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# Syntheses of enantiomerically pure (*R*)- and (*S*)-bicalutamide

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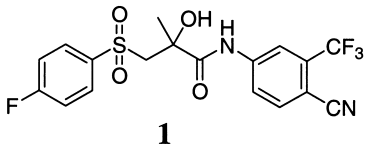
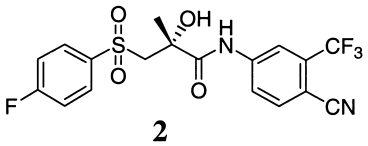
**Abstract**—The racemic antiandrogen bicalutamide is the leading antiandrogen used for the treatment of prostate cancer. The (*R*)-isomer possesses virtually all of the activity, but both isomers are metabolized by the liver. A convenient synthetic route to the active enantiomer would be an attractive option for patients who are hepatically impaired. We now demonstrate a rather short synthesis of (*R*)-bicalutamide, starting with a naturally occurring, chiral precursor. © 2002 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

The non-steroidal antiandrogen bicalutamide (**1**), which is sold under the trade name Casodex®,[1] is the leading antiandrogen used for the treatment of prostate cancer. The drug competes with testosterone and dihydrotestosterone for binding sites on the prostate and other androgen-sensitive tissues. Bicalutamide does not bind as tightly to the receptors as do testosterone and dihydrotestosterone. However, it has the advantages that it has little or no agonist activity,[2,3] binds preferentially to receptors located outside the central nervous system and thus causes little increase in testosterone levels,[3,4] and is well tolerated with few side effects.[5] Bicalutamide is a racemic mixture[6–8] with most of its activity residing in the (*R*)-enantiomer (**2**).

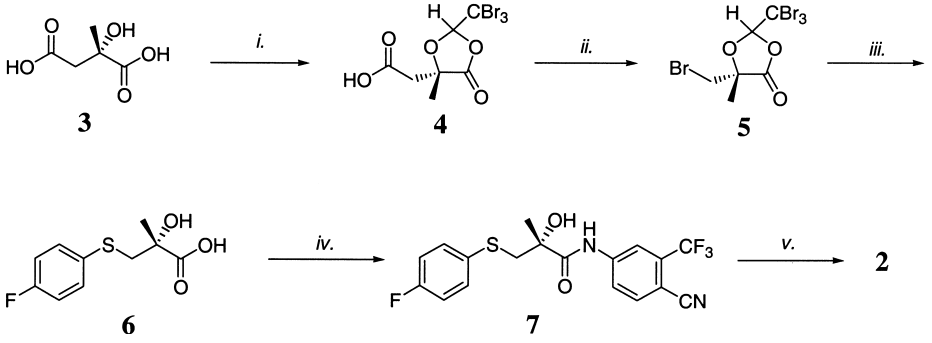


**1**



**2**

Both enantiomers of bicalutamide are metabolized in the liver.[9] The (*S*)-isomer is metabolized and eliminated much faster than is the (*R*)-isomer thus putting much stress on the liver, particularly for patients with hepatic impairment. Bicalutamide is undergoing clinical evaluations as a monotherapy for advanced prostate cancer with doses being 3–4 fold higher than those that are currently used in conjunction with hormone therapy.[10–16] It is therefore advantageous to administer a single active enantiomer to reduce the dosage



**Scheme 1.** (i) Bromal, $H_2SO_4$; (ii) 2-mercaptopyridine *N*-oxide, DCC, $CBrCl_3$; (iii) 1, NaOH; 2, 4-fluorobenzenethiol; (iv) thionyl chloride, 4-amino-2-trifluoromethylbenzonitrile; (v) *m*CPBA.

*Keywords*: antiandrogen; enantiomeric purity; bicalutamide; Casodex®; citramalic acid.

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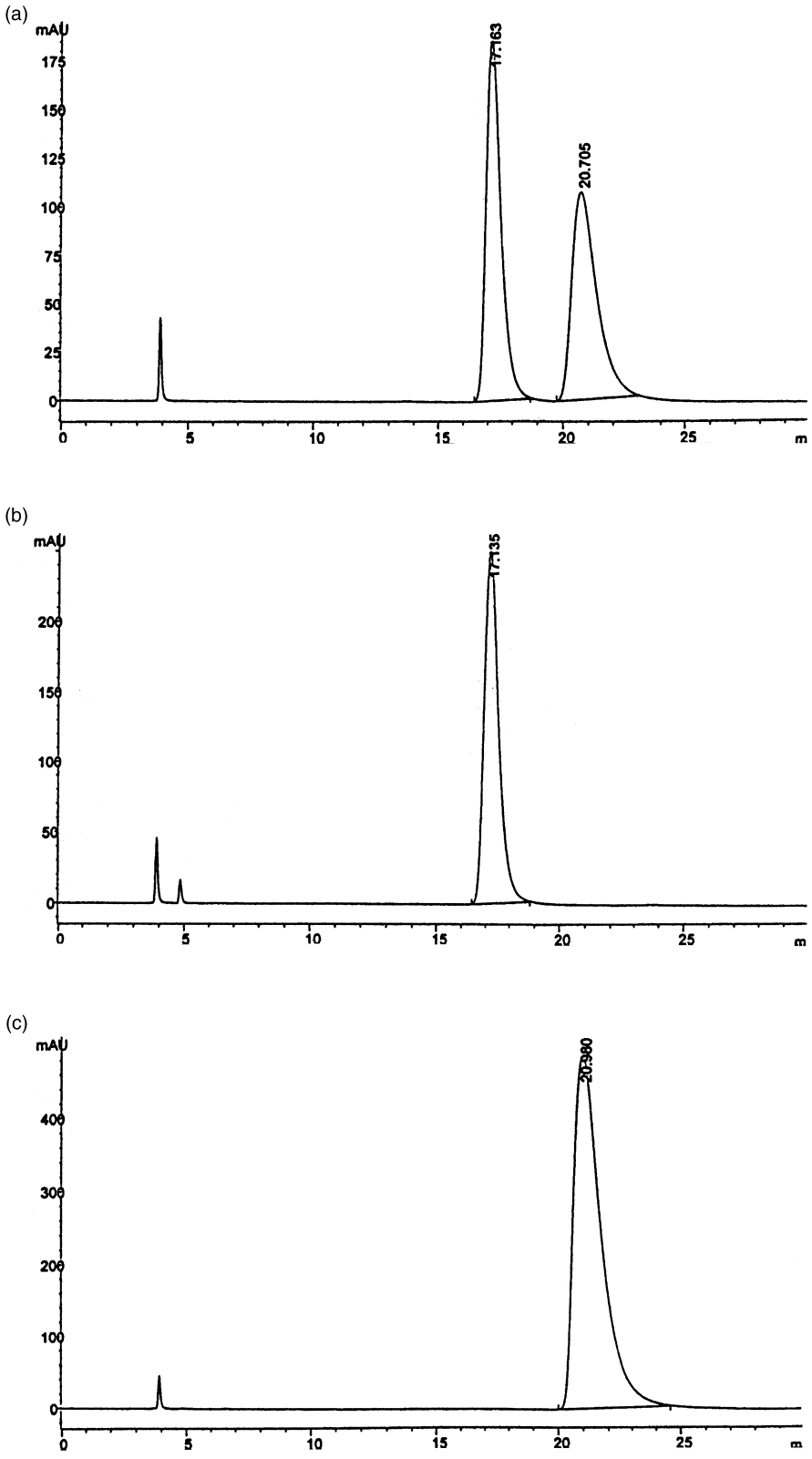


**Figure 1.** (a) Chromatogram for a mixture of (*R*)- and (*S*)-bicalutamide. (b) Chromatogram for (*R*)-bicalutamide. (c) Chromatogram for (*S*)-bicalutamide.

and demand on the liver. One means of obtaining an excess of one enantiomer is by chiral resolution of racemic material, and different means have been demonstrated.[17,18] More appealing, however, would be to have a suitable synthetic route to the active enantiomer.

## 2. Results and discussion

A synthesis of (*S*)-bicalutamide has been demonstrated starting from L-proline.[17] In this six-step synthesis, the stereocenter is established by the use of proline as a chiral

auxiliary.[19] The proline moiety is later removed by hydrolytic cleavage. This route has also been applied successfully to synthesize the active (*R*)-isomer from D-proline.[20,21]

Because the chiral auxiliary to the active isomer of bicalutamide is the unnatural isomer of the amino acid, synthesis of (*R*)-bicalutamide via this route would not be desirable from a cost perspective. More desirable would be to employ a naturally occurring compound having the desired stereochemistry. We have synthesized the active (*R*)-bicalutamide from the natural isomer of citramalic acid (Scheme 1). Starting with (*S*)-citramalic acid, we protected the α-hydroxyacid by forming the dioxolanone **4** using bromal. Barton's decarboxylative bromination method[22] was then employed, which enabled us to avoid the use of expensive and toxic materials associated with the Hunsdiecker reaction. Due to the change in the priority of substituents, at this stage the nomenclature of the chiral center changed from (*S*) to (*R*). Deprotection was accomplished both under aqueous acidic and basic conditions. Basic hydrolysis was preferred because, unlike acid hydrolysis, the reaction proceeded nicely at room temperature and enabled formation of the sulfide **6** to be accomplished in the same pot.

Formation of the acylanilide **7** was attempted by various means. Carbodiimide couplings did not lead to acceptable yields, even at elevated temperatures. Amidation via active esters also proved unsuitable. Mixed anhydride couplings led to the formation of the undesired product. The amidation was thus accomplished via in situ generation of the acid chloride. Thionyl chloride proved to be the best reagent for this procedure. With the acylanilide **7** in hand, oxidation to the sulfone **2** proceeded smoothly with *m*CPBA. We have also used this procedure to synthesize the less active (*S*)-bicalutamide from the unnatural (*R*)-citramalic acid. Analyses of both the synthesized (*R*)-bicalutamide and (*S*)-bicalutamide by HPLC using a chiral column revealed no detectable amounts of the undesired enantiomer (Fig. 1a–c).

## 3. Conclusion

We believe that administration of pure (*R*)-bicalutamide will be an attractive option for hepatically impaired patients who use bicalutamide either as monotherapy or in conjunction with other treatments. The method described in this article provides a short synthetic route to the active enantiomer of the most widely prescribed non-steroidal antiandrogen in the world. The use of a naturally occurring chiral precursor ensures that the correct stereochemistry has been established via a readily available starting compound.

## 4. Experimental

### 4.1. General

Unless otherwise stated, all reagents were purchased from Aldrich and were used without further purification. Citramalic acid was purchased from Acros. 4-Amino-2-trifluoromethylbenzonitrile was purchased from Maybridge. Coupling constants are reported in hertz. All melting points are uncorrected. Enantiomeric excess was determined using a Chiralcel OJH column (Chiral Technologies).

**4.1.1. [(4*S*)-4-Methyl-5-oxo-2-(tribromomethyl)-1,3-dioxolan-4-yl]acetic acid (4).** Bromal (25.0 g; 89.1 mmol) and (*S*)-citramalic acid (11.0 g; 74.2 mmol) were cooled to 0°C in a 125 mL flask under inert atmosphere. Sulfuric acid/acetic acid (1/1; 25 mL) was added dropwise with stirring. After 2 h the contents were a yellow solution with a white precipitate. The ice bath was removed and the reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ice and extracted 4× with ethyl acetate. The organic layer was back extracted with water and then was dried with $MgSO_4$. After filtration, the filtrate was concentrated to an oil. The product was obtained as a white solid after crystallization from toluene/hexanes. Yield: 23.2 g (77%); mp 151°C (sublimes); MS ($FAB^+$) 433 (M+Na); $^1H$ NMR (300 MHz, $CDCl_3$, $\delta$): 5.77 (s, 1H), 3.07 (d, $J$=18.3 Hz, 1H), 3.06 (d, $J$=18.3 Hz, 1H), 1.74 (s, 3H); $^{13}C$ NMR (75.4 MHz, $CDCl_3$, $\delta$): 174.1, 172.3, 105.6, 79.6, 43.7, 42.7, 25.4; IR: 3158, 2939, 1825, 1792, 1732; UV: $\lambda_{max}$ 208, $\lambda_{1/2max}$ 237. Anal. Calcd for $C_7H_7Br_3O_5$: C, 20.46; H, 1.72. Found: C, 20.89; H, 1.74.

**4.1.2. (5*R*)-5-(Bromomethyl)-5-methyl-2-(tribromomethyl)-1,3-dioxolan-4-one (5).** The dioxolanone **4** (102.5 mg; 0.250 mmol) and 2-mercaptopyridine *N*-oxide (34.4 mg; 0.280 mmol) were suspended in $CBrCl_3$ (1.5 mL). The reaction mixture was heated to reflux and a solution of DCC (103 mg; 0.500 mmol) in $CBrCl_3$ (1.0 mL) was added slowly over the course of 30 min. The reaction mixture was stirred for an additional hour. The product was purified by silica gel chromatography ($CH_2Cl_2$/hexanes (1/2)) and was obtained as white needles from the same solvents. Yield: 72 mg (65%); mp 110–113°C; MS ($FAB^+$) no parent ion; $^1H$ NMR (300 MHz, $CDCl_3$, $\delta$): 5.93 (s, 1H), 3.66 (d, $J$=11.5 Hz, 1H), 3.65 (d, $J$=11.5 Hz, 1H), 1.79 (s, 3H); $^{13}C$ NMR (75.4 MHz, $CDCl_3$, $\delta$): 170.6, 105.4, 83.0, 43.5, 36.0, 23.4. IR: 2926, 1825, 1176. UV: $\lambda_{max}$ 210, $\lambda_{1/2max}$ 242. Anal. Calcd for $C_6H_6Br_4O_3$: C, 16.17; H, 1.36. Found: C, 16.38; H, 1.29.

**4.1.3. (2*R*)-3-[(4-Fluorophenyl)thio]-2-hydroxy-2-methylpropanoic acid (6).** The protected hydroxyacid **5** (184 mg; 0.413 mmol) was dissolved in 4 mL of a 1:1 mixture of isopropanol: 1 M NaOH. After 3 h, the reaction mixture was a solution and no starting material was detectable by TLC. 4-Fluorobenzenethiol (70 μL; 0.65 mmol) was then added and the reaction mixture was stirred overnight. The reaction mixture was then adjusted to pH 8 with HCl and was extracted 2× with $CH_2Cl_2$. The aqueous layer was then adjusted to pH 1 and was extracted with $CH_2Cl_2$. This organic layer was concentrated to an oil, which crystallized on standing. The hydroxyacid was either used in the next reaction without further purification or was recrystallized from chloroform/petroleum ether. Yield 76 mg (80%); $^1H$ NMR (300 MHz, $CDCl_3$, $\delta$): 7.43 (dd, $J$=9.0, 5.1 Hz, 2H), 6.96 (dd, $J$=9.0, 9.0 Hz, 2H), 3.40 (dd, $J$=13.8, 0.9 Hz, 1H), 3.15 (dd, $J$=13.8, 0.9 Hz, 1H), 1.53 (s, 3H); $^{13}C$ NMR (75.4 MHz, $CDCl_3$, $\delta$): 180.1, 162.4 (d, $^1J_{FC}$=247.2 Hz), 133.9 (d, $^3J_{FC}$=8.0 Hz), 130.3, 116.3 (d, $^2J_{FC}$=22.0 Hz), 75.0, 46.2, 25.8; $^{19}F$ NMR (282.3 MHz, $CDCl_3$, $\delta$):

−114.2. IR: 3065, 1719. UV: $\lambda_{max}$ 251; HRMS-FAB (*m*/*z*): Calcd for $C_{10}H_{11}FO_3S$, 230.0413; found 230.0417.

**4.1.4. (2*R*)-*N*-[4-Cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)thio]-2-hydroxy-2-methylpropanamide (7).** The hydroxyacid **6** (1.89 g; 8.22 mmol) and 4-amino-2-trifluoromethylbenzonitrile (2.05 g; 11.0 mmol) were dissolved in dry DMA (15 mL) under inert atmosphere. After the solution had been cooled to −10°C, thionyl chloride (0.75 mL; 10 mmol) was added slowly. The reaction mixture was stirred for 15 min at −10°C, and then the ice bath was removed. After stirring overnight at room temperature, the reaction mixture was diluted with $CH_2Cl_2$ and was extracted one time with satd $NaHCO_3$. The organic layer was dried with $MgSO_4$ and concentrated. The product was purified by silica gel chromatography (6% ethyl acetate in $CH_2Cl_2$). Yield 1.38 g (42%); $^1$H NMR (300 MHz, $CDCl_3$, $\delta$): 8.98 (s, 1H), 7.91 (s, 1H), 7.74 (m, 2H), 7.39 (dd, *J*=8.9, 5.1 Hz, 2H), 6.88 (dd, *J*=8.9, 8.5 Hz, 2H), 3.75 (d, *J*=14.1 Hz, 1H), 3.54 (s, 1H), 3.10 (d, *J*=14.1 Hz, 1H), 1.53 (s, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$, $\delta$): 172.8, 161.8 (d, $^1J_{FC}$=248.7 Hz), 140.9, 135.2, 133.4 (q, $^2J_{FC}$=33.3 Hz), 133.2 (d, $^3J_{FC}$=8.0 Hz), 128.4 (d, $^4J_{FC}$=3.7 Hz), 121.6 (q, $^1J_{FC}$=273.9 Hz), 121.3, 116.8 (q, $^3J_{FC}$=4.7 Hz), 115.7 (d, $^2J_{FC}$=21.9 Hz), 115.1, 103.8, 75.0, 45.3, 25.6; $^{19}$F NMR (282.3 MHz, $CDCl_3$, $\delta$): −62.7, −113.2. IR: 3357, 3095, 2981, 2232, 1685; HRMS-FAB (*m*/*z*): Calcd for $C_{18}H_{14}F_4N_2O_2S$, 398.0712; found 398.0705.

**4.1.5. (2*R*)-*N*-[4-Cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanamide (2).** To a solution of the sulfide **7** (1.27 g; 3.19 mmol) in $CH_2Cl_2$ (43 mL) was added *m*CPBA (1.65 g; 9.57 mmol). After stirring overnight at room temperature, the reaction mixture was diluted with ethyl acetate and extracted with $Na_2SO_3$ and $NaHCO_3$ (2×). The organic layer was dried with $MgSO_4$ and concentrated. After purification by silica gel chromatography using a step gradient of ethyl acetate in $CHCl_3$, the product was obtained as white crystals from benzene/petroleum ether. Yield 1.29 g (94%); ee $\gg$ 99%; mp 178°C; MS (FAB$^+$) 431 (M+1); $^1$H NMR (300 MHz, $CDCl_3$, $\delta$): 9.16 (s, 1H), 8.00 (d, *J*=1.5 Hz, 1H), 7.88–7.93 (m, 2H), 7.79–7.80 (m, 2H), 7.14–7.20 (m, 2H), 5.02 (s, 1H), 4.00 (d, *J*=14.5 Hz, 1H), 3.51 (d, *J*=14.5 Hz, 1H), 1.61 (s, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$, $\delta$): 171.4, 166.0 (d, $^1J_{FC}$=256.7 Hz), 141.0, 135.7, 135.0, 133.9 (q, $^2J_{FC}$=32.4 Hz), 130.8 (d, $^3J_{FC}$=9.7 Hz), 121.9 (q, $^1J_{FC}$=272.0 Hz), 121.8, 117.2, 116.8 (d, $^2J_{FC}$=22.7 Hz), 115.3, 104.8, 74.4, 61.8, 27.8; $^{19}$F NMR (282.3 MHz, $CDCl_3$, $\delta$): −62.7, −101.6. IR: 3449, 3333, 3104, 2984, 2933, 2231, 1697, 1587, 1517. UV: $\lambda_{max}$ 214, 271. [$\alpha$]−82° (*c* 1.0, MeOH). Anal. Calcd for $C_{18}H_{14}F_4N_2O_4S$: C, 50.23; H, 3.28; N, 6.51. Found: C, 50.01; H, 3.26; N, 6.23.

**4.1.6. (2*S*)-*N*-[4-Cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanamide.** ee $\gg$ 99%; Anal. Calcd for $C_{18}H_{14}F_4N_2O_4S$: C, 50.23; H, 3.28; N, 6.51. Found: C, 50.38; H, 3.41; N, 6.46.

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