98	91
3	c	ethanol	40.3	40.9	96	93
4	d	2-propanol	44.2	42.3	99	98
5	e	ethanol	43.5	39.7	98	93
6	f	methanol	45.0	41.4	99	95
7	g	ethanol	42.8	38.3	97	91
8	h	2-propanol	33.0	35.2	90	92
9	i	2-propanol	34.2	30.1	91	94

[a]Refers to isolated yield according to alcohol (±)-**2** as the starting material. [b]Phthalic anhydride as the reacting material. [c]Maleic anhydride as the reacting material.

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auxiliaries, and convenient work-up, especially, the amines could be recovered in good yields. Hence its commercial advantage was obvious.

EXPERIMENTAL

All melting points were uncorrected. IR spectra were recorded on a Nexus FI-IR 470 spectrophotometer. ^{1}H NMR spectra were measured on Bruker MSL-300 instrument using TMS as internal standard. Elemental analyses were performed on a Carlo Erba 1106-type analyzer. Optical rotations were taken on a WZZ-15 automatic polarimeter. GC analyses were performed on β-DEXTM 120 (GC-14BPTF). The amines were prepared according to the known procedure,[6–9] other reagents were purchased from Aldrich Chemical Co. All reactions were carried out under nitrogen and stirred magnetically.

General Procedure for the Preparation of Ester (+)-3

A mixture of racemic alcohol (±)-**2** (1.7 g, 5.0 mmol), anhydride (5.0 mmol), pyridine (1 ml) and toluene (20 ml) was stirred at 100°C for 2 h. After cooling, ethyl acetate (50 ml) and 2 N H_2SO_4 (2 ml) were added. The organic phase was separated, washed with saturated brine, dried with Na_2SO_4, and concentrated to give the racemic ester (±)-**3** as dark red oil, the oil was diluted in methanol, ethanol or 2-propanol (20 ml) and treated at 65°C with (+)-amines (5 mmol). After slow cooling to about 5°C, the precipitate was recovered by filtration and rinsed with the same cold alcohol. The resulting solid was dried, refluxed with methanol, ethanol or 2-propanol (20 ml) for 1.5 h, cooled at 0°C, and filtered to give the pure salt between ester (+)-**3** and (+)-amines, the salt was suspended in ethyl acetate. After removing (+)-amines by acidic washing with H_2SO_4, the solvent was evaporated under vacuum to give the enantiomerically pure ester (+)-**3** as dark red oil. To the water phase, 2 N NaOH was added, extracted with ethyl acetate to afford (+)-amines in good yields (>30% of the starting amines).

Select Analytical Data for Ester (+)-3I (As Dark Red Oil)

IR (KBr): 3065, 2927, 1756, 1700, 1468, 1436 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 2.74 (d, 1H, $J = 10.4$ Hz), 3.06 (2d, 1H, $J = 4.1$, 10.4 Hz), 3.68 (d, 1H, $J = 7.6$ Hz), 4.20 (2d, 1H, $J = 4.7$, 7.9 Hz), 4.22, 4.36, 4.60, 4.78 (4d, 4H, $J = 14.3$ Hz), 5.10 (s, 1H), 7.01–7.68 (m, 14H); MS (EI),

m/z: 488 (M^+): Elem. anal., found% (calcd for $C_{27}H_{24}N_2O_5S$): C 66.2 (66.4), H, 4.90 (4.92), N 5.78 (5.74); $[\alpha]_D^{30} + 130$ (c, 0.2, $CHCl_3$).

Select Analytical Data for Ester (+)-3II (As Dark Red Oil)

IR (KBr): 3274, 2967, 2689, 2496, 1702, 1658, 1584, 1452 cm^{-1}; ^1H NMR (300 Hz, $CDCl_3$), δ, ppm: 2.65 (d, 1H, $J = 10.8$ Hz), 3.01 (2d, 1H, $J = 4.1$, 10.4 Hz), 3.48 (d, 1H, $J = 8.6$ Hz), 3.86 (dd, 2H, $J = 7.8$ Hz), 4.25 (2d, 1H, $J = 5.6$, 7.4 Hz), 4.20, 4.44, 4.68, 4.82 (4d, 4H, $J = 13.3$ Hz), 5.16 (s, 1H), 7.31–7.73 (m, 10H); MS (EI), *m/z*: 438 (M^+); Elem. anal., found % (calcd for $C_{23}H_{22}N_2O_5S$): C 62.64 (63.01), H 4.99 (5.02), N 6.38 (6.39); $[\alpha]_D^{30} + 180$ (c, 0.5, $CHCl_3$).

General Procedure for the Preparation of Alcohol (+)-2

The ester **(+)-3** (1.0 mmol) was refluxed with 2 N NaOH (10 ml) in 1,4-dioxane (20 ml) for 4 h. The solvent was evaporated, water was added, and the product was extracted into chloroform (5 × 10 ml). The organic extract was washed with saturated brine, dried over Na_2SO_4. The solvent was evaporated, and the solid was recrystallized from dichloromethane and hexane to give the enantiomerically pure alcohol **(+)-2** (0.30 g, 91%): m.p. 164–166°C, $[\alpha]_D^{30} + 75.8$ (c, 0.6, $CHCl_3$). (literature[4]: m.p. 164–165°C, $[\alpha]_D^{22} + 76.0$ (c, 0.76, $CHCl_3$)).

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