Organic Process Research & Development **2003**, *7*, 583–584

Technical Notes

Effective Nonenzymatic Kinetic Resolution of (±)-*trans*-2-Arylcyclohexanols Using 3β-Acetoxyetienic Acid, DCC, and DMAP

Masato Matsugi,† Yuri Hagimoto,‡ Masatomo Nojima,† and Yasuyuki Kita*,‡

Department of Materials Chemistry and Frontier Research Center, Graduate School of Engineering, Osaka University, 2-1, Yamada-oka, Suita, Osaka 565-0871, Japan and Graduate School of Pharmaceutical Sciences, Osaka University, 1-6, Yamada-oka, Suita, Osaka 565-0871, Japan

Abstract:

(1*R*,2*S*)-*trans*-2-Arylcyclohexanols of high enantiomerically purity were obtained by the simple stirring of the corresponding (±)-arylcyclohexanols with 3β-acetoxyetienic acid, DCC, and DMAP at room temperature.

The kinetic resolution of racemic alcohols is one of the most useful methods to obtain various chiral nonracemic alcohols. So far, a number of enzymatic methods,[1] nonenzymatic methods with stoichiometric chiral acyl transfer agents,[2] and catalytic systems based on a chiral nonenzymatic catalyst with an achiral acyl donor have been reported,[3] focusing on the achievement for the high levels of efficiency, the *s* value.[4] In these circumstances, it is likely that an efficient method using an easily available chiral auxiliary under mild conditions must also be a practical method. Here, we show an effective nonenzymatic kinetic resolution of racemic *trans*-2-arylcyclohexanols with easily available[5] 3β-acetoxyetienic acid as the chiral acyl donor with dicyclohexylcarbodiimide (DCC) and 4-*N*,*N*-(dimethylamino)-pyridine (DMAP).[6] This methodology is available to determine the stereochemistry of the resolved alcohols as well.

We have already reported the novel determination method of the absolute configuration of various useful 2-arylcyclohexanols[7] utilizing an intramolecular CH/π interaction[8] by way of the modification to the corresponding diastereomeric ester, chiral etienic acid ester.[9] In these cases, the interaction was only observed in the (1*S*,2*R*)-isomer (**3**),[10] and kinetic resolution with a slight excess of (1*S*,2*R*)-isomer (~7% *de*) has been observed in the esterification using acid chloride (**2**) (Figure 1). Thus, we assumed that an effective nonenzymatic kinetic resolution of (±)-*trans*-2-arylcyclohexanols along with the determination of the absolute configurations would be achievable by optimizing the reaction condition with simple esterification.

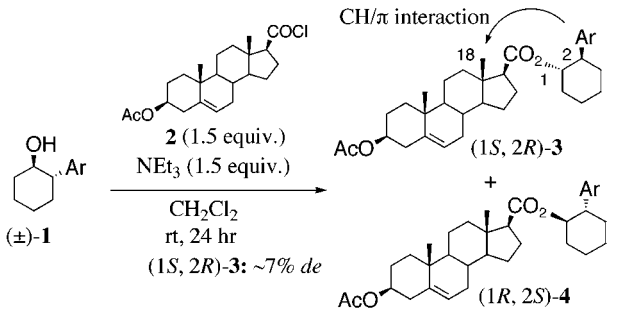


Figure 1. **Esterification of (±)-1 with chiral acid chloride 2.**

Among the examinations implemented by using various esterifications, we found that DCC esterification gave the best result of resolution efficiency. Although the methods using simple chiral carboxylic acids by way of DCC esterification are already known to give good results, however, their selectivities are not necessarily high (*s* value 2.1−7.0).[11,12] Our examinations found that the DCC esterification with chiral acid (**5**)[13] under the condition depicted

* Author for correspondence. Fax: +81-6-6879-8229. E-mail: kita@phs.osaka-u.ac.jp.

† Department of Materials Chemistry and Frontier Research Center, Graduate School of Engineering, Osaka University.

‡ Graduate School of Pharmaceutical Sciences, Osaka University.

(1) For reviews of the enzyme-catalyzed acyl transfer, see: Faber, K.; Riva, S. *Synthesis* **1992**, 895. Carrea, G.; Riva, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2226.

(2) For reviews of the nonenzymatic kinetic resolution, see: Spivey, A. C.; Maddaford, A.; Redgrave, A. J. *Organic Prep. Proced. Int.* **2000**, *32*, 331. Somfai, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2731.

(3) Recent examples and references therein: Clapham, B.; Cho, C. W.; Janda, K. D. *J. Org. Chem.* **2001**, *66*, 868. Sekar, G.; Nishiyama, H. *J. Am. Chem. Soc.* **2001**, *123*, 3603. Spivey, A. C.; Fekner, T.; Spey, S. E. *J. Org. Chem.* **2000**, *65*, 3154.

(4) The selectivity factor (*s*) was determined using the following equation: $s = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where C = conversion. Kagan, H. B.; Fiaud, J. C. In *Topics in Stereochemistry*; Eliel, E. L., Ed.; Wiley & Sons: New York, 1988; Vol. 18, p 249.

(5) The 3β-Acetoxyetienic acid can be easily prepared from the commercially available pregnenolone acetate (Aldrich; 59.7USD/25 g): Staunton, J.; Eisenbraun, E. J. *Org. Synth.* **1962**, *42*, 4. Djerassi, C.; Hart, P. A.; Warawa, E. J. *J. Am. Chem. Soc.* **1964**, *86*, 78.

(6) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.

(7) The utilities of 2-arylcyclohexanols as chiral auxiliaries in synthesis: Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953.

(8) For reviews of the CH/π interaction, see: Nishio, M.; Umezawa, Y.; Hirota, M.; Takeuchi, Y. *Tetrahedron* **1995**, *51*, 8665. Nishio, M.; Umezawa, Y.; Hirota, M. *The CH/π Interaction*; Wiley-VCH: New York, 1998.

(9) Matsugi, M.; Itoh, K.; Nojima, M.; Hagimoto, Y.; Kita, Y. *Tetrahedron Lett.* **2001**, *42*, 6903. Matsugi, M.; Itoh, K.; Nojima, M.; Hagimoto, Y.; Kita, Y. *Tetrahedron Lett.* **2001**, *42*, 8019. Matsugi, M.; Nojima, M.; Hagimoto, Y.; Kita, Y. *Tetrahedron Lett.* **2001**, *42*, 8039.

(10) The numbering positions on the steroid ring and hexane ring are respectively depicted by the positions of 3β-acetoxyetienic acid and 2-arylcyclohexanols before esterification for the simple discussion.

(11) The kinetic resolution of racemic alcohols by using the DCC: Chinchilla, R.; Najera, C.; Yus, M.; Heumann, A. *Tetrahedron: Asymmetry* **1990**, *1*, 851. Chinchilla, R.; Najera, C.; Yus, M.; Heumann, A. *Tetrahedron: Asymmetry* **1991**, *2*, 101.

10.1021/op0200928 CCC: $25.00
Published on Web 05/01/2003

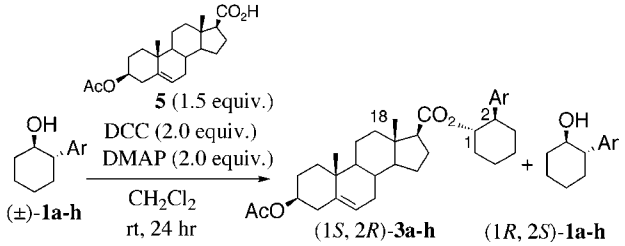


Figure 2. **An optimized condition of the esterification.**

in Figure 2 gave extremely high *s* values, considering the nonenzymatic method for the resolution of the (±)-*trans*-2-arylcyclohexanols series.

As listed in Table 1, the (1*S*,2*R*)-alcohols always predominantly preceded to give the corresponding esters, which showed the CH/π interaction in ^{1}H NMR.[14] The chemical shifts of protons on C18−CH_3 in **3** [δ (ppm)] were **3a**, 0.039; **3b**, 0.068; **3c**, 0.006; **3d**, 0.116; **3e**, −0.214; **3f**, −0.248; **3g**, 0.115; and **3h**, −0.226, respectively, and the stereochemistry of resolved alcohols of **1c**, **1f**, and **1g** was also confirmed by the crystallographic analysis of the corresponding esters **3**.[9] Since the stereo-defined **1a** is available, the stereochemistry of the resolved **1a** was easily confirmed. The other resolved alcohols are estimated by the remarkable high field shift of the corresponding C18−CH_3 protons of **3** in ^{1}H NMR, which seems to be responsible for the interaction.

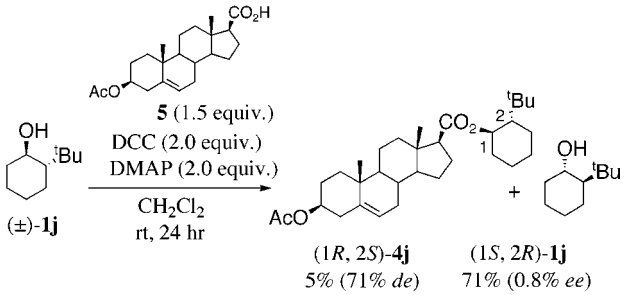
The efficiency for the kinetic resolution was significantly high when the alcohols bearing a condensed-aromatic ring was used (Table 1, entries 5, 6, 8). The almost enantiomerically pure (1*R*,2*S*)-2-arylcyclohexanols were available by only mixing the corresponding racemic alcohol with the other reagents at room temperature when Ar function was *p*-chlorophenyl or 1-naphthyl or 2-naphthyl (entries 4−6).

Table 1. **Kinetic Resolution of (±)-1a−i by Esterification Using Chiral Acid 5 and DCC−DMAP**

		(1*S*,2*R*)-**3**		(1*R*,2*S*)-**1**		
entry	Ar	yield (%)	*de*[a] (%)	yield (%)	*ee*[b] (%)	selectivity (*s* value)
1[c]	Ph (**1a**)	59	49	40	74	6.6
2	*p*-tolyl (**1b**)	51	58	48	61	7.0
3	*p*-methoxyphenyl (**1c**)	48	68	40	78	28.0
4	*p*-chlorophenyl (**1d**)	74	34	17	>99	9.0
5	1-naphthyl (**1e**)	63	56	37	97	14.2
6	2-naphthyl (**1f**)	58	52	32	>99	30.5
7	2-pyridyl (**1g**)	50	51	47	50	4.8
8	2-quinolyl (**1h**)	52	77	44	92	39.9
9	Ph (cis: **1i**)	15	74	69	14	9.9
		(1*S*,2*S*)-**3i**		(1*R*,2*R*)-**1i**		

[a] The *de* was determined by ^{1}H NMR except for **3a**. [b] The *ee* was determined by HPLC analysis. **1b−d, h**: CHIRAL CEL OJ, hexane/^{i}PrOH = 99/1. **1e**: CHIRAL CEL OD, hexane/^{i}PrOH = 95/5. **1f**: CHIRAL CEL OJ, hexane/^{i}PrOH = 95/5. **1g**: CHIRAL CEL OD, hexane/^{i}PrOH = 98/2. **1i**: CHIRAL CEL OD-H, hexane/^{i}PrOH = 98/2. [c] The *de* and *ee* values were determined by HPLC analysis (CHIRAL CEL OD, hexane/^{i}PrOH = 99/1).

Scheme 1. **Esterification of (±)-1j Having a ^{t}Bu Group**



The use of a *cis*-type cyclohexanol such as **1i** gave a moderate selectivity (entry 9).[15] Furthermore, an interesting result was obtained when (±)-*trans*-2-*tert*-butylcyclohexanol[16] was used as the substrate (Scheme 1).

In this case, the esterification was very sluggish, but the moderate selectivity (71% *de*) was observed in crude **4j**. It is noteworthy that the major acylated substrate was (1*R*,2*S*)-isomer (**1j**), whose stereosense of diastereoselection is opposite to what was seen with 2-arylcyclohexanols under the same condition.[17] When 2-arylcyclohexanols were used as a substrate, the esterification predominantly proceeded in (1*S*,2*R*)-alcohol, which would make the CH/π interaction[18] possible to exist in the transition state; however, the participation of the interaction in the acylation process remains to be elucidated at the moment. Nevertheless, it is strongly suggested that the high electron density of the aromatic moiety and/or the spreadability of the π plane is important to achieve the high selectivity and that the sense of the selectivity would be determined by the presence of the π moiety on the Ar group and not with the steric effect.

The present nonenzymatic kinetic resolution method[19] of (±)-2-arylcyclohexanols under mild conditions is simple and useful for large-scale syntheses. The application to various acyclic aryl alcohols is now being investigated.

Received for review November 11, 2002.

OP0200928

(12) The kinetic resolution of racemic carboxylic acids by using the DCC: Camps, P.; Perez, F.; Soldevilla, N. *Tetrahedron: Asymmetry* **1997**, *8*, 1877. Calmes, M.; Glot, C.; Michel, T.; Rolland, M.; Martinez, J. *Tetrahedron: Asymmetry* **2000**, *11*, 737.

(13) The chiral 3β-acetoxyetienic acid can be easily prepared from a commercially available pregnenolone acetate via the two steps; see: ref 5.

(14) Bovey, F. A. *Nuclear Magnetic Resonance Spectroscopy*; Academic: New York, 1969; p 64.

(15) The absolute configuration of the **1i**, which was predominantly proceeded in the esterification, was determined by the comparison of the sense of $[\alpha]_D$ of the remaining **1i** in the acylation process. Berti, G.; Macchia, B.; Macchia, F.; Monti, L. *J. Org. Chem.* **1968**, *33*, 4045.

(16) Djerassi, C.; Hart, P. A.; Warawa, E. J. *J. Am. Chem. Soc.* **1964**, *86*, 78. Esser, P.; Buschmann, H.; Meyer-Stork, M.; Scharf, H.-D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1190.

(17) The absolute configuration of the **1j**, which was predominantly proceeded in the esterification, was determined by the comparison of the sense of $[\alpha]_D$ of the corresponding **1j** after the removal of the steroid moiety, see: ref 16.

(18) For recent reports on the participation of the CH/π attractive force, see Yamakawa, M.; Yamada, I.; Noyori, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2818. Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931.

(19) A typical procedure: (±)-*trans*-2-(2-naphthyl)-1-cyclohexanol **1f** (5.0 g, 22.1 mmol), 3β-acetoxyetienic acid[5] **5** (12.0 g, 33.3 mmol), dicyclohexylcarbodiimide (9.1 g, 44.2 mmol), and 4-*N*,*N*-(dimethylamino)pyridine (5.4 g, 44.3 mmol) were dissolved in dry CH_2Cl_2 (519 mL), and the reaction mixture was stirred at room temperature. After the reaction mixture was stirred for 6.5 h, it was washed with 5% aq NaOH 3 times and then water once. The organic phase was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (eluent: hexane/AcOEt = 1/6 to 1/1, then hexane/CH_2Cl_2 = 8/1) to give 6.8 g of **3f** (54.4%, 71% *de*) and 1.9 g of (1*R*, 2*S*)-**1f** (38.1%, 99% *ee*). The 3β-acetoxyetienic acid (457 mg, 3.8%) was recovered by the neutralization of the aqueous alkaline phase.