Tetrahedron Vol 45, No 13, pp 4243 to 4252, 1989
Printed in Great Britain

0040-4020/89 $3.00+.00

A STEREOCONVERGENT STRATEGY FOR THE SYNTHESIS OF ENANTIOMERICALLY PURE (R)-(-) AND (S)-(+)-2-(6-METHOXY-2-NAPHTHYL)-PROPANOIC ACID (NAPROXEN)

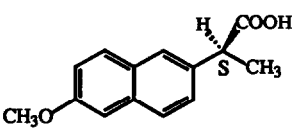
Claudio Giordano*, Graziano Castaldi,
Silvia Cavicchioli, Marco Villa.
"G. Zambon" Chemistry Research Institute
Zambon Group S.p.A.
Via Cimabue, 26/28 - 20032 Cormano (Milan) - Italy

(*Received in UK* 13 *April* 1989)

Abstract: A synthetic strategy for resolving diastereoselective imperfections associated with using a chiral auxiliary has been designed. The impact of this imperfection is a lower enantiomeric purity of the final product.
A solution for the synthesis of Naproxen **1**, an important antiinflammatory drug, using tartaric acid as chiral auxiliary, derives from an equivalent of a kinetic resolution. Using the differential rate of a rearrangement versus an intramolecular carboxylate alkylation, enantiomerically pure Naproxen **1** can be obtained from diastereomeric mixtures of bromo acetals diacids **9a,b** enriched in **9a**. Furthermore, the product coming from the intramolecular carboxylate alkylation of the minor diastereomer **9b** is also converted into Naproxen **1**. This stereoconvergence permits complete productive utilization of the diastereomeric mixture **9a,b**.

2-(S)-(+)-2-(6-Methoxy-2-naphthyl)-propanoic acid **1** (**Naproxen**)[1] (Figure 1), one of the twenty top-selling products in the U.S. retail pharmaceutical market,[2] is one the most potent and best tolerated antiinflammatory drugs.

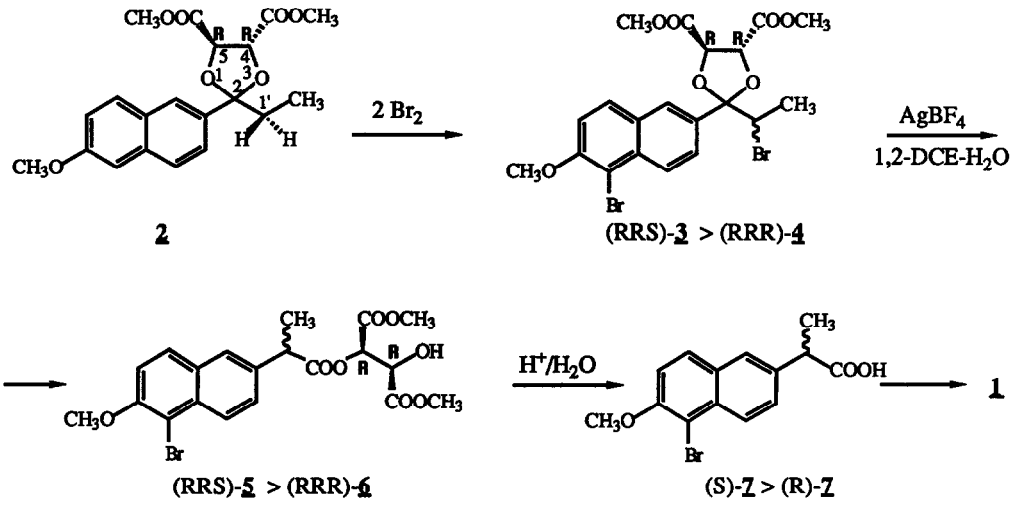
Figure 1



1

Recently, we reported the asymmetric synthesis of **1** based on a new diastereoselective bromination of enantiomerically pure acetals **2**[3,4] and the stereospecific silver promoted rearrangement of the corresponding diastereomeric bromo acetals **3** and **4** (Scheme 1).[4]

Scheme 1



2 (RRS)-**3** > (RRR)-**4**

(RRS)-**5** > (RRR)-**6** (S)-**7** > (R)-**7**

Our earlier work has the limitation that the enantiomeric excess of **1** reflects the diastereomeric excess of the starting bromo acetals **3** and **4**, requiring diastereomerically pure bromo acetals to obtain enantiomerically pure **1**.[4]

Now, by changing the nature of the substrate as well as the rearrangement conditions we have fulfilled the equivalent of a kinetic resolution. The overall result is a stereoconvergent process which allows the transformation of both the diastereomeric acetals into Naproxen **1**. Furthermore the new process is quite unique in giving the possibility of synthesizing enantiomerically pure **1** starting from **3**,**4** mixtures enriched in **3** and enantiomerically enriched **1** starting from a 1:1 mixture of **3** and **4**, from which racemic **1** is expected on the bases of previous knowledge.[4]

The new strategy envisions two competitive processes, a stereospecific 1,2-aryl shift versus an alternative nucleophilic substitution of the bromine.

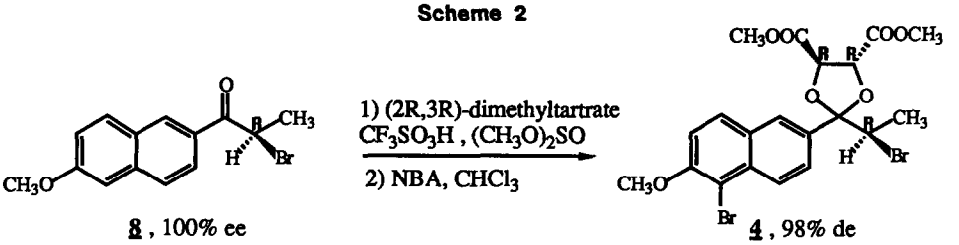
The conversion of the carboxylic esters of **3** and **4** into the corresponding carboxylic acids **9a** , **9b** and their rearrangement in water at pH 4-6, where monosalts of the substrates are present, offers the possibility to realize a competitive intramolecular displacement of bromine.

For our investigation we need **3** and **4** in diastereomerically pure form. The diastereomerically pure (>99.9%) bromo acetal dimethyl ester **3** is isolated by column chromatography from the 94 : 6 diastereomeric mixture of **3** and **4**[4].

The preparation of epimeric bromo acetal dimethyl ester **4** has shown to be more problematical, since its chromatographic separation from enriched mixtures failed. Moreover, the available enantiomerically pure (2R)-2-bromo-2-(6-methoxy-2-naphthyl)-propan-1-one **8**,[5] (Scheme 2) can not be ketalized with (2R,3R)-dimethyl tartrate under usual conditions.

Finally, the ketalization of ketone **8** with dimethyl sulfite and trifluoromethanesulfonic acid in dichloromethane at low conversion (not higher than 5%) gives rise, after nuclear bromination, to **4** with high de [6] (see Experimental, Scheme 2).

Scheme 2



8, 100% ee

4, 98% de

The bromo acetal diesters **3** and **4** are quantitatively hydrolyzed, without stereomutation, into the bromo acetal diacid **9a** and **9b**, respectively .[5]

Heating an aqueous solution of **9a** at 90°C at pH 5.2 (initial) - 4.6 (final) (reaction time 68 h) (Table, entry 1) provides the acid (S)-**7** (80% yield, ee >99%), the hydroxy acetal **12a** (1-2% yield), and a small amount of the bicyclic lactone **11a** (Scheme 3). On the contrary, under identical reaction conditions, **9b** (98% de) (reaction time 24 h) (Table, entry 5) gives only 12% yield of (R)-**7** (86% ee),[7] a small amount of bicyclic lactone **11b** and the hydroxy acetal **12b** (68% yield, de >98%) as the overwhelming major product. In both cases (2R,3R)-tartaric acid is isolated in enantiomerically pure form.

The acid (S)-**7** is quantitatively converted by reductive debromination into Naproxen **1** with undiminished enantiomeric purity.

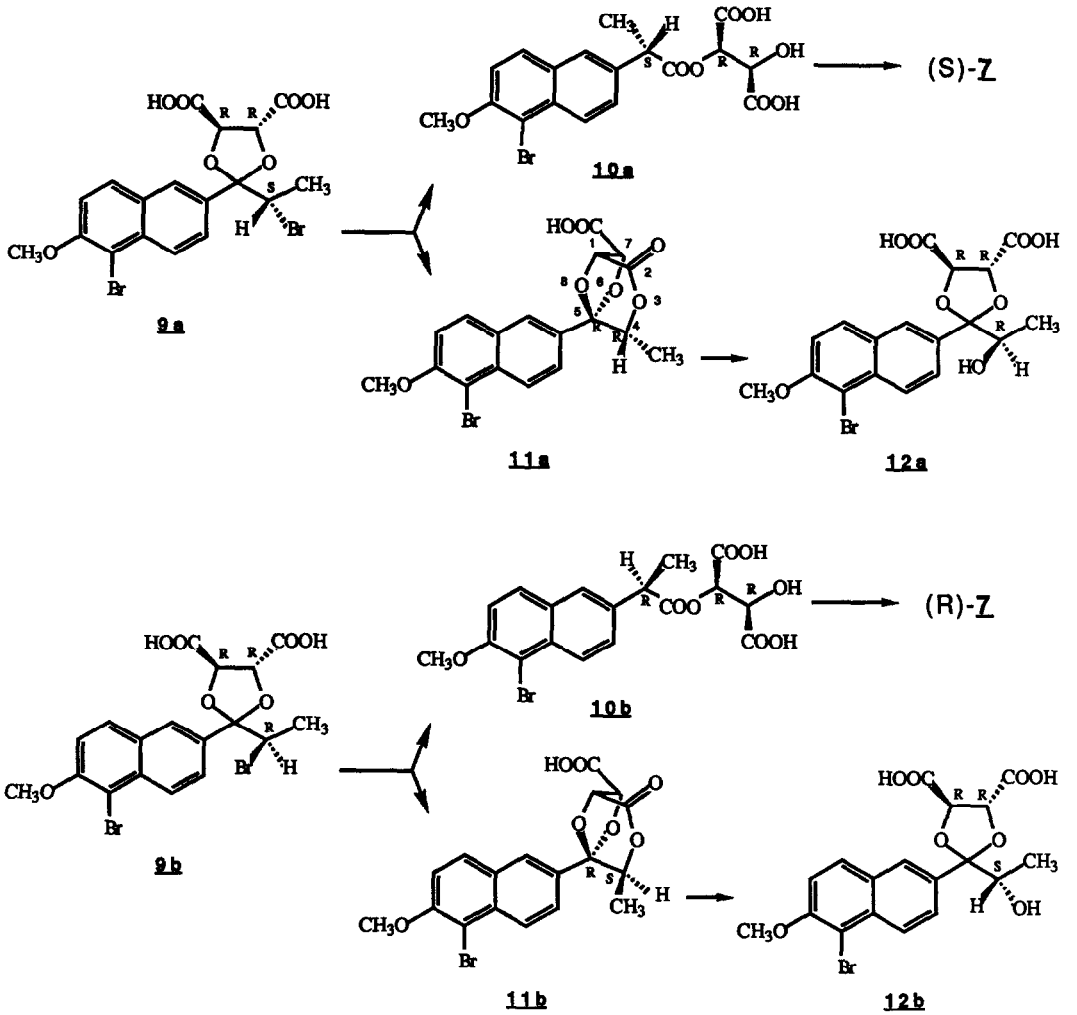
Table

Entry	Ratio **9a** : **9b**	Yield **7** [%]	Ratio[a] (S) **7** : (R) **7**	Yield **12a,b** [%]	Ratio[b] **12b** : **12a**
1	100: 0	80	>99 : 1	1 - 2	-
2	94 : 6	74	99.0 : 1.0	6 - 8	50-65 : 50-35
3	92 : 8	72	98.5:1.5	6 - 8	50-65 : 50-35
4	50 : 50	45	84.0:16.0	26	85-90 : 15-10
5	1 : 99	12	7.0 :93.0	68	>99 : 1

a) The (S)7 and (R)7 values are ±0.5.

b) Entries 1-4: reaction time 68 h; entry 5: reaction time 24 h.

Scheme 3



The formation of (S)-7 and (R)-7 occurs through the intermediate esters **10a** and **10b** respectively which hydrolyze, without epimerization, under the reaction conditions. Running the reaction on **9a** to 50-70% conversion produces a product mixture from which the intermediate ester **10a** is isolated by crystallization from dichloromethane (see Experimental Section).

It is worth noting that, carrying out the reaction at neutral or alkaline pH, epimerization at the carbon α to the ester group of **10a,b** is observed together with a net decrease of the enantiomeric purity of 7.

From the above data appears that the 1,2-aryl shift proceeds stereospecifically[8] with inversion of configuration at the migration terminus.

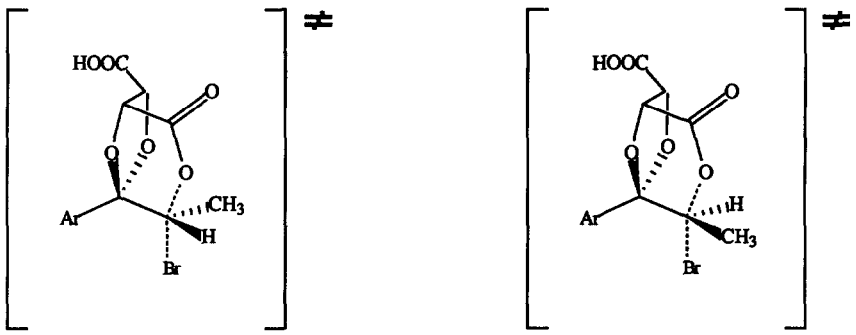
The formation of the bicyclic lactones arises from an alternative displacement reaction, i.e. intramolecular alkylation of the carboxylic group cis to the bromoalkyl unit. Based on the sensitivity of bicyclic lactones to aqueous conditions we assume that the hydroxy acetals come from hydrolysis of the lactones under the reaction conditions.

All the compounds are fully characterized by ^{1}H-NMR and I.R., mass spectral, and elemental analyses. The bicyclic lactones **11a** and **11b** are prepared independently by heating in DMF, under anhydrous conditions, the monosodium salt of bromo acetals **9a** and **9b** at 130°C for 95 h and at 110°C for 24 h, respectively.

The configuration at C_4 of **11a** and **11b** is assigned by assuming inversion of configuration in the lactones formation, while the R configuration at C_5 for both **11a** and **11b** comes from the ring closure.

It is worth noting that the alternative intramolecular displacement of bromine both in DMF and water is faster in the case of **9b** compared to diastereomer **9a** (see Experimental Section, Table, entries 1 and 5, Note a). The different sterochemical situation in the two proposed diastereomeric transition states **13a** towards **11a** and **13b** towards **11b** (Figure 2) can account for the difference in reactivity. The transition state **13a** is disfavored since it places the methyl group on the more congested concave face of the bicyclic compound.

Figure 2

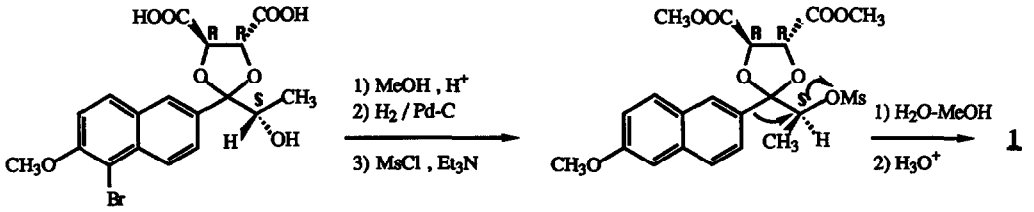


13a **13b**

The hydroxy acetal **12b**, obtained from the minor diastereomer **9b**, can be converted via 1,2-aryl shift into enantiomerically pure Naproxen **1** (Scheme 4). Thus, **12b** (>99% de) is esterified with methanol, reductively debrominated with hydrogen in the presence of Pd on charcoal, and the hydroxy group converted into the corresponding mesyl derivative. The mesyloxy acetal **14** is rearranged, by heating in aqueous methanol at 150°C, with complete inversion of configuration, into the methyl ester of **1** (90% yield, ee >99%) (see Experimental Section).

Consequently, the present method allows the preparation of Naproxen **1** starting from the bromo acetal **9a** as well as from **9b**, thus resulting in a stereoconvergent process.

Scheme 4



12b **14**

The above findings have important synthetic consequences because the acid (S)-7 is obtained in ee >99% (Table, entries 2-3) starting from either a 94:6 or 92:8 diastereomeric mixture of **9a** and **9b**.

Furthermore, an enantiomerically enriched (S)-7 (68% ee) is obtained even when starting from a 1:1 mixture of **9a** and **9b** (Table, entry 4).

The observed enantiomeric enrichment of (S)-7 (Table: entries 2-4) is mainly due to the 99-100% stereospecificity of the 1,2-aryl shift in **9a** together with the fact that the rearrangement strongly prevails *over substitution in the case of* **9a** *while the reverse is observed in the case of* **9b**.

The availability of ent-**2**, prepared from 1-(6-methoxy-2-naphthyl)-propan-1-one and (2S,3S)-tartaric acid, makes the method also suitable for the preparation of ent-**1**.

This new approach to Naproxen **1** now corrects for the somewhat less than 100% diastereoselectivity in the bromination of acetal diester **2** without the need to resort to any purification.

The diastereoselective bromination and the acidic aqueous rearrangement resulted in an industrial process for the production of Naproxen.

Experimental Section

^{1}H-NMR spectra were taken at 300 MHz. The chemical shifts are expressed in ppm (delta) and are relative to internal tetramethylsilane. Coupling constants are expressed in hertz. Optical rotations were measured in a 1-dm cell on a Perkin-Elmer 241 polarimeter. IR spectra were taken on a Perkin-Elmer 1420 instrument; positions of interesting absorptions are quoted to ±2,5 cm^{-1}. HPLC analyses were carried out on a Hewlett-Packard 1090 liquid chromatograph equipped with a HIBAR Lichrospher (5 μm; 250 mm x 4 mm) column (oven temperature = 50°C; flow = 1.8 - 2.0 ml/min).

Chromatographic separations were accomplished by flash column chromatography[9] by using silica gel (230-400 mesh) (Merck).

Melting points were measured on a Koefler apparatus and were not corrected. Chemical ionization mass spectra were recorded on a Finnigan MAT 8220 mass system operating at 110 eV, equipped with a Data General Nova 4X data system, with isobutane as ionizing agent. Satisfactory elemental analyses (C ±0.2%; H ±0.2%; Br ±0.3%) were obtained for all new compounds. The removal of solvent in vacuo refers to the evaporation of solvent at ca. 20 mmHg on a Büchi rotary evaporator. All reactions were run under nitrogen

atmosphere. All solvents and reagents were commercially available (reagent grade) and were used without further purification.

9a and mixtures of **9a,b** (Table, entries 2, 3, 4) were prepared starting from the corresponding dimethyl esters as previously described.[5]

9a: Mp 187-8°C (CH_2Cl_2) (Lit.[5] 184-6°C); $[\alpha]_D^{20}$ +39.9°, $[\alpha]_{546}^{20}$ +87.6° (c1, acetone); ^{1}H-NMR (acetone-d_6) 1.64 (d, 3H, J = 7.1), 4.57 (q, 1H, J = 7.1), 4.86 (2H, ABq, $\Delta\nu$ = 65.2, J = 6.9), 7.35 - 7.60 (5H, aromatic protons).

Preparation of bromo acetal diacid 9b. Trifluoromethanesulfonic acid (19.0 g, 0.127 mol) was added, at 40°C in 15 min, to a well stirred solution of (2R,3R)-tartaric acid dimethyl ester (116.0 g, 0.652 mol), dimethyl sulfite (43.0 g, 0.391 mol), dichloromethane (40 ml) and (2R)-2-bromo-1-(6-methoxy-2-naphthyl)-propan-1-one **8**[5] (ee >99.9%) (31.0 g, 0.106 mol). As soon as the addition of trifluoromethanesulfonic acid is over, the solution was poured into a vigorously stirred 10% aqueous sodium bicarbonate solution (200 ml) and extracted with diethyl ether (2 x 200 ml). The combined organic extracts were washed with water (2 x 200 ml) and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave a residue that was suspended in methanol (325 ml), heated at reflux for 30 min, and cooled to ambient temperature. The starting bromo ketone **8** (ee >99%) (16.1 g, 53% yield) was collected by filtration. Mp 78-80°C (Lit.[5] 78-80°C); $[\alpha]_D^{20}$ -202.3°, (c1, $CHCl_3$) (Lit.[5] -202.7°).

Evaporation of the solvent from the mother liquor gave a residue that after purification by column chromatoghraphy (eluent n-hexane : diethyl ether = 7 : 3) furnished the bromo acetal dimethyl esters (1.3 g, 2.87 mol, 2.7% yield) in the ratio 99 : 1.

N-bromoacetamide (0.73 g, 5.29 mmol) was added at ambient temperature to a stirred solution of the bromoacetal dimethyl esters (2.18 g, 4.81 mmol) in chloroform (26 ml).

The reaction mixture was kept under stirring for 2 h at ambient temperature, diluted with dichloromethane, washed with water, and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave a mixture of **4** and **3** (2.53 g, 4.76 mmol, 99% yield) in ratio **4** : **3** = 99 : 1. A solution of NaOH (0.4 g, 10 mmol) in water (3.5 ml) was added, at 20°C over 1 h, to a stirred solution of **4** and **3** (2.53 g, 4.76 mmol) in methanol (12 ml). The mixture was kept at 20°C for 2 h, then methanol was distilled off while keeping the volume constant by addition of water. The aqueous solution was extracted with dichloromethane and acidified with conc. HCl to pH 1. The mixture was extracted with diethyl ether and the combined organic extracts washed with water, dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave a mixture of bromo acetal diacids **9b** and **9a** (2.21 g, 4.38 mmol, 92% yield) in ratio **9b** : **9a** = 99 : 1. **9b**: ^{1}H-NMR (acetone-d_6) 1.68 (d, 3H, J = 6.9), 4.06 (s, 3H), 4.67 (q, 1H, J = 6.9), 4.95 (ABq, 2H, $\Delta\nu$ = 49.9, J = 6.4), 7.4 - 8.2 (5H, aromatic protons).

Reaction of bromo acetal diacids 9a,b in acidic water (Table). General Procedure. A mixture of **9a** and **9b** (3.24 g, 6.4 mmol), in the ratio given in Table, was added at 25°C to a stirred aqueous solution (pH = 5.3 at 25°C), obtained by dissolving KH_2PO_4 (12.8 g, 94.0 mmol) and NaOH (0.64 g, 11.4 mmol) in water (90 ml). The resulting solution (pH = 5.15 at 25°C) was heated at 90°C (pH = 5.16 at 90°C) and kept

at this temperature to reach conversions higher than 97%. The reaction time was 68 h for entries 1-4 and 24 h for entry 5. The heterogeneous reaction mixture (pH = 4.6 - 4.8 at 90°C) was cooled to 25°C, acidified to pH 1 with concentrated HCl and extracted with diethyl ether (3 x 50 ml). The combined organic extracts were washed with water (30 ml) and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave a residue. The amounts of **9a,b**, **10a,b**, **7**, and **12a,b** were determined via HPLC analysis (eluent: mixtures of CH_3CN and 0.04 M aqueous solution of KH_2PO_4 acidified to pH 3 with H_3PO_4). The diasteromeric composition of **9a,b**, **10a,b**, **12a,b** were determined via HPLC analysis of the corresponding dimethyl esters (eluent for **9a,b**: mixtures of CH_3OH/H_2O and for **10a,b** and **12a,b** mixtures of CH_3CN/H_2O). Analysis of the crude reaction mixture revealed that: i) a small amount (<5%) of intermediate ester **10a** (entry 1) and mixtures of esters **10a,b** in ratios **10a** : **10b** = 95 : 5 (entries 2-3), 80 : 20 (entry 4), 50 : 50 (entry 5) were present; ii) the **9a** : **9b** ratio of the unconverted bromo acetals (less than 3%) was higher than 99 : 1 for entries 1-4 and 84 : 16 for entry 5.

The enantiomeric purity of **7** was determined by HPLC analysis of the corresponding (+)-2(S)-octyl ester[10] and by ^{1}H-NMR analysis of the corresponding methyl ester in the presence of $Eu(hfc)_3$.

Purification by column chromatography on silica gel of the reaction crudes (eluent: toluene/acetic acid = 7/3) afforded pure **7**. Pure **7** was dissolved at 40°C into a solution of KOH (2.8 g, 50 mmol) in water (30 ml). The solution was added with Raney-nickel alloy (0.1 g). 35% aqueous hydrazine (1.1 g) was added, in 2 h, to the reaction mixture stirred at 40°C. The reaction mixture was kept at 40°C for 2 h, cooled to ambient temperature, filtered, acidified with HCl conc to pH 1, and extracted with diethyl ether. The combined organic extracts were washed with water and dried over sodium sulfate. Evaporation of the solvent under vacuum gave **1** or ent-**1** with unchanged enantiomeric purity with respect to that of (S)-**7** or (R)-**7**.

Isolation of the ester 10a. The bromo acetal diacid **9a** (3.24 g, 6.4 mmol) was added to a stirred solution of KH_2PO_4 (12.8 g) and NaOH (0.64 g) in water (90 ml). The reaction mixture was heated at 90°C for 16 h, cooled to ambient temperature, acidified to pH 1 with conc. HCl, and extracted with diethyl ether (3 x 50 ml). The combined organic extracts were washed with water and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave a residue that after crystallization from dichloromethane afforded **10a** (0.56 g, 1.28 mmol). M.p. 184-6°C; ^{1}H-NMR (acetone-d_6) 1.58 (d, 3H, J = 7.1), 4.04 (s, 3H), 4.05 (q, 1H, J = 7.1), 4.81 (d, 1H, J = 2.2), 5.50 (d, 1H, J = 2.2), 7.5 - 8.1 (5H, aromatic protons).

Preparation of the bicyclic lactones 11b and 11a. Sodium hydride (0.17 g, 7.0 mmol) was added at 20°C to a stirred solution of **9b** (**9a** / **9b** = 1 / 99) (3.07 g, 6.1 mmol) in dimethylformamide (40 ml). The reaction mixture was heated at 110°C for 24 h, then cooled to 40°C and concentrated under vacuum (20 mmHg). The residue was diluted with dichloromethane (60 ml) and washed with an aqueous solution (30 ml) (pH = 5.2 at 20°C) of potassium dihydrogen phosphate (4.08 g) and of dipotassium hydrogen phosphate (0.27 g). The organic phase was dried over sodium sulfate and concentrated in vacuo to give crude **11b** (2.0 g). IR (1%; CH_2Cl_2): 1760 cm^{-1} (stretching C = O); ^{1}H-NMR ($CDCl_3$) 1.13 (d, 3H, J = 6.6), 4.05 (s, 3H), 4.90 (q, 1H, J = 6.6), 4.93 (s, 1H), 5.31 (s, 1H). 7.33 - 8.33 (5H, aromatic protons). A sample was treated with diazomethane and chromatographed on a preparative tlc (eluent: diethyl ether / n-hexane =

7 / 3) to give the methyl ester of **11b**. IR (1%, CH_2Cl_2): 1765 cm^{-1} (stretching C = O). ^{1}H-NMR ($CDCl_3$) 1.15 (d, 3H, J = 6.8), 3.67 (s, 3H), 4.05 (s, 3H), 4.89 (q, 1H, J = 6.8), 4.93 (s, 1H), 5.28 (s, 1H). 7.3 - 8.3 (5H, aromatic protons).

Lactone **11a** was prepared analogously to **11b** with a reaction time of 95 h at 130°C starting from **9a**.

IR (1%; CH_2Cl_2): 1765 cm^{-1} (stretching C = O). ^{1}H-NMR ($CDCl_3$) 1.27 (d, 3H, J = 6.6), 4.05 (s, 3H), 4.90 (q, 1H, J = 6.6), 4.95 (s, 3H), 5.24 (s, 1H). 7.3 - 8.3 (5H, aromatic protons).

Preparation of the hydroxy acetal 12b and 12a from 11b and 11a, respectively. A two phase system consisting of a solution of **11b** (0.16 g, 0.38 mmol) in dichloromethane (1.0 ml) and of an aqueous solution (1.0 ml) of sodium hydroxide (33.0 mg, 0.82 mmol) was stirred at 20°C for 2 h. The aqueous phase was separated, acidified with hydrochloric acid to pH 1.0, and extracted with diethylether (2 x 3 ml). The combined organic phases were washed with water and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave **12b** (0.12 g). ^{1}H-NMR (acetone-d_6) 1.03 (d, 3H, J = 6.6), 4.05 (s, 3H), 4.32 (q, 1H, J = 6.6), 5.08 (ABq, 2H, $\Delta\nu$ = 38.4, J = 4.0), 7.5 - 8.2 (5H, aromatic protons).

Hydroxy acetal **12a** was prepared starting from **11a** according to the above procedure. ^{1}H-NMR (acetone-d_6) 1.12 (d, 3H, J = 6.6), 4.05 (s, 3H), 4.15 (q, 1H, J = 6.6), 5.00 (ABq, 2H, $\Delta\nu$ = 31.9, J = 5.13), 7.5 - 8.4 (5H, aromatic protons).

Preparation of Naproxen 1 from 12b. Methanesulphonic acid (0.05 g, 0.52 mmol) was added at 20°C to a stirred solution of the hydroxy acetal diacid **12b** (de >98%) (2.65 g, 6.0 mmol) in methanol (26.5 ml). The resulting solution was heated to 65°C and stirred at this temperature for 2 h. The reaction mixture was cooled to room temperature, diluted with dichloromethane, and poured into water under stirring. The organic phase was washed with water, with a 2% aqueous solution of sodium bicarbonate, and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave the hydroxy acetal dimethyl ester of **12b** (1.56 g, 3.3 mmol, 85% yield). ^{1}H-NMR ($CDCl_3$) 1.07 (d, 3H, J = 6.6), 3.30 (s, 3H), 3.87 (s, 3H), 4.03 (s, 3H), 4.13 (q, 1H, J = 6.6), 5.05 (ABq, 2H, $\Delta\nu$ = 46.2, J = 4.0), 7.2 - 8.2 (5H, aromatic protons).

A mixture of the hydroxy acetal dimethyl ester of **12b** (1.56 g, 3.3 mmol), 5% palladium on charcoal (150 mg) and methanol (30 ml) was stirred at ambient temperature under hydrogen atmosphere for 1 h. The catalyst was removed by filtration, evaporation of the solvent under reduced pressure gave the hydroxy acetal dimethyl ester (1.25 g. 3.2 mmol, 97% yield).

^{1}H-NMR ($CDCl_3$) 1.06 (d, 3H, J = 6.6), 3.13 (d, 1H, J = 7.5), 3.30 (s, 3H), 3.83 (s, 3H), 3.90 (s, 3H), 4.16 (dq, 1H, $J_{CH\text{-}CH}$ = 6, $J_{CH\text{-}OH}$ = 7.5), 5.06 (ABq, 2H, $\Delta\nu$ = 2.94, J = 4.2), 7.13 - 8.0 (6H, aromatic protons).

Methanesulphonyl chloride (0.44 g, 3.8 mmol) was added, at 0°C in 10 min, to a stirred solution of the hydroxy acetal dimethyl ester (1.25 g, 3.2 mmol) and of triethylamine (0.40 g, 4.0 mmol) in dichloromethane (15 ml). The reaction mixture was kept at room temperature for 1 h, poured into water, extracted with dichloromethane (2 x 20 ml), and the combined organic extracts dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave the mesyloxy acetal dimethylester **14**: (1.45 g, 3.1

mmol, 97% yield). ^{1}H-NMR ($CDCl_3$) 1.38 (d, 3H, J = 6.6), 2.93 (s, 3H), 3.37 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 4.80 (q, 1H, J = 6.6), 5.03 (ABq, 2H, $\Delta\nu$ = 5.09, J = 4.2), 7.1 - 8.0 (6H, aromatic protons).

A mixture of **14** (1.45 g, 3.1 mmol), methanol (11 ml) and water (0.4 ml) was heated in a sealed tube at 150°C for 5 h. The reaction mixture was cooled to room temperature, diluted with water (15 ml), and extracted with dichloromethane (2 x 25 ml). The combined organic extracts were washed with water and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave a crude product that after column chromatography (eluent: dichloromethane) afforded the enantiomerically pure methyl ester of **1** (0.64 g, 2.63 mmol, 85% yield) as determined by ^{1}H-NMR analysis in the presence of $Eu(hfc)_3$. Mp 88°C (Lit.[11] 88°C); $[\alpha]_D^{20}$ +78°; (c1, $CHCl_3$) (Lit.[11]); $[\alpha]_D^{20}$ +77°; (c1, $CHCl_3$). A mixture of the methyl ester of **1** (0.64 g, 2.63 mmol), acetic acid (2.5 ml), concentrated HCl (3 ml), and water (22.5 ml) was stirred at 85°C up to complete hydrolysis (the reaction was monitored by tlc). The reaction mixture was cooled to room temperature and extracted with dichloromethane. The organic phase was washed with water and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave a residue that after chromatography on silica gel (eluent: diethyl ether / n-hexane) afforded the enantiomerically pure Naproxen **1** (0.54 g, 2.37 mmol, 90% yield). Mp 154-5°C (Lit.[12] 154-155°C); $[\alpha]_D^{20}$ +68.5°; (c1, $CHCl_3$) [Lit.[12] $[\alpha]_D^{20}$ +68.5°; (c1, $CHCl_3$)].

References

1. Rahway, *The Merck Index.* Merck & Co., Inc. **1983**, 10th Ed., 920.
2. *Scrip World Pharm. News* **1986**, **26**, 12.
3. Castaldi, G.; Cavicchioli, S.; Giordano, C.; Uggeri, F. *Angew. Chem.* **1986**, **98**, 273. *Angew. Chem. Int. Ed. Engl.* **1986**, **25** , 259.
4. Castaldi, G.; Cavicchioli, S.; Giordano, C.; Uggeri, F. *J. Org. Chem.* **1987**, **52**, 3018; *ibidem* **1987**, 52, 5642; Giordano, C.; Castaldi, G.; Cavicchioli, S.; Uggeri, F. *Eur. Pat. Appl.* EP 158255, **1985**; *USP* 4,697,036, **1987**; *USP* 4,734,507, **1988**.
5. Castaldi, G.; Giordano, C. *Synthesis* **1987**, 1039.
6. Attempts to enhance the de value by crystallization or by column chromatography failed.
7. This corresponds to ≥99% ee when starting from diastereomerically pure **9b**, which corresponds to highly stereospecific reaction with inversion of configuration.
8. The term stereospecific and is used as defined in Eliel, E.L. "Stereochemistry of Carbon Compounds"; McGraw-Hill, New York, **1962**, 434-446.
9. Still, A. C.; Kahn, M.; Mitra A. *J. Org. Chem.* **1978**, **43**, 293.
10. Johnson, D. M.; Reuter, A.; Collins, J. M.; Thompson, G. F. *J. Pharm. Sci.*.**1979**, 68, 112.
11. Harrison, I. T.; Lewis, B.; Nelson, P.; Rooks, W.; Ruszkowski, A.; Tomolonis, A.; Fried, J. H. *J. Med. Chem.* **1970**, **13**, 203.
12. *British Pharmacopœia* **1973**, A66.