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LETTERS

Determination of stereochemistry and separation of diastereomeric derivatives of *trans*-2-pyridylcyclohexanols by extraction

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Abstract—The example of the determination of the stereochemistry and separation of diastereomeric derivatives of *trans*-2-pyridylcyclohexanols by extraction is shown here. The facile separation of the corresponding diastereomers is based on a difference in the basicity of the diastereomers. © 2001 Elsevier Science Ltd. All rights reserved.

Optical resolution using chiral auxiliary has widely been used as a method to obtain various optically active molecules,[1] although it involves somewhat troublesome procedures such as recrystallization,[2] column chromatography,[3] etc. We report here the first example of the prediction of the stereochemistry and a novel optical resolution method of diastereomeric derivatives of *trans*-2-pyridylcyclohexanols by extraction with organic solvent after treatment with aqueous acid. Previously,[4] we reported a simple prediction method of the absolute configuration of *trans*-2-arylcyclohexanols using intramolecular aryl-induced ^{1}H NMR shifts probably caused by intramolecular CH/π interaction.[5,6] During the course of the study, we unexpectedly observed that diastereomers (**3** and **4**) derived from 3β-acetoxy-Δ^5-etiocholenic acid chloride[7] and (±)-*trans*-2-pyridylcyclohexanols **1**,[8] could be separated by extraction with organic solvent after treatment with aqueous acid (Table 1). That is, partitioning between organic solvent such as diethyl ether and aq. HCl effectively made the separation of the diastereomers.

The ability of distribution was influenced by the concentration of the aqueous acid used and the optimum concentration of aq. HCl was based on the mixtures of the obtained diastereomers. Thus, in the case of **3a** and **4a**, a 93% *de* of **4a** was obtained in 25% yield by concentration of the 3.0 wt.% aq. HCl and a 41% *de* of **3a** in 73% yields from the organic layer (Table 1, entry 2). Further extraction of the organic phase (41% *de*) with 7.0 wt.% aq. HCl improved the *de* of **3a** to 80% (70% yield).

The chemical shift of β-methyl proton on 18-position (C18-CH_3)[9] of the major isomer in organic phase showed an unusual high field shift in ^{1}H NMR (for example, **3a**: δ 0.115) (see Fig. 1).[10]

This phenomenon strongly suggested the presence of the affinity between C18-CH_3 and the π moiety, which had already been reported in the previous paper,[4] even in the case of nitrogen containing heteroaromatics. This is confirmed by the X-ray crystallographic analysis[11] of pure (1*S*,2*R*)-isomer **3b**, which is obtained by recrystallization of the corresponding diastereomers. C18-CH_3 was found to be in close proximity to the π-face of the pyridyl group, which was consistent with the remarkably high field shift of the C18-CH_3 in ^{1}H NMR (Fig. 2).

On the other hand, the (1*R*,2*S*)-isomer **4b**, which did not show the effective aryl-induced ^{1}H NMR shift was preferentially obtained from the aqueous acid phase. The chemical shift of the C18-CH_3 of the major isomer from the aqueous acid phase showed a lower value of δ 0.463 (see Fig. 1).

It is quite interesting to note that the isomer showing aryl-induced ^{1}H NMR mostly existed in the organic phase on extraction. The p*K*a value of pyridinium chloride of the corresponding diastereomers is quite

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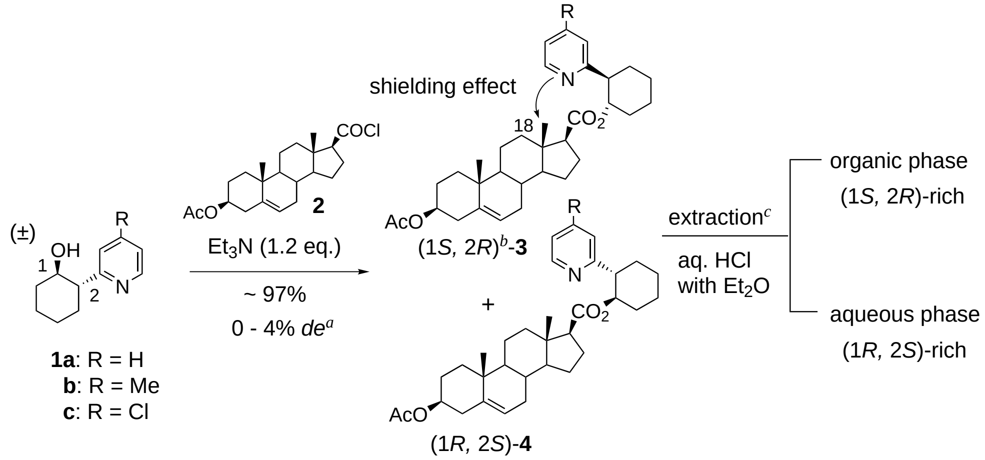
Table 1. The simple separation of diastereomers (**3** and **4**) by extraction technique



Entry	R	Concentration of HCl aq. (wt.%)	Organic phase		Aqueous phase	
			Yield (%)	*De* (%)[d]	Yield (%)	*De* (%)[d]
1	H (**3a**+**4a**)[e]	2.5	88	15 (**3a**)	9	95 (**4a**)
2		3.0	73	41 (**3a**)	25	93 (**4a**)
3		5.0	49	74 (**3a**)	50	57 (**4a**)
4	Me (**3b**+**4b**)[f]	1.0	81	19 (**3b**)	16	88 (**4b**)
5		2.0	56	67 (**3b**)	44	82 (**4b**)
6		3.0	33	73 (**3b**)	63	37 (**4b**)
7	Cl (**3c**+**4c**)[g]	7.0	97	0	0	–
8		10.0	82	11 (**3c**)	12	55 (**4c**)
9		15.0	42	82 (**3c**)	56	54 (**4c**)

[a] The kinetic resolution of **1** was observed in the acylation process when the reaction stopped under the situation remaining unreacted **1**.

[b] The indication of '(1*S*,2*R*)' is depicted by the numbering position of 2-pyridylcyclohexanols before acylation.

[c] The ratio used was as follows: a mixture of diastereomers **3a** and **4a**/aq. HCl/diethyl ether = 0.3 g/20 ml/50 ml.

[d] The *de* value was determined by ^{1}H NMR (300 MHz).

[e] Chemical shift of protons on C18-Me; **3a**: 0.115, **4a**: 0.463.

[f] Chemical shift of protons on C18-Me; **3b**: 0.098, **4b**: 0.464.

[g] Chemical shift of protons on C18-Me; **3c**: 0.128, **4c**: 0.479.

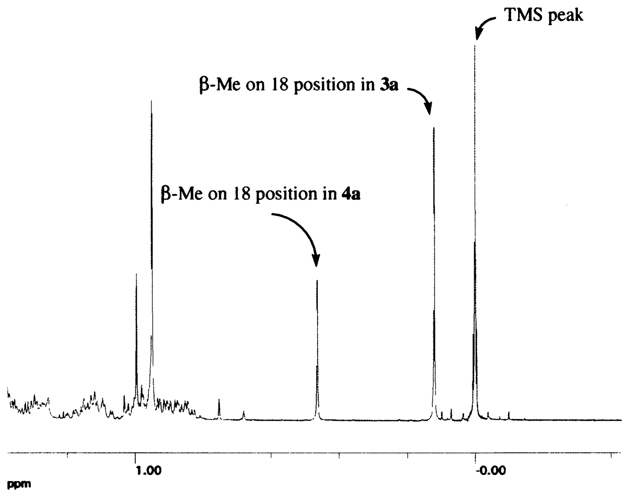


Figure 1. Partial ^{1}H NMR spectrum (600 MHz) of a mixture of diastereomeric isomers **3a** and **4a** (41% *de*) obtained from the organic phase in CDCl$_3$ at 25°C.

different (p*K*a of **3a**: 3.81 and p*K*a of **4a**: 4.15, respectively),[12] and the isomer showing the aryl-induced shift has lower p*K*a value. Although we cannot give a clear account of this phenomenon, it can be assumed that the intramolecular CH/π interaction would reduce the electron density of the nitrogen atom on pyridine ring and lead to a decrease in basicity of compounds **3a**[13] (Fig.

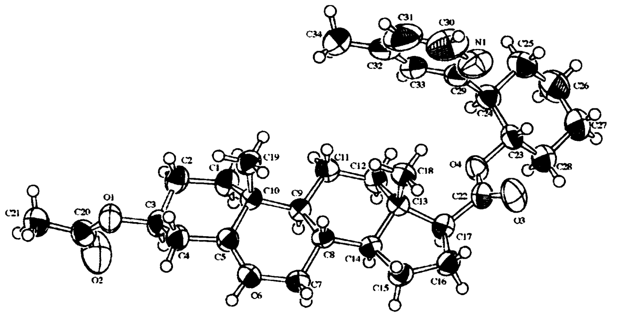


Figure 2. ORTEP drawing of **3b**.

3). An alternative possibility is a significant difference of the steric bulkiness around the nitrogen atom in the diastereomers.

Finally, deprotection of the steroid moiety gave the optically active pyridyl alcohols in good yields (Table 2).

Here we have shown a novel optical resolution technique by simple extraction using achiral-organic solvent and acid solution. The facile separation of the corresponding diastereomers takes advantage of the distribution technique based on a difference in p*K*a values of the diastereomers. We find that the (1*S*,2*R*)-isomer **3** of the diastereomers showing aryl-induced ^{1}H NMR shift has a lower p*K*a value and proves to exist in the organic phase on extraction. These results thus provide a simple optical resolution method of *trans*-2-pyridylcyclohexanols. Attempts to extend the method to other substrates are in progress.

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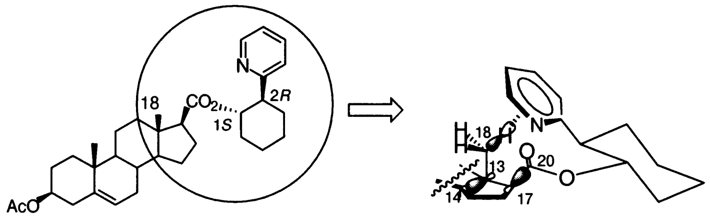
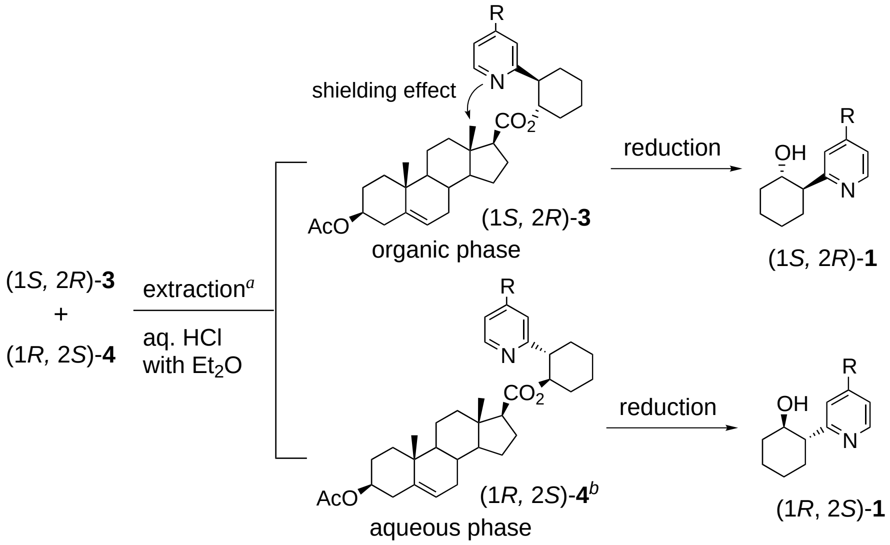


(1*S*, 2*R*)-**3a**

Figure 3. Speculation: charge-transfer interaction via ideal overlap of orbitals.

Table 2. Deprotection of the diastereomers (**3** or **4**) to pyridylalcohols



Diastereomer	*De* of starting diastereomer **3** or **4** (%)[c]	Method of reduction[d]	Yield (%)	*Ee* of product (%)[e]
R = H (**3a**)	81	A	68	77 (1*S*,2*R*)
R = H (**4a**)	93	A	90	93 (1*R*,2*S*)
R = Me (**3b**)	67	A	83	64 (1*S*,2*R*)
R = Me (**4b**)	82	A	90	80 (1*R*,2*S*)
R = Cl (**3c**)	82	B	70	79 (1*S*,2*R*)
R = Cl (**4c**)	54	B	89	50 (1*R*,2*S*)

[a] The ratio used was as follows : a mixture of diastereomers/aq. HCl/diethyl ether = 0.3 g/20 ml/50 ml.

[b] These products were obtained by neutralizing the aqueous phase with $NaHCO_3$ (pH 8).

[c] The *de* value was determined by ^{1}H NMR (300 MHz).

[d] Method A: $LiAlH_4$ (10 equiv.), THF, rt, 2.0 h; method B: DIBAL-H (5 equiv.), THF, −78°C, 2.0 h.

[e] The *ee* value was determined by HPLC (CHIRALCEL OD®, hexane:*i*PrOH = 95:5).

ture of **3b** and Mr. Shinji Hirose, Sumika Chemical Analysis service, for the p*K*a value measurements of HCl salt of **3a** and **4a**.

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