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Unprecedented racemization of (*S*)-(+)-naproxen during a BOP-mediated esterification. X-Ray structures of diastereomeric esters

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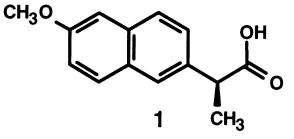
Abstract

During esterification of enantiomerically pure (*S*)-(+)-naproxen under mild conditions with the use of the BOP-reagent, a complete racemization was observed.

1. Introduction

The 2-arylpropionic acid derivatives, or 'profens,' are important classes of nonsteroidal anti-inflammatory drugs that have been in clinical use for over 20 years. Members of this drug class include, among others, naproxen, ibuprofen, ketoprofen, flurbiprofen, and tiaprofenic acid.[1] The profens have been used clinically as racemic agents with the exception of (*S*)-(+)-naproxen [(*S*)-2-(6-methoxy-2-naphthyl)propanoic acid] **1**, which has been developed and used only as a single enantiomeric drug.[2]



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Due to the fact that (*S*)-(+)-naproxen **1** is commercially available in an enantiomerically pure form even in large quantities, it has gained much attention as a chiral agent for the kinetic resolution of racemates on an analytical as well as on a preparative scale. Thus, for example, an easy inexpensive and accurate method to determine the enantiomeric excess of cyanohydrins has been proposed.[3] The method consists in derivatization of cyanohydrins with (*S*)-naproxen chloride and analysis of the products by HPLC. Also, the use of two novel chiral derivatizing agents derived

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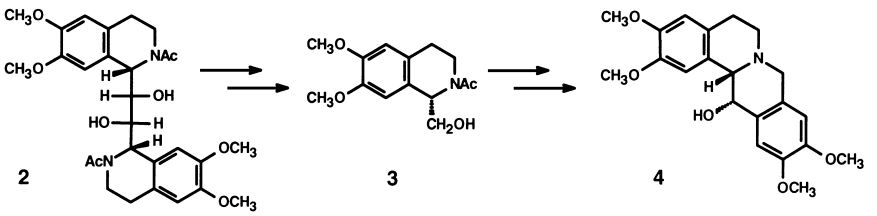
from (*S*)-(+)-naproxen, 1-(6-methoxy-2-naphthyl)ethyl isothiocyanate and 2-(6-methoxy-2-naphthyl)-1-propyl chloroformate, turned out to be very effective in separating the enantiomers of chiral drugs on achiral HPLC columns.[4] Preparative scale separations in the form of appropriate amides have been described in the case of (±)-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine derivatives.[5] Transformation of enantiomerically pure nonsteroidal anti-inflammatory carboxylic acids into their esters and amides may also serve as a source of antioxidants and antiproliferative agents.[6] The efficiency and reliability of the above methods rely greatly on the assumption of high configurational stability of (*S*)-(+)-naproxen **1** which has never been questioned. In the present report we would like to inform that this assumption might not be well founded in some cases.

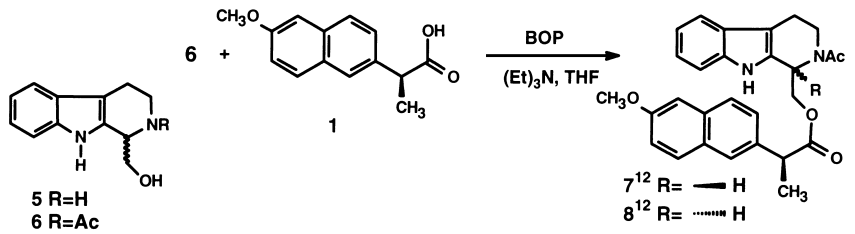
2. Results and discussion

As part of our program for the synthesis of enantiomerically enriched tetrahydroisoquinolines from chiral pool derivatives of natural or synthetic origin, we proposed the use of, among others, L-(+)-tartaric acid as an efficient asymmetric inductor (Scheme 1).[7,8]



Scheme 1.

We have found that several types of isoquinoline alkaloids can be constructed using this approach, including benzylisoquinolines, aporphines and protoberberines.[7,8] In Scheme 1, compound **3** served as a key chiral intermediate. Recently we turned our attention to a broad and equally important class of indole alkaloids,[9] and with the use of L-(+)-tartaric acid, as a source of chirality, we were able to prepare compound **6** which, being an analog of **3**, could play the same role in indole alkaloid synthesis, as **3** does in the synthesis of isoquinolines. Unfortunately, **6** has not been described yet and therefore we decided to make the correlation of its absolute configuration with the observed chiroptical properties. The racemic modification of **6** can be easily prepared on a several-gram scale from the known indole derivative **5**[10] by standard acetylation procedure (Scheme 2). This allowed us to plan resolution on a relatively large scale, aimed at the preparation of a sample suitable for X-ray crystallographic studies. However, despite prolonged efforts we



Scheme 2.

were unable to prepare a crystalline derivative from racemic **6** with Mosher's acid,[11] *O*,*O*-diacetyl-, nor *O*,*O*-dibenzoyltartaric acids. The fact that (*S*)-(+)-naproxen **1** is commercially available in an enantiomerically pure form and its successful use as reagent for kinetic resolution and derivatization, encouraged us to investigate the possibility of applying it in our investigations.

Starting racemic aminoalcohol **5** was prepared on the basis of the known procedure.[10] Treatment of **5** with acetic anhydride under standard conditions gave its N_b-acetyl derivative **6** in good yield. Literature methods for derivatization with (*S*)-(+)-naproxen **1**, oriented towards formation of esters or amides, were often based upon the use of (*S*)-(+)-naproxen chloride.[3] Because the possibility of racemization might be considerable in this case, we decided to use a BOP reagent (Castro's reagent[13]) known from the peptide chemistry as very safe, highly efficient and seldom promoting racemization.

In our hands, the reaction of (*S*)-(+)-naproxen **1** with racemic **6** gave, after standard work up, a mixture of two derivatives of very similar polarity in equimolar ratio. Careful separation on silica gel using toluene/chloroform/methanol allowed the separation of both compounds **7** and **8**.[12] The absence of measured optical activity of **7** and **8** appeared quite suspicious. Prolonged efforts brought about the formation of two monocrystals suitable for X-ray studies. As a result, we found that the crystals, despite the use of chiral, nonracemic acid, were both centrosymmetric (space group $P2_1/n$ and $P2_1/c$, respectively) racemic compounds. They also had the same number of molecules in the unit cell and almost the same cell volume and density.

The molecular conformations of **7** and **8** are shown in Figs. 1 and 2, respectively. The configuration at the asymmetric carbon atoms C(2) and C(14) in **7** is *RS*, respectively (for the diastereomer shown in the drawing). The characteristic feature of **7** is the co-planarity of the atoms C(2), C(12), O(1), C(13), O(2) and C(14) and the intramolecular hydrogen bond N–H···O between atoms N(1) and O(1). Contrary to **7**, the linker atoms in **8** do not lie in plane. The configuration at the asymmetric centers C(2) and C(14) is *RR*. Accordingly, due to centrosymmetricity of the crystal, molecules of *RR* and *SS* configuration coexist in a crystal lattice. It is worthy to note that molecule **8** is more extended. The intermolecular hydrogen bond N–H···O is observed in the crystal structure instead of the intramolecular bond present in **7**.

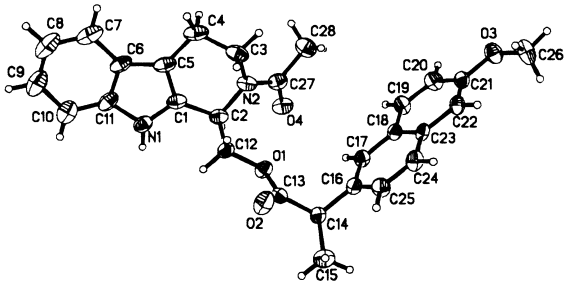


Figure 1. ORTEP view of compound **7**

In order to ensure the total stereochemical outcome of the described process we subjected esters **7** and **8** to both base and acid catalyzed hydrolysis and we found that alcohol **6** thus obtained was optically inactive in each case. The above results indicated that despite relatively mild esterification conditions racemization of the acid component was observed. The mechanism of the process may not be obvious although it probably involves an enol-type intermediate. In the case of naproxen **1**, a base catalyzed racemization was indeed observed[14] but under quite harsh conditions.

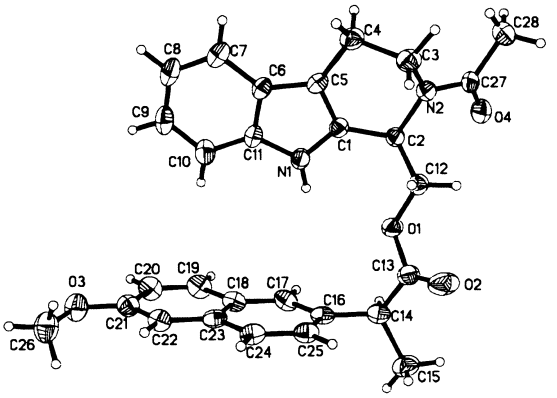


Figure 2. ORTEP view of compound **8**

Great care should therefore be undertaken with the use of (*S*)-(+)-naproxen **1** as a popular and easily accessible chiral derivatizating agent.

3. Experimental

NMR spectra were recorded on a Varian Unity Plus spectrometer operating at 500 MHz for ^{1}H NMR and at 125 MHz for ^{13}C NMR. Tetramethylsilane (TMS) or solvents were used as internal standards. The ^{19}F NMR spectra were recordered on a Varian UNITY plus-500 with C_6F_6 as external reference. Chemical shifts are reported in (δ) ppm. Mass spectra were collected on an AMD 604 apparatus; high-resolution mass spectra were acquired using LSIMS (positive ion mode). Optical rotation was measured on a Perkin–Elmer 247 MC polarimeter. TLC analyses were performed on Merck 60 silica gel glass plates and visualized using iodine vapor. Column chromatography was carried out at atmospheric pressure using silica gel 60 (230–400 or under 400 mesh, Merck)

Preparation of **6**: To a solution containing 5.00 g (25 mmol) of compound **5**[10] and 4 g (100 mmol) of sodium hydroxide in an 80 mL mixture of water:methylene chloride (1:1, v/v), 7.1 mL (75 mmol) of acetic anhydride and 2.05 g (25 mmol) of sodium acetate were added and the resulting mixture was stirred vigorously for 24 h. The organic phase was washed with satd $NaCl_{aq.}$ and dried ($MgSO_4$). Evaporation of the solvent gave a solid, which was dissolved in 50 mL of methanol containing 1.0 mL of ammonia solution ($25\%_{aq.}$). The reaction mixture was stirred for 12 h (TLC monitoring). Evaporation of the solvent gave a solid that after column chromatography (silica gel, 90:10 chloroform:methanol) afforded 4.68 g (19 mmol, 77%) of compound **6**.

Analytical data of **6**: mp 189–191°C, ^{1}H NMR ($CDCl_3$, 500 MHz): 8.91 (1H, s, disappeared with D_2O), 8.62 (1H, disappeared with D_2O), 7.48 (1H, d, J = 7.5 Hz), 7.35 (1H, d, J = 8 Hz), 7.18 (1H, dt, J = 8 Hz, J = 7.5 Hz, J = 1 Hz), 7.10 (1H, dt, J = 8 Hz, J = 7.5 Hz, J = 1 Hz), 5.76 (1H, t, J = 6.5 Hz), 4.06–3.88 (3H, m, J = 6.5 Hz), 3.51–3.45 (1H, m), 2.85 (2H, m), 2.25 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz): 171.06, 136.22, 131.69, 126.29, 121.96, 119.45, 117.99, 111.22, 108.16, 64.09, 51.67, 42.51, 22.09, 21.96; LSIMS (+) NBA 8 kV *m*/*z* (%): 91 (100), 95 (82), 121 (30), 171 (33), 226 (45), 245 $(M+H)^+$ (31), 267 $(M+H)^+$ (12). LSIMS HR: calculated for $C_{24}H_{32}N_2O_7SNa$ $(M+Na)^+$ 267.11096; found: 267.11016.

Preparation of esters **7** and **8**: To a solution containing 300 mg (1.2 mmol) of alcohol **6**, 475 mg (1.2 mmol) of (*S*)-(+)-naproxen **1** and 1.0 mL of triethylamine in 30 mL of dry tetrahydrofuran a

sample of 575 mg (1.3 mmol) of BOP reagent was added. The reaction mixture was stirred under argon for 24 h. The solvent was evaporated in vacuo, the residue was dissolved in 20 mL of methylene chloride. The organic solution was washed with $NaCl_{aq.}$, dried ($MgSO_4$) and concentrated in vacuo affording a white mass, which was chromatographed on silica gel. Elution with 1% (v/v) methanol in chloroform gave 720 mg of a mixture of two derivatives of very similar polarity in equimolar ratio. Very careful chromatography (silica gel, under 400 mesh, 49.5:49.5:1 toluene:chloroform:methanol) allowed separation of compounds **7** and **8**.

Analytical data of **7**: (more polar), mp 170–172°C, ^{1}H NMR ($CDCl_3$, 500 MHz): 7.8–6.9 (10H, m), 5.8 (1H, t, J = 5.5 Hz), 4.6 (2H, dd, J = 5.5 Hz), 3.9 (3H, s), 3.9–3.8 (1H, m), 3.3 (2H, m), 2.7 (2H, m) [2.2 (s, -$NCOCH_3$), 2.1 (s, -$NCOCH_3$), stable conformers in the ratio 7:1], 1.5 (3H, d, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): 174.1, 169.7, 158.3, 157.9, 135.9, 135.3, 133.7, 130.1, 129.3, 128.8, 127.5, 126.2, 126.1, 121.9, 119.4, 119.3, 117.9, 110.9, 109.1, 105.8, 64.5, 55.3, 47.9, 45.6, 42.2, 21.9, 21.8, 18.4.

Analytical data of **8**: (less polar), mp 189–193°C, ^{1}H NMR ($CDCl_3$, 500 MHz): 7.8–6.9 (10H, m), 5.8 (1H, dt, J = 5.5 Hz, J = 3 Hz), 4.4 (2H, m, J = 5.5 Hz), 3.9 (3H, s), 4–3.9 (1H, m), 3.3 (2H, m), 2.7 (2H, m) [2.3 (s, -$NCOCH_3$), 2.2 (s, -$NCOCH_3$), stable conformers in the ratio 7:1], 1.5 (3H, d, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): 173.8, 169.7, 158.1, 158.0, 135.8, 135.5, 133.8, 130.7, 129.4, 128.9, 127.6, 126.2, 126.0, 121.7, 119.5, 119.3, 117.7, 110.9, 108.6, 105.8, 65.0, 55.4, 47.5, 45.3, 42.4, 21.9, 21.9, 17.8.

X-Ray crystallography: Intensity data for **7** and **8** were measured on a Kuma KM4 diffractometer with MoKα radiation ($\lambda = 0.71073$ Å) at $T = 293$ K. Structures were solved by direct methods, aided by program XS, and refined with full-matrix least-squares program XL, from SHELXTL.[15]

Crystal data for compound **7**: $C_{28}H_{28}N_2O_4$, $M = 456.52$, monoclinic space group $P2_1/n$; $a = 15.997(3)$, $b = 8.9380(18)$, $c = 16.641(3)$ Å, $\beta = 90.71(3)°$, $V = 2379.2(8)$ Å^3, $Z = 4$, and $D_x = 1.275$ Mg/m^3. Clear colorless columnar 0.6×0.4×0.3 mm crystal, μ(MoKα) = 0.086 mm^{-1}, 4347 reflections measured, 4194 independent ($R_{int} = 0.0298$), 1579 observed [$I > 2s(I)$]. Least squares on F^2 (all reflections), $R = 0.0382$, $wR = 0.1397$ (all).

Crystal data for compound **8**: $C_{28}H_{28}N_2O_4$, $M = 456.52$, monoclinic space group $P2_1/c$; $a = 9.860(2)$, $b = 12.847(3)$, $c = 18.506(4)$ Å, $\beta = 92.50(3)°$, $V = 2342.0(9)$ Å^3, $Z = 4$, and $D_x = 1.295$ Mg/m^3. Clear colorless columnar 0.8×0.3×0.25 mm crystal, μ(MoKα) = 0.087 mm^{-1}, 3914 reflections measured, 3678 independent ($R_{int} = 0.0601$), 1460 observed [$I > 2s(I)$]. Least squares on F^2 (all reflections), $R = 0.0436$, $wR = 0.1741$ (all).

Acknowledgements

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