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SYNTHESIS OF OPTICALLY ACTIVE 2-ARYLALKANOIC ACIDS BY THE USE OF 1,2-REARRANGEMENT OF THE ARYL GROUP

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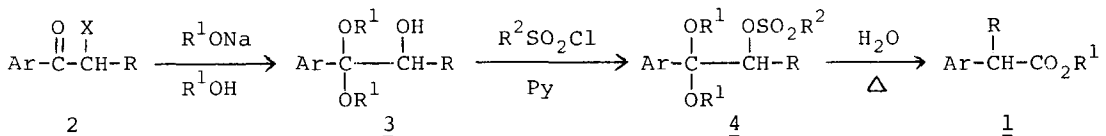
Abstract: A new route to the synthesis of optically active 2-arylalkanoic acids was accomplished by using stereospecific 1,2-rearrangement of the aryl group in chiral 1-aryl-2-sulfonyloxy-1-alkanone acetals.

2-Arylalkanoic acids are the group which involves many biologically active compounds. Among them, 2-arylpropionic acids such as 2-(4-isobutylphenyl)-propionic acid and 2-(6-methoxy-2-naphthyl)propionic acid show potent anti-inflammatory activity[1] and 2-arylisovaleric acids such as 2-(4-chlorophenyl)-isovaleric acid are used as the acid-moiety of synthetic pyrethroids.[2] These acids have an asymmetric center at 2-position, and one of the enantiomers of each acid often shows higher activity than its antipode. For example, (S)-2-(6-methoxy-2-naphthyl)propionic acid is 28 times more active than its (R)-isomer and used for an antiinflammatory agent, naproxen.[3] Recently, we developed a new method of synthesizing a 2-arylalkanoic ester (1), which consists of the derivation of a 1-aryl-2-sulfonyloxy-1-alkanone acetal (4) from a 1-aryl-2-halo-1-alkanone (2) through a 1-aryl-2-hydroxy-1-alkanone acetal (3), and the conversion of 4 to 1 by 1,2-rearrangement of the aryl group (see Scheme 1).[4] It is expected that this rearrangement proceeds stereospecifically and optically active 1 might be produced starting from a chiral form of the α-sulfonyloxy acetal 4. In this letter, we wish to report our study on the stereochemical course of the 1,2-rearrangement and a new method for the synthesis of optically active 2-arylalkanoic acids.

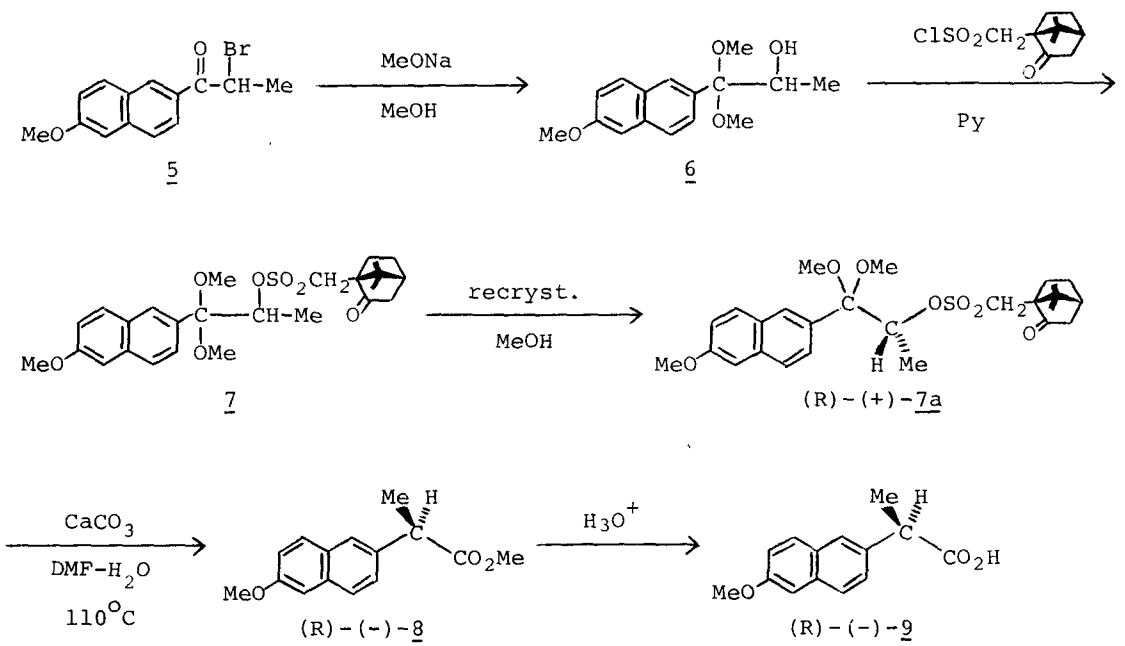
Scheme 1



2 3 4 1

A mixture of 2-bromo-1-(6-methoxy-2-naphthyl)-1-propanone (5) and sodium methoxide (1.5 equiv) in methanol was stirred at room temperature for 24 h to

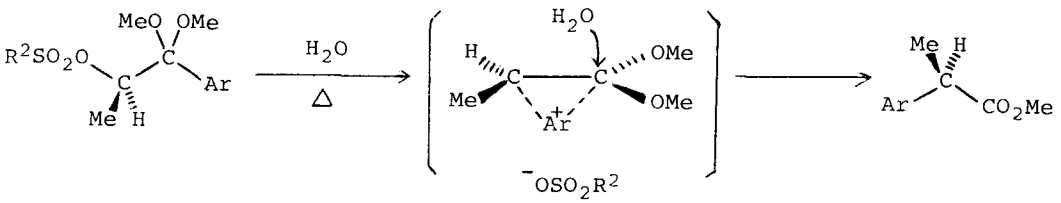
Scheme 2



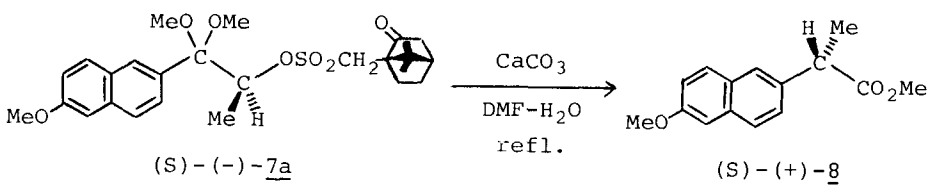
yield 2-hydroxy-1-(6-methoxy-2-naphthyl)-1-propanone dimethyl acetal (6), quantitatively. Treatment of the α-hydroxy acetal 6 with *d*-10-camphorsulfonyl chloride (1.0 equiv) in pyridine at room temperature for 45 min afforded 2-(*d*-10-camphorsulfonyloxy)-1-(6-methoxy-2-naphthyl)-1-propanone dimethyl acetal (7) in 77% yield. NMR and HPLC analyses showed that it consisted of two diastereomers in a ratio of 1 : 1. From the mixture, one diastereomer, (+)-7a, was isolated in 33% yield (theoretical yield, 66%) by recrystallization from methanol as colorless crystals: mp 102-105°C, $[\alpha]_D^{25}$ +32.5° (c 1.000, $CHCl_3$). The absolute configuration of the carbon atom at 2-position was determined to be (R) by X-ray crystallographic analysis.[5] In the presence of an equimolar amount of calcium carbonate,[6] (R)-(+)-7a was heated at 110°C for 14 h in a mixture of water and DMF (weight ratio 1 : 4) to give methyl (R)-(-)-2-(6-methoxy-2-naphthyl)-propionate [(R)-(-)-8] in 80% yield: mp 94.5-95°C, $[\alpha]_D^{20}$ -78.2° (c 1.000, $CHCl_3$); lit.[3] for (S)-(+)-8,[7] mp 88°C, $[\alpha]_D$ +77° ($CHCl_3$). Its optical purity was found to be 100% by NMR measurement using a chiral shift reagent, $Eu(TFC)_3$, and by comparison of the rotation with that of (S)-(+)-8. Heating thus obtained (R)-(-)-8 with hydrochloric acid in dimethoxyethane at 50°C for 23 h afforded (R)-(-)-9, the antipode of naproxen,[7] in 63% yield: mp 155-157°C, $[\alpha]_D^{20}$ -67.2° (c 1.096, $CHCl_3$); lit.[3] for naproxen, mp 152-154°C, $[\alpha]_D$ +66° ($CHCl_3$). The hydrolysis of (R)-(-)-8 to (R)-(-)-9 was found to proceed without any loss of optical purity.[8,9]

These results clearly show that the 1,2-rearrangement proceeds with 100% inversion of the configuration of the carbon atom at 2-position (see Scheme 3).

Scheme 3



For the synthesis of naproxen, an α-sulfonyloxy acetal having (S) configuration at the 2-position should be needed. Fortunately, less common *l*-camphor was also found to occur in nature[10] and ammonium salt of *l*-10-camphorsulfonic acid is commercially available.[11] The ammonium salt was easily converted to *l*-10-camphorsulfonyl chloride,[12] which was subjected to the reaction with the α-hydroxy acetal 6, followed by recrystallization of the resulting diastereomeric mixture to yield (S)-(-)-2-(*l*-10-camphorsulfonyloxy)-1-(6-methoxy-2-naphthyl)-1-propanone dimethyl acetal [(S)-(-)-7a]: mp 93-96°C, $[\alpha]_D^{23}$ -32.2° (c 0.801, $CHCl_3$).[13] NMR and HPLC data were in every respect identical with those of (R)-(+)-7a. Thus obtained (S)-(-)-7a was subjected to the 1,2-rearrangement reaction by heating under reflux for 20 h in a mixture of water and DMF (1 : 4) in the presence of calcium carbonate[6] to afford the desired methyl (S)-(+)-(6-methoxy-2-naphthyl)propionate [(S)-(+)-8] in 90% yield: $[\alpha]_D^{25}$ +75.0° (c 0.949, $CHCl_3$).[14]



(S)-(-)-7a (S)-(+)-8

Thus, a new method for the synthesis of an optically active 2-arylalkanoic acid by the rearrangement of a chiral α-sulfonyloxy acetal is established. The method has following advantageous features. 1) *d*- or *l*-10-Camphorsulfonyloxy group, which is used for resolution of (R)- or (S)-7a, plays a role of the leaving group in the rearrangement process. 2) The chirality involving C-O bond is transformed to the chirality of the final product and the former can be created easily by usual methods, e.g. resolution of an alcohol or asymmetric reduction of a carbonyl group.[15]

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3) I. T. Harrison, B. Lewis, P. Nelson, W. Rooks, A. Roszkowski, A. Tomolonis, and J. H. Fried, J. Med. Chem., 13, 203 (1970).

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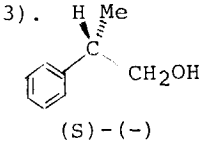
5) S. Ohba, Y. Saito, K. Kitajima, S. Mitamura, and G. Tsuchihashi, unpublished results.

6) As the reaction proceeds, camphorsulfonic acid is produced. Neutralization of the acid by calcium carbonate is necessary to prevent the acid-catalyzed decomposition of the acetal-moiety in 7a.

7) Harrison et al. already prepared (S)-(+)-8 by methylation of (S)-(+)-2-(6-methoxy-2-naphthyl)propionic acid (naproxen); see reference 3). The absolute configuration of naproxen was determined by degradation to (-)-2-phenyl-1-propanol, whose configuration was known to be (S); see, J. Riegl, M. L. Maddox, and I. T. Harrison, J. Med. Chem., 17, 377 (1974).



(S)-(-)

8) The resulting (R)-(-)-9 was found to have 100% optical purity by comparison of its rotation with that of naproxen and by NMR measurement of the corresponding methyl ester using $Eu(TFC)_3$. The ester was derived by the reaction of (R)-(-)-9 with diazomethane.

9) In general, 2-arylalkanoic esters easily racemize in alkaline conditions; see, J. Kenyon and D. P. Young, J. Chem. Soc., 216 (1940). Acid-catalyzed hydrolysis of methyl (-)-2-phenylpropionate was reported to yield the corresponding acid in an optically active form; see, H. Pracejus, Justus Liebigs Ann. Chem., 634, 9 (1960).

10) S. Coffey, Ed., "Rodd's Chemistry of Carbon Compounds," 2nd ed, Vol II part C, Elsevier Publishing Company, Amsterdam, London, New York (1969) p 199.

11) Supplied from Aldrich Chemical Co.

12) mp 58-64°C, $[\alpha]_D^{26}$ -32.3° (c 1.363, $CHCl_3$). It was obtained according to the procedure for the preparation of *d*-10-camphorsulfonyl chloride; see, a) S. Smiles and T. P. Hilditch, J. Chem. Soc., 91, 519 (1907); b) H. Sutherland and R. L. Shriner, J. Am. Chem. Soc., 58, 62 (1936).

13) The yield of (S)-(-)-7a from 6 was almost the same as that of (R)-(+)-7a.

14) The optical purity was determined to be 94.3% by NMR measurement using $Eu(TFC)_3$. Contamination with (R)-isomer (calculated to be about 3%) may be due to insufficiency of optical purity of the starting *l*-10-camphorsulfonic acid ammonium salt.

15) Asymmetric reduction yielding a chiral α-hydroxy acetal is under investigation and the results will be presented shortly.

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