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New Chiral Stationary Phases with Two Chiral Centers for the Liquid Chromatographic Resolution of Racemic Anti-inflammatory Drugs Related to α-Arylpropionic Acids

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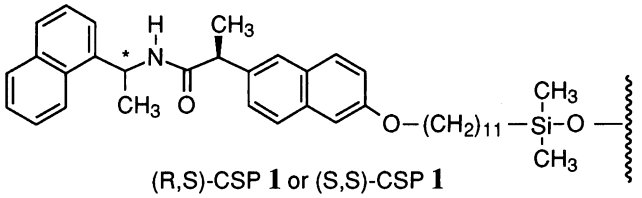
New chiral stationary phases (CSPs) with two chiral centers were prepared from (R)- or (S)-α-naphthylethylamine and (S)-naproxen. The (R,S)-CSP prepared from (R)-α-naphthylethylamine and (S)-naproxen was found to be very successful in resolving 3,5-dinitroanilide derivatives of anti-inflammatory drugs related to α-arylpropionic acids.

Two enantiomers of racemic drugs often show different biological activities.[1] In consequence, the enantiomeric composition of pharmaceuticals is an important issue in the drug development and in the clinical use of drugs.[2] Now various methods are available for the determination of enantiomeric composition or purity of optically active pharmaceuticals.[3] However, the liquid chromatographic separation of enantiomers on chiral stationary phases (CSPs) has been known to be the most accurate and convenient means of measuring the stereoisomeric composition of pharmaceutical importance.[4]

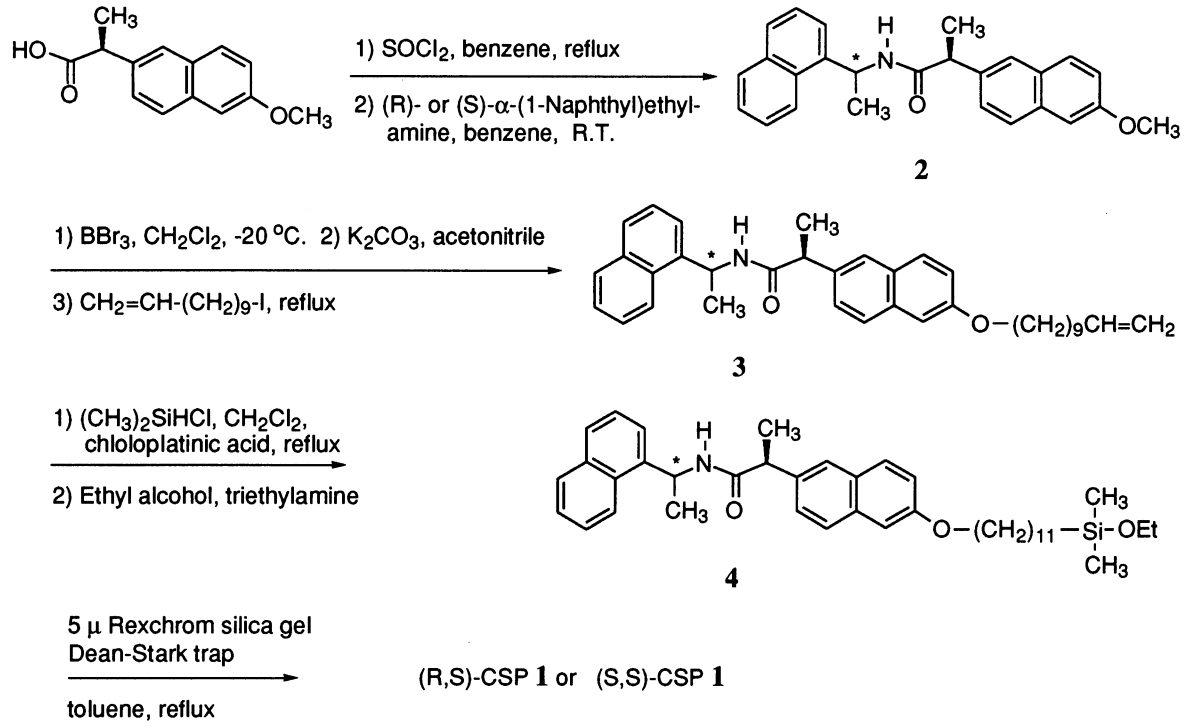
Since the introduction of the commercial (R)-N-(3,5-dinitrobenzoyl)phenylglycine CSP by Pirkle in 1981,[5] a number of CSPs based on helical polymers,[6] cellulose derivatives,[7] proteins,[8] and cyclodextrins[9] have been developed and applied to the resolution of racemic drugs. In this area, our efforts have been focused on the development or improvement of Pirkle type CSPs and their applications. As results CSPs based on α-arylalkylamines such as (R)-α-naphthylethylamine or (R)-1-(6,7-dimethyl-1-naphthyl)isobutylamine were developed and applied in resolving racemic drugs and other racemates including chiral amines, chiral alcohols, chiral carboxylic acids, chiral carbonyl compounds and dipeptides as their appropriate derivatives.[10] In this paper, we want to report that CSP **1** derived from (R)- or (S)-α-naphthylethylamine and (S)-naproxen can be successfully utilized in resolving racemic drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) related to α-arylpropionic acids. Each of (R)- or (S)-α-naphthylethylamine and (S)-naproxen which constitute CSP **1** is commercially available and has been adopted as a chiral stationary phase after bonding to solid column support such as silica gel.[11] The combination of (R)- or (S)-α-naphthylethylamine and other optically active chiral unit such as (S)-valine, (S)-proline or (S)-*t*-leucine have also been utilized as CSPs in resolving racemates.[12] However, the combination of (R)- or (S)-α-naphthylethylamine and (S)-naproxen has not been applied as a chiral



(R,S)-CSP **1** or (S,S)-CSP **1**

stationary phase.

New CSPs with two chiral centers, (R,S)-CSP **1** and (S,S)-CSP **1**, were prepared from (R)- or (S)-α-naphthylethylamine and (S)-naproxen via the procedures shown in Scheme 1.[13] These two CSPs were used in resolving 3,5-dinitroanilide derivatives **5** of NSAIDs related to α-arylpropionic acids. The chromatographic resolution results are summarized in Table 1. As shown in Table 1, NSAIDs are resolved quite well on the two CSPs as their π-acidic 3,5-dinitroanilide derivatives. The separation factors, α, on (R,S)-CSP **1** are greater than those on (S,S)-CSP **1**. The elution orders, which were determined by eluting configurationally known samples through the chiral columns, are opposite on the two CSPs.

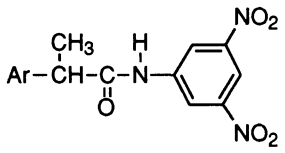


Scheme 1.

For the enantioseparation, in general, Pirkle type CSPs have been known to interact with the two enantiomers of racemates through the stereoselective π-π complexation.[10] Both (R,S)-CSP **1** and (S,S)-CSP **1** contain two strong π-basic functionalities such as the 1-naphthyl group of the (R)- or (S)-α-naphthylethylamine part and the 6-substituted-2-naphthyl group of the (S)-naproxen part of the CSPs. Therefore, either π-basic group of the CSPs can be utilized in the stereoselective π-π complexation with the π-acidic 3,5-dinitroanilide group of analytes **5**. However, the elution orders of the two enantiomers are dependent on the absolute stereochemistry of the (R)- or (S)-α-naphthylethylamine part of the CSPs as shown in Table 1 and, in consequence, it can be deduced that the (R)- or (S)-α-naphthylethylamine part of the CSPs plays the major role in the chiral recognition. In this context, it can also be deduced that the greater chiral recognition ability of (R,S)-CSP **1** than that of (S,S)-CSP **1** denoted by the separation factors shown in Table 1 stems from the subordinate effect on the chiral recognition exerted by the (S)-naproxen part of the CSPs.

To elucidate the role of the two chiral components of (R,S)-CSP **1** and (S,S)-CSP **1** in the chiral recognition more precisely, additional experimental results such as spectroscopic and/or X-ray crystallographic data for the

Table 1. Resolution of 3,5-dinitroanilide derivatives **5** of NSAIDs on (R,S)-CSP **1** and (S,S)-CSP **1**[a)]



5

Ar[b)]	(R,S)-CSP **1**				(S,S)-CSP **1**			
	k_1'[c)]	k_2'[c)]	α[d)]	Conf[e)]	k_1'[c)]	k_2'[c)]	α[d)]	Conf[e)]
Phenyl	3.92	9.84	2.51	S	20.65	39.64	1.92	R
4-Isobutylphenyl (Ibuprofen)	3.79	9.39	2.48	S	16.02	31.10	1.94	R
6-Methoxy-2-naphthyl (Naproxen)	7.41	23.73	3.20	S	38.22	76.77	2.01	R
3-Phenoxyphenyl (Fenoprofen)	4.74	11.29	2.38		30.49	51.67	1.69	
3-Benzoylphenyl (Ketoprofen)	4.36	8.67	1.99		34.40	53.11	1.54	
2-Fluoro-4-biphenylyl (Flurbiprofen)	5.11	10.92	2.14		28.59	49.94	1.75	
4-(2-Thienylcarbonyl)phenyl (Suprofen)	9.79	18.12	1.85		51.05	74.40	1.46	
5-Benzoyl-2-thienyl (Tiaprofenic acid)	9.68	12.87	1.33		63.45	81.95	1.29	

a) Chromatography was performed with a Waters Model 510 pump, a Rheodine Model 7125 Injector with a 20 μl sample loop, a Youngin model 710 Absorbance Detector and a Youngin D520B Computing Integrator. All data were obtained by using 20% isopropyl alcohol in hexane as a mobile phase with flow rate of 2 ml/min at 254 nm UV. Derivatives **5** were prepared by simply stirring the acid chlorides of NSAIDs with 3,5-dinitroaniline in dry methylene chloride at room temperature. b) The original names of NSAIDs before derivatization are in the parenthesis. c) Capacity factors. The large capacity factors on (S,S)-CSP **1** may be originated from the high loading of chiral selector on silica gel.[14)] d) Separation factors. e) Absolute configuration of the second eluted enantiomers. For blanks, the elution orders have not been established.

stereoselective π-π complexation are required. The efforts to obtain the additional data and to apply (R,S)-CSP **1** and (S,S)-CSP **1** in resolving other racemates are underway in our laboratory.

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12) N. Ôi and H. Kitahara, *J. Liq. Chromatogr.*, **9**, 511 (1986) and Brochure for Sumichiral OA by Sumika Chemical Analysis Service, Ltd., Osaka, Japan.
13) The detailed synthetic procedure will be described in a full paper. All new compounds gave satisfactory spectroscopic data. Selected spectral properties of compounds **2**, **3**, and **4** are as following: compound (R,S)-**2** ; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.52(d, 3H), 1.58(d, 3H), 3.63(q, 1H), 3.93(s, 3H), 5.62(broad d, 1H), 5.89-5.98(m, 1H), 7.12-8.11(m, 13H). IR (NaCl, CCl_4) cm^{-1} 3286, 3053, 1714. (S,S)-**2** ; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.57(d, 3H), 1.59(d, 3H), 3.71(q, 1H), 3.92(s, 3H), 5.62(broad d, 1H), 5.83-5.92(m, 1H), 7.09-7.95(m, 13H). IR (NaCl, CCl_4) cm^{-1} 3318, 3047, 1715. (R,S)-**3** ; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.32(broad s, 10H), 1.48-1.60(imbedded m, 2H), 1.52(d, 3H), 1.59(d, 3H), 1.80-1.89(m, 2H), 2.01-2.08(m, 2H), 3.63(q, 1H), 4.07(t, 2H), 4.91-5.04(m, 2H), 5.58(broad d, 1H), 5.76-5.89(m, 1H), 5.90-5.96(m, 1H), 7.11-8.11(m, 13H). IR (NaCl, CCl_4) cm^{-1} 3286, 3014, 1638. (S,S)-**3** ; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.33(broad s, 10H), 1.48-1.53(m, 2H), 1.57(d, 3H), 1.59(d, 3H), 1.80-1.90(m, 2H), 2.02-2.09(m, 2H), 3.71(q, 1H), 4.06(t, 2H), 4.92-5.05(m, 2H), 5.64(broad d, 1H), 5.76-5.84(m, 1H), 5.85-5.92(m, 1H), 7.08-7.96(m, 13H). IR (NaCl, CCl_4) cm^{-1} 3286, 3052, 1632. (R,S)-**4** ; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.09(s, 6H), 0.57-0.63(m, 2H), 1.19(t, 3H), 1.29(broad s, 14H), 1.46-1.56(imbedded m, 2H), 1.52(d, 3H), 1.59(d, 3H), 1.78-1.90(m, 2H), 3.60-3.74(mix of m and q, 3H), 4.07(t, 2H), 5.59(broad d, 1H), 5.90-6.00(m, 1H), 7.11-8.11(m, 13H). IR (NaCl, CCl_4) cm^{-1} 3263, 3050, 1632. (S,S)-**4** ; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.10(s, 6H), 0.57-0.63(m, 2H), 1.20(t, 3H), 1.30(broad s, 14H), 1.42-1.52(m, 2H), 1.57(d, 3H), 1.59(d, 3H), 1.80-1.87(m, 2H), 3.64-3.72(mix of m and q, 3H), 4.06(t, 2H), 5.67(broad d, 1H), 5.85-5.92(m, 1H), 7.08-7.96(m, 13H). IR(NaCl, CCl_4) cm^{-1} 3320, 3066, 1713.
14) Elemental analysis of the CSPs showed the following loading of chiral selector on silica gel. (R,S)-CSP **1** ; 0.07 mmole (based on C) and 0.05 mmole (based on N) of chiral selector per gram of stationary phase. (S,S)-CSP **1** ; 0.19 mmole (based on C) and 0.17 mmole (based on N) of chiral selector per gram of stationary phase.

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