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Optical resolution of (±)-1-furo[2,3-*c*]pyridin-5-yl-ethanol using extraction technique: formal total synthesis of PNU-142721, HIV-1 reverse transcriptase inhibitor

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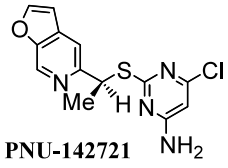
Abstract—A formal total synthesis of PNU-142721 was effectively carried out to prepare the chiral non-racemic synthon 1-furo[2,3-*c*]pyridin-5-yl-ethanol. It was easily obtained utilizing the optical resolution of the corresponding diastereomeric derivatives derived from 3β-acetoxyetienic acid by using the extraction technique.

(−)-6-Chloro-2-[(1-furo[2,3-*c*]pyridin-5-yl-ethyl)thio]-4-pyrimidinamine (PNU-142721)[1] (Fig. 1) has been announced as a HIV-1 specific non-nucleoside reverse transcriptase inhibitor and evaluated for its inhibitory activity against various reverse transcriptases and a panel of mutant RT enzymes etc.[2]

The reported synthetic route of the optically pure PNU-142721 involves an optical resolution of (±)-1-furo[2,3-*c*]pyridin-5-yl-ethanol (**1a**)[3] or (±)-(7-chloro-furo[2,3-*c*]pyridin-5-yl)-ethanol (**1b**)[4] using enzymatic acylation[5] or asymmetric reduction of the corresponding pyridylethanol[6] as a key step to introduce the chirality to the molecule. Although these synthetic routes are excellent, the kinetic resolution of **1a** has somewhat disadvantages such as the use of the expensive acyl-reagent and a long reaction time (9 days).[3] We wish to report here that the convenient optical resolution technique of (±)-**1a** via extremely simple extraction of the corresponding diastereomeric derivatives.

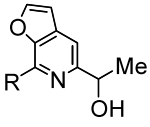


PNU-142721

Figure 1.

Recently, we disclosed that a mixture of the diastereomers derived from (±)-*trans*-2-(2-pyridyl)-cyclohexanols and 3β-acetoxyetienic acid[7] could be effectively separated by the extraction technique with achiral organic media and aqueous acid.[8] This phenomenon was responsive to the difference in the pK_a value between the diastereomers, which would be based on an intramolecular CH/π interaction[9] in only one isomer.[10] By using this technique, we assumed that the concise synthesis of the optically pure biologically active compounds containing the pyridylalcohol moiety can be effectively achieved and planned to prepare both enantiomerically pure 1-furo[2,3-*c*]pyridin-5-yl-ethanols [(*S*)-**1a** and (*R*)-**1a**], chiral synthons for PNU-142721 as the candidate (Fig. 2).

First, we examined whether this technique can be applied to the diastereomers derived from more simple (±)-1-(2-pyridyl)ethanols (**1c**–**1e**)[11] and 3β-acetoxyetienic acid or not (Scheme 1). As a result, the diastereomers could be separated with moderate distribution ability in each case if there is no electron-with-



R = H: **1a**
Cl: **1b**

Figure 2.

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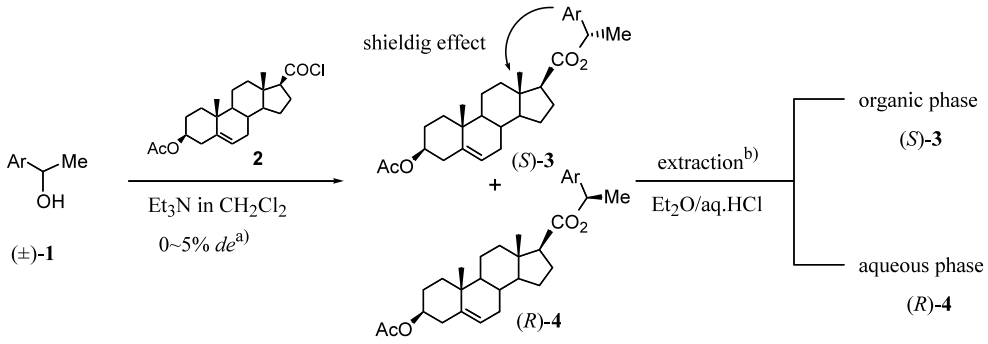


Scheme 1. Separation of the diastereomers by extraction. a) The kinetic resolution was observed in acylation process; b) diastereomeric mixture (**3a** and **4a**)/Et_2O/aq. HCl = 300 mg/20 ml/50 ml.

Table 1. Separation of the diastereomers (**3** and **4**) by extraction

Entry	Ar	aq. HCl (%)	Organic phase		Aqueous phase	
			(*S*)-**3** (%)	*de* (%)	(*R*)-**4** (%)	*de* (%)
1	2-Pyridyl: **1c**	3.0	99	3	0	–
2		5.0	97	2	1	43
3		6.0	80	15	17	70
4		7.0	63	34	33	67
5	2-(6′-Methy)pyridyl: **1d**	5.0	60	54	30	71
6		6.0	63	48	30	85
7		7.0	38	61	58	31
8	2-(6′-Bromo)pyridyl: **1e**	7.0	97	6	0	–
9		15.0	95	2	0	–
10		30.0	99	3	0	–
11	2-Furo[2,3-*c*]pyridin-5-yl: **1a**	3.0	77	34	18	87
12		5.0	39	91	57	49
13		7.0	37	95	54	53

The *de* were determined by ^{1}H NMR (270 MHz).

drawing group on the pyridine ring (Table 1, entries 3–7). Thus, we found that this separation technique could be applicable not only to the reported cyclic-type *trans*-(±)-2-(2-pyridyl)cyclohexanols[8] but also to the acyclic-type pyridylalcohols such as **1c** and **1d**. The absolute configuration of the diastereomer, which mainly existed in an organic phase, was (*S*)-isomer[12] and the shielding effect of the C18–CH_3 on steroid ring was also observed in ^{1}H NMR. The chemical shifts of protons on C18–CH_3 in **3** [δ (ppm) in $CDCl_3$] were **3c**: 0.59; **3d**: 0.60; **3e**: 0.60, respectively. On the other hand, the chemical shifts of protons in **4** on C18–CH_3 were δ 0.73 in all cases.[13] These results have strongly suggested that our target diastereomers[14] derived from (±)-furo[2,3-*c*]pyridin-5-yl-ethanol, which has no electron-withdrawing group on the pyridine ring, can also be separated in a similar manner. In fact, we separated the corresponding diastereomers with higher efficiency than we expected (Table 1, entries 11–13).

The favorable concentration of aq. HCl was ca. 5.0∼7.0 wt% (Table 1, entries 12 and 13). The MO calculation[15] of **3a** suggested the presence of an intramolecular CH/π interaction as well. The shortest distance between the CH moiety and the π moiety was 2.82 Å, which was shorter than the sum of each van der Waals radius (Fig. 3).[16] We assume that the spread π plane of furopyridyl ring acted as a factor of stabilizing the interaction.

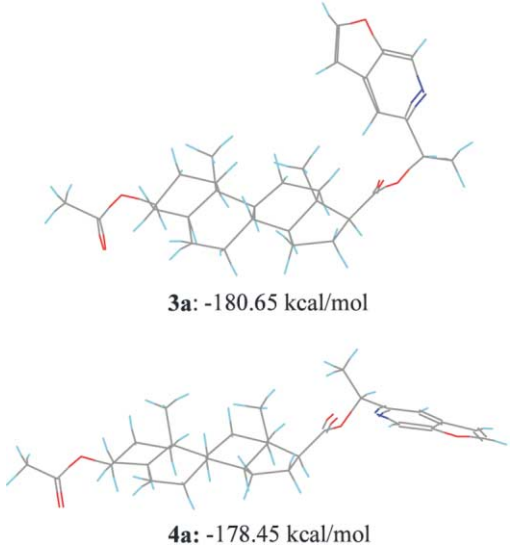


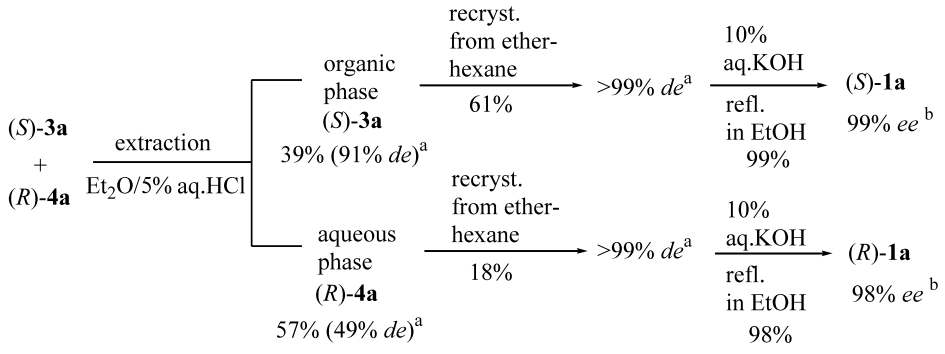
Figure 3.

With this technique, we could make each diastereomeric excess of the diastereomers from the organic phase and the aqueous phase diastereomerically pure corresponding ones by one recrystallization from diethyl ether/*n*-hexane (Scheme 2). As described at the beginning, the synthetic route of PNU-142721 from both enantiomers of chiral non-racemic furo[2,3-*c*]-pyridin-5-yl-ethanol [(*S*)-**1a** and (*R*)-**1a**] has already been known.[3]

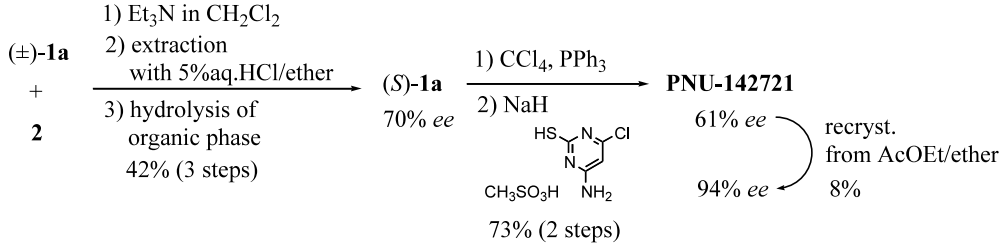
Furthermore, we tried a more practical synthetic route of PNU-142721 without recrystallization at the diastereomer-resolution stage on the basis of the information that the enantiomeric excess of PNU-142721 could be raised with recrystallization.[3] The route is shown in Scheme 3. In this case, the distribution ability of the crude diastereomers was somewhat different from the former case. This is probably responsive to the change of the acidity of aq. HCl due to the presence of the excess acyl reagent 3β-acetoxyetienic acid, which remained in the reaction mixtures. The obtained (*S*)-furo[2,3-*c*]pyridin-5-yl-ethanol (70% *ee*) from the organic phase after alkaline hydrolysis was derived to the PNU-142721 (61% *ee*) according to the reported method.[3] Recrystallizing once of the crude product from ethylacetate/ether gave the PNU-142721 with 94% *ee* (Scheme 3). This synthetic route has a benefit that can be dispensed with troublesome purifications such as recrystallization or column chromatography all through the derivation from (±)-**1a** to the crude PNU-142721.

Some remarkable features of this optical resolution technique by extraction† are summarized below: (1) The absolute configurations of the resolved pyridylethanols can be briefly determined because of the fact that the (*S*)-isomer showing the shielding effect exists in the organic phase upon extraction. (2) The almost enantiomerically pure pyridylethanols can be conveniently prepared by recrystallizing once, since the extraction process can make the diastereomeric excess high enough. (3) It does not require a long reaction time to obtain the chiral alcohols. (4) When the target compound is a conglomerate such as PNU-142721, we can achieve a concise synthesis by recrystallization of the final product without recrystallization of the diastereomeric isomer at the extraction stage.

We believe that this technique will play an important role in a large-scale synthesis of similar optically active pyridylethanols with high practical value.



Scheme 2. Optical resolution of (±)-**1a** by extraction. (a) The *de* was determined by ^{1}H NMR; (b) the *ee* was determined by HPLC (CHIRALCEL OD®).



Scheme 3. An alternative route for PNU-142721.

† Typical procedure for a separation of the diastereomers: To a solution of **3a** and **4a** (300 mg, 1:1 of diastereomeric mixture) in ether (50 ml) was added aq. 5.0 wt% HCl (20 ml, diluted 36% HCl with dist. H_2O). After vigorous shaking, the ethereal solution was separated from the aqueous layer, dried over Na_2CO_3 and filtered. The filtrate was concentrated in vacuo to give **3a** in 39% yield with 91% *de*. The aqueous layer was made alkaline with $NaHCO_3$ (pH 8) to precipitate white solid. The precipitation was collected by suction filtration and dried to give **4a** in 57% yield with 49% *de*.

Acknowledgements

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13. The ^{1}H NMR spectra in diethylether-D10 also showed the remarkable high field shift of C18–CH_3 in **3a** than **4a** (δ 0.53 versus δ 0.76).
14. Data for **3a** (>99% *de*): colorless solid; mp 126.5–127.0°C; IR (KBr): 1727 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ 8.85 (s, 1H), 7.76 (d, J=2.2 Hz, 1H), 7.63 (s, 1H), 6.80 (d, J=2.2 Hz, 1H), 6.04 (q, J=6.5 Hz, 1H), 5.37 (m, 1H), 4.61 (m, 1H), 2.46–1.08 (m, 20H), 2.03 (s, 3H), 1.64 (d, J=6.8 Hz, 3H), 0.98 (s, 3H), 0.54 (s, 3H). Data for **4a** (72% *de*): colorless solid; mp 124.0–125.0°C; IR (KBr): 1727 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ 8.84 (s, 1H), 7.75 (d, J=2.2 Hz, 1H), 7.62 (s, 1H), 6.80 (d, J=2.2 Hz, 1H), 6.06 (q, J=6.5 Hz, 1H), 5.38 (m, 1H), 4.61 (m, 1H), 2.49–1.11 (m, 20H), 2.04 (s, 3H), 1.65 (d, J=6.5 Hz, 3H), 1.03 (s, 3H), 0.73 (s, 3H). Mixture of diastereomers **3a** and **4a**: HRMS calcd for $C_{31}H_{39}NO_5$: 505.2828 [M^+]; found: 505.2821.
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