tube in volumes of 2 mL/kg. When indicated, intraperitoneal, subcutaneous, or intravenous routes are used. Hypertensive rats are anesthetized with ether. A polyethylene catheter (PE 10 fused to PE 50, 7.5–9.5 cm long depending on body weight) is inserted into the abdominal aorta via the caudal artery. The skin incision is closed with sutures. Animals are then placed into plastic restrainers where they quickly recover consciousness. A 5% dextrose in water solution is infused into the arterial line (0.2 mL/h) via a T-adapter to assure patency of the cannula. The catheter is connected to a P23Gb pressure transducer. Analog blood pressure signals are recorded on an oscillograph. A cardiovascular monitoring system (Buxco Electronics Inc.) and a digital computer may be used to provide averages over 30 min. Mean values are used for comparative purposes. Heart rate is derived from the Buxco system or from the pulse-pressure trace by a tachometer. Animals are removed from the restrainer after approximately 90 min, dosed, returned to the holders, and usually observed for 4 h. Animals are fasted prior to the test. Blood pressure and heart rate values are usually noted at half-hour intervals.

Acknowledgment. We thank E. Eynon and S. Nelson for testing selected compounds in the spontaneously hypertensive rat.

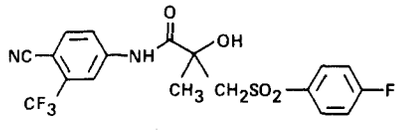
Resolution of the Nonsteroidal Antiandrogen 4′-Cyano-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-3′-(trifluoromethyl)-propionanilide and the Determination of the Absolute Configuration of the Active Enantiomer

Howard Tucker* and Glynne J. Chesterson

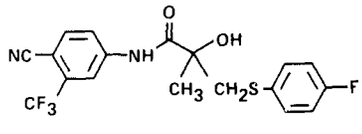
Imperial Chemical Industries PLC, Pharmaceuticals Division, Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4TG Great Britain. *Received September 29, 1987*

The nonsteroidal antiandrogen 4′-cyano-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-3′-(trifluoromethyl)-propionanilide (1) (ICI 176334) has been resolved by chromatographic separation of the diastereomeric (*R*)-camphanyl esters of the precursor thioether **2** followed by hydrolysis and oxidation of the isolated enantiomers. In addition, an asymmetric synthesis of (*S*)-3-bromo-2-hydroxy-2-methylpropanoic acid (**11**) and subsequent conversion into the (*S*)-sulfone **6a** has established that the more potent enantiomer of **1** has the *R* absolute configuration.

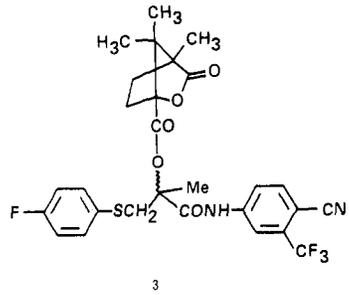
We have reported the discovery of a novel, peripherally selective, nonsteroidal antiandrogen, 4′-cyano-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-3′-(trifluoromethyl)propionanilide (1) (ICI 176334), which is currently being developed for the treatment of androgen-responsive benign and malignant diseases.[1,2] We report here the preparation of the enantiomers of 1 together with their biological activities and the assignment of the absolute stereochemistry of the more active enantiomer.



1

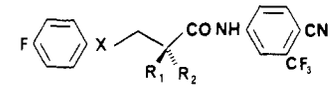


2



3

Our route to the enantiomers of 1 focused on the resolution of the thioether **2**,[2] the enantiomers of which could then be oxidized to the required sulfones by known means.[2] Reaction of **2** with (*R*)-(−)-camphanoyl chloride in pyridine furnished the diastereomeric esters **3**, which were separated by careful flash chromatography on silica gel and were judged to be pure on the basis of TLC and 400-MHz NMR analysis. The individual pure diastereomeric esters were each hydrolyzed, without racemization, with methanolic sodium hydroxide to give the enantiomeric alcohols **4** and **5**. The optical purity of these enantiomeric alcohols was



	X	R_1	R_2	Configuration
4	S	CH_3	OH	S
5	S	OH	CH_3	R
6	SO_2	CH_3	OH	S
7	SO_2	OH	CH_3	R

determined by a HPLC method with use of a Spherisorb 5μ-NH_2 column doped with (*R*)-(−)-*N*-benzoylphenylglycine.[3] This method was able to detect 1% of the (+)-enantiomer in the (−)-enantiomer, but because of unfavorable peak overlap, the limit of detection of the (−)-enantiomer in the (+)-enantiomer was only 5%. The observed rotations of the enantiomeric thioethers **4** and **5** could be consistent with the presence of 5% of the (−)-enantiomer **5** in **4**. Both enantiomeric thioesters **4** and **5** were oxidized to the corresponding sulfones **6** and **7** with use of *m*-chloroperoxybenzoic acid in methylene chloride solution.

Although this method of resolution proved satisfactory for preparing the enantiomers **4** and **5**, we were seeking

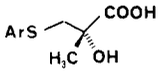
(1) Furr, B. J. A.; Valcaccia, B.; Curry, B.; Woodburn, J. R.; Chesterson, G.; Tucker, H. *J. Endocrinol.* **1987**, *113*, R7-9.
(2) Tucker, H.; Chesterson, G. J.; Crook, J. W., submitted for publication in *J. Med. Chem.*
(3) We thank R. Gaskell, Physical Chemistry Section, who carried out this analysis.

0022-2623/88/1831-0885$01.50/0

Table I

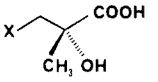
compd	mp, °C	formula	analysis	optical rotation, deg	solvent	ED_{50}, mg/kg
4	95–97	$C_{18}H_{14}F_4N_2O_2S$	C, H, N	+2.42	MeOH	30
4a	94.5–96.5	$C_{18}H_{14}F_4N_2O_2S$	C, H, N	+2.32	MeOH	
5	94–96	$C_{18}H_{14}F_4N_2O_2S$	C, H, N	−3.06	MeOH	0.5
6	179–180	$C_{18}H_{14}F_4N_2O_4S$	C, H, N	+81.22	MeOH	30
6a	178–179	$C_{18}H_{14}F_4N_2O_4S$	C, H, N	+81.47	MeOH	
7	179–180	$C_{18}H_{14}F_4N_2O_4S$	C, H, N	−80.04	MeOH	0.5
11	109–113	$C_4H_7BrO_3$	C, H, N	−11.78	MeOH	
12	157–159	$C_9H_{12}BrNO_3$	C, H, N	−126.5	$CHCl_3$	
13	106–107	$C_{12}H_{10}BrF_3N_2O_2$	C, H, N	+50.73	MeOH	
1						0.5
2						0.5

a more convergent, asymmetric synthesis that would provide easy access for a variety of resolved analogues. The obvious target for an asymmetric synthetic approach would be the enantiomeric α-hydroxy acids **8** or precursors such as the epoxy acid **9** or halohydrin acids **10** (only the *S* enantiomers shown). Terashima and co-workers[4,5] have



8

9

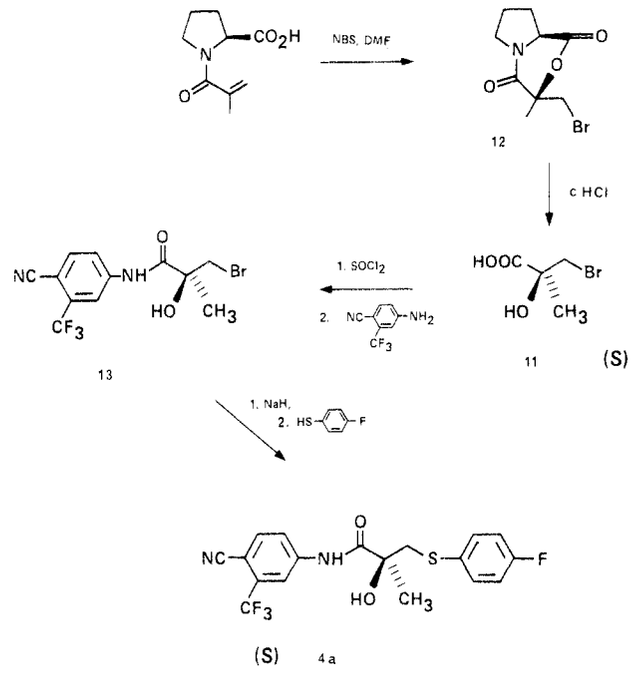


10 X = Halogen
11 X = Br

described an asymetric synthesis of α-hydroxy acids based on a bromolactonization reaction of α,β-unsaturated amides of (*S*)-proline, and we felt that a suitable modification of this reaction should furnish the bromohydrin acid **11**, which from the mechanistic arguments advanced by the Japanese workers should have the *S* absolute configuration. Thus reaction of the *N*-methacrylamide of (*S*)-proline with *N*-bromosuccinimide in dimethylformamide gave a 50% yield of the bromolactone **12**, which was shown to be a single diastereoisomer by proton and ^{13}C NMR. Acid hydrolysis yielded the bromohydrin acid **11**, which again on the basis of literature precedent should be optically pure.[6] The acid **11** was coupled with 4-cyano-3-(trifluoromethyl)aniline. The amide **13** obtained was further reacted with the sodium salt of 4-fluorothiophenol to give the dextrorotatory thioether **4a**,[7] (Scheme I), which was identical with the thioether **4** prepared earlier by hydrolysis of the less polar camphanyl ester of **2**. Oxidation provided the dextrorotatory sulfone **6a**, which, from its method of synthesis, has the *S* absolute configuration.

The thioether and sulfone enantiomers were tested for antiandrogen activity in intact male rats by the method described earlier.[2] It is clear from the test data presented in Table I that the enantiomer with the *R* absolute configuration is 60-fold more potent as an antiandrogen than the *S* enantiomer. We had shown previously[2] that the thioether **2** was oxidized rapidly in vivo to the sulfone **1**, and this appears to be true for the enantiomers also.

Scheme I



Although this approach is not suitable for the general synthesis of the active enantiomers of analogous antiandrogens, which would require the inaccessible and expensive (*R*)-proline as starting material, it has enabled us to assign the absolute configuration to the more active enantiomer of **1**. This will be useful in molecular modeling studies of antagonists–receptor interactions in our series of nonsteroidal antiandrogens, especially because of the importance of the hydroxyl group interactions in these compounds.[8]

Experimental Section

All melting points are uncorrected and were obtained with an Electrothermal capillary melting point apparatus. NMR spectra were recorded on either a JEOL FX90Q, a Varian EM390, or a Bruker WM400 instrument. Spectra were run on all isolated intermediates and final products and were consistent with the structural assignments. Optical rotations were recorded on a Perkin-Elmer 241 instrument at 24 °C with use of the sodium D line.

A. Resolution of 2 via the (*R*)-Camphanoyl Esters. A solution of **2**[2] (10.5 g) and (*R*)-(−)-camphanoyl chloride (8.8 g) in pyridine (85 mL) was heated on a steam bath for 3 h. The reaction mixture was cooled and evaporated to dryness. The residue was flash chromatograhed on silica gel (Merck Type 9385) with 2.5% ethyl acetate in methylene chloride as solvent. The pure fractions were collected, and mixed fractions were rechromatographed. The

(4) Jew, S.-S.; Terashima, S.; Koga, K. *Tetrahedron* **1979**, *35*, 2337.
(5) Jew, S.-S.; Terashima, S.; Koga, K. *Tetrahedron* **1979**, *35*, 2345.
(6) During the preparation of the manuscript, a paper appeared describing inter alia the synthesis of the bromo acid **11** by using the same modification of Terashima's route (Corey, P. F. *Tetrahedron Lett.* **1987**, *28*, 2801).
(7) The suffix **a** refers to enantiomers prepared by the synthetic route and, as is shown, **4** and **4a** are identical, as are **6** and **6a**.
(8) Glen, A. T.; Hughes, L. R.; Morris, J. J.; Taylor, P. J. Proceedings of the Third SCI-RSC Medicinal Chemistry Symposium; Lambert, R. W., Ed.; Royal Society of Chemistry: London, 1986; p 345.

fractions containing the less polar product were evaporated to dryness, and the residue was crystallized from a mixture of petroleum ether, bp 60–80 °C, and toluene to give 5.05 g of less polar **3**, mp 124–126 °C.

The more polar product was collected in a like manner as a foamy solid: yield 6.7 g; mp 56–66 °C.

To a suspension of the less polar camphanic ester **3** (1.0 g) in methanol (7.5 mL) was added aqueous sodium hydroxide (75 mg in 3 mL of water), and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with water (50 mL) and extracted with ether (5 × 25 mL). The combined ether extracts were washed successively with 25-mL portions of 2 N HCl, water, and brine and were dried ($MgSO_4$). The solvent was evaporated, and the residue was crystallized from a mixture of petroleum ether, bp 60–80 °C, and toluene to give **4**: yield 480 mg (70%); mp 95–97 °C; [α] +2.42° (*c* 0.987, MeOH). Anal. C, H, N.

The more polar diastereomer **3** was treated in a like manner to yield **5** (32%): mp 94–96 °C; [α] −3.06° (*c* 1.01, MeOH). Anal. C, H, N.

Alcohol **4** was oxidized to sulfone **6** with *m*-chloroperoxybenzoic acid in CH_2Cl_2 as described earlier.[2] Sulfone **6** was obtained in 56% yield: mp 179–180 °C; [α] +81.22° (*c* 1.20, MeOH). Anal. C, H, N.

Similarly, **5** yielded **7** (74%): mp 179–180 °C; [α] −80.04° (*c* 1.02, MeOH). Anal. C, H, N.

B. Asymmetric Synthesis. 3(*S*)-(Bromomethyl)-3(*S*)-methyl-1,4-dioxo-3,4,6,7,8,8a(*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine (12). A DMF solution of NBS (2.9 g in 20 mL of DMF) was added to a stirred solution of (*S*)-*N*-methacrylolyproline (3.0 g) in DMF (20 mL) under argon at room temperature. The reaction mixture was stirred for 20 h and then evaporated to dryness. The residue was diluted with water (100 mL) and extracted twice with ethyl acetate (75 mL each time). The combined ethyl acetate extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was crystallized from ethyl acetate to give **12**: yield 2.1 g (49%); mp 157–159 °C; [α] −126.5° (*c* 1.19, $CHCl_3$). Anal. C, H, N.

(*S*)-(−)-3-Bromo-2-hydroxy-2-methylpropanoic Acid (11). A mixture of **12** (4.28 g) in concentrated HCl (35 mL) was heated under reflux for 8 h. The cooled reaction mixture was diluted with brine (70 mL) and extracted with ethyl acetate (3 × 30 mL). The combined ethyl acetate extracts were washed with saturated $NaHCO_3$ solution (3 × 30 mL). The $NaHCO_3$ extracts were acidified (HCl) and extracted with EtOAc (3 × 30 mL). The EtOAc extracts were dried ($MgSO_4$) and evaporated to dryness. The residue was crystallized from toluene: yield 2.18 g (73%); mp 109–113 °C; [α] −11.78° (*c* 1.16, MeOH). Anal. C, H, N.

(*S*)-(+)-3-Bromo-4′-cyano-2-hydroxy-2-methyl-3′-(trifluoromethyl)propionanilide (13). Thionyl chloride was added to a stirred solution of **11** (1.0 g) in *N*,*N*-dimethylacetamide (20 mL) maintained at −5 °C. The resulting mixture was stirred at −5 °C for 30 min, and a solution of 4-cyano-3-(trifluoromethyl)aniline (0.92 g) in *N*,*N*-dimethylacetamide (3 mL) was added rapidly. The reaction mixture was stirred at −5 to 0 °C for 3 h and was allowed to warm to room temperature. The *N*,*N*-dimethylacetamide was distilled off, and the residue was diluted with sodium bicarbonate solution and then extracted with ether (3 × 50 mL). The ether extracts were dried ($MgSO_4$) and evaporated to dryness to give an oil, which crystallized on standing. The solid was crystallized from a mixture of petroleum ether, bp 60–80 °C, and toluene to give **13**: 1.05 g (60%); mp 106–107 °C; [α] +50.73° (*c* 1.1, MeOH). Anal. C, H, N.

(*S*)-(+)-4′-Cyano-3-[(4-fluorophenyl)thio]-2-hydroxy-2-methyl-3′-(trifluoromethyl)propionanilide (4a). A solution of **13** (400 mg) in THF (5 mL) was added to a suspension of the sodium salt of 4-fluorothiophenol [prepared from a 60% sodium hydride dispersion in oil (60 mg)] and 4-fluorothiophenol (195 mg) in THF (15 mL). The mixture was stirred under argon for 20 h. Water (20 mL) was added carefully, and the mixture was extracted with ethyl acetate (3 × 25 mL). The combined EtOAc extracts were dried ($MgSO_4$) and evaporated to dryness, and the residue was crystallized from a toluene–petroleum ether, bp 60–80 °C, mixture (1:1) to give **4a**: 220 mg; mp 94.5–96.5 °C; [α] +2.32° (MeOH). Anal. C, H, N.

(*S*)-(+)-4′-Cyano-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-3′-(trifluoromethyl)propionanilide (6a). Compound **4a** was oxidized to sulfone **6**, with *m*-chloroperoxybenzoic acid in CH_2Cl_2 as described previously.[2] The sulfone melted at 178–179 °C, [α] +81.47° (*c* 0.84, MeOH). Anal. C, H, N.

Pharmacology. Antiandrogen Activity in Intact Rats. Groups of five male rats (170–190 g) were dosed orally with the test compound, ball-milled in 0.5% polysorbate, once daily for 4 days at various doses. Animals were killed 24 h after the last dose, and the seminal vesicles were dissected, blotted, and weighed. Each test had a control group that received 0.5% polysorbate alone. The percent inhibition was calculated with use of a cumulative castrate control group as the 100% effect. The ED_{50} values were calculated from the dose–response curves.

Acknowledgment. We thank Dr. B. J. A. Furr, B. Valcaccia, B. Deegan, and C. Lunning for providing the biological data.

Book Reviews

Trends in Medicinal Chemistry. Edited by E. Mutschler and E. Winterfeldt, VCH Publishers, New York, NY. 1987. ix + 634 pp. 17 × 24 cm. ISBN 0-89573-616-0. $99.50.

This book is a collection of the inaugural, plenary, and main lectures presented at the IXth International Symposium on Medicinal Chemistry which was held in West Berlin in September 1986. As stated in the preface, it represents an excellent overview of current and future trends in medicinal chemistry. Following the inaugural lecture by K. H. Büchel on "Achievements, Problems and Future Aspects of Drug Research", four plenary lectures on "New Trends and Developments in Synthesis of Biologically Active Compounds" (E. Winterfeldt), "Drug–Receptor Interactions: A Dual Perspective" (D. J. Triggle), "Cell Cultures in Pharmacobiological Research" (M. Lazdunski and colleagues), and "Strategies in Drug Design" (J. K. Seydel) are presented. All of these lectures are well written, thoroughly covered and referenced with recent citations, and will clearly appeal to a broad range of medicinal chemists.

Following the initial presentations, this volume is divided into five main areas dedicated to "General Methodological Approaches", "Instrumental Techniques Useful for Medicinal Chemistry", "Progress in Organic Synthesis Useful for Drug Development", "How to Prevent Toxicity?", and "New Trends in Receptor Research". Each one of these areas is addressed by two to four presentations on more specific descriptions of more specialized topics in the area. Each subject is treated by well-known authorities in the field. Again each field is addressed in clearly understood, well-written presentations that certainly will appeal to almost all medicinal chemists.

The remaining approximately half of the volume is directed toward 10 "Specialized Topics", namely: "Agents Influencing Learning and Memory", "Drugs Acting at the Dopamine Receptors", "New Trends in Central Analgesics", "Adenosine Receptor Agonists and Antagonists", "New Cardiovascular Agents", "New Antiulcer Agents", "Antimicrobial and Antiviral Agents with New Mechanism of Action", "Immunomodulating