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Bacillus subtilis epoxide hydrolase-catalyzed preparation of enantiopure 2-methylpropane-1,2,3-triol monobenzyl ether and its application to expeditious synthesis of (*R*)-bicalutamide

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Abstract—Expeditious synthesis of (*R*)-bicalutamide (**1**), a synthetic antiandrogen, from enantiopure 2-methylpropane-1,2,3-triol monobenzyl ether (**4**) was achieved. An engineered *Bacillus subtilis* epoxide hydrolase worked enantioselectively on the racemic epoxide (**7**) to provide the above starting material in highly enantiomerically enriched state.

Being a potent antiandrogen of a non-steroidal structure, bicalutamide [Casodex®, (**1**)][1] has been used in drug therapy to treat prostate cancer (Fig. 1). While the clinically prescribed entity is a racemic mixture,[1,2] its (*R*)-isomer was deduced to be an active principle from the following experimental evidences:[3] the (*R*)-isomer of **1** exhibited higher affinity to androgen receptors[4] and was less susceptible to metabolic degradation compared to the antipodal (*S*)-isomer.[5]

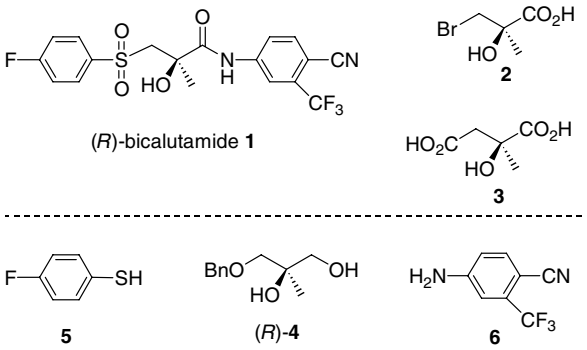
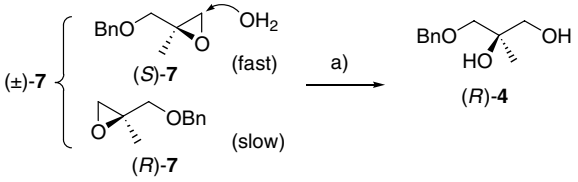


Figure 1.

So far, (*R*)-**1** and analogs thereof were assembled using two kinds of enantiomerically enriched 2-methyl-2-hydroxypropanoic acid derivatives: (1) (*R*)-3-bromo-2-hydroxy-2-methylpropanoic acid (**2**) prepared via asymmetric bromolactonization effected under the influence of D-proline as chiral auxiliary;[6–9] (2) (*S*)-citramalic acid (**3**) obtained by resolution.[10] Once its latent symmetry was recognized with **1**, terminally differentiated 2-methylpropane-1,2,3-triol, (*R*)-**4**, might well serve the synthesis of (*R*)-**1** providing that thiophenol (**5**) and aniline (**6**) could be installed at the proper ends of (*R*)-**4** (Fig. 1).

Preparation of an enantiomerically enriched form of **4** has been known by epoxide hydrolase (EH)-catalyzed enantioselective hydrolysis[11] of easily accessible racemic epoxide **7**.[12] While diverse catalytic activities and stereochemical courses have been reported,[13] we chose an



Scheme 1. Reagents and conditions: (a) *B. subtilis* epoxide hydrolase, 30 °C, 7 days, conv. 52%; (*R*)-**4**: 46%, 79.0% ee; (*R*)-**7**: 37%, 100% ee.

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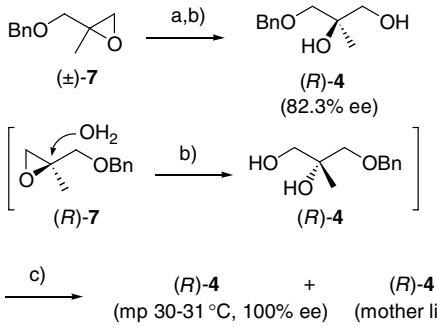
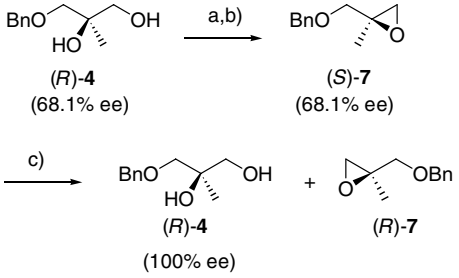


Scheme 2. Reagents and conditions: (a) *B. subtilis* epoxide hydrolase, 30 °C, 7 days, conv. 53%; (b) dil H_2SO_4, room temperature; (c) recrystallization from Et_2O at −30 °C, (*R*)-**4** as crystalline solid: 43%, 100% ee; as mother liquor, 40%, 68.1% ee.



Scheme 3. Reagents and conditions: (a) TsCl, pyridine; (b) K_2CO_3, MeOH, 94%; (c) *B. subtilis* epoxide hydrolase, 30 °C, 2 days, conv. 82%; (*R*)-**4**: 82%, 100% ee; (*R*)-**7**: 18%, 68.1% ee.

engineered enzyme, with high catalytic activity and availability in quantity, from an origin of *Bacillus subtilis* (BSEH).[14] When harvested cells of the engineered *B. subtilis* were incubated with (±)-**7** at 30 °C for a week, (*S*)-selective hydrolysis proceeded in 52% conversion to give (*R*)-**4** of 79.0% ee and unconsumed (*R*)-**7** of 100% ee in 46% and 37% isolated yield, respectively (Scheme 1).[15] For this BSEH-mediated kinetic resolution of (±)-**7**, the *E* value[16] was estimated to be as high as 73.

Now that BSEH had proven to be efficacious in resolving (±)-**7** kinetically to (*R*)-epoxide (**7**) and its antipodal diol (**4**) via (*S*)-selective hydrolysis on a preparative scale, attention was turned to defining the conditions to obtain only the hydrolysate (*R*)-**4** from (±)-**7** in a stereoconvergent manner[17] (Scheme 2). The above-mentioned cells of *B. subtilis* were incubated with (±)-**7** in 53% conversion. The resulting mixture of (*R*)-**4** and (*R*)-**7** as a whole was treated with dilute H_2SO_4,[18] whereby (*R*)-**4** underwent acid-catalyzed hydrolysis with stereochemical inversion at its quaternary stereogenic center[19,20] to afford (*R*)-**4** of 82.3% ee in 83% overall yield (Scheme 2). This was further crystallized from Et_2O at −30 °C, and enantiomerically pure (*R*)-**4** was obtained as a solid in 43% yield (52% recovery).[21]

The mother liquor (68.1% ee) in the previous crystallization procedure still contained the (*R*)-enantiomer (ca. 84% of the mixture). It was then attempted to reuse the (*R*)-**4**, recovered with a moderate enantiomeric purity, by converting it back to (*S*)-epoxide (**7**) and subjecting the latter to the BSEH-catalyzed kinetic resolution again (Scheme 3). Then, diol (*R*)-**4** was derived to enantiomerically enriched (*S*)-**7** (68.1% ee) in two conventional steps (94%).

Under the kinetically resolving conditions, pursuing high ee of the digested products (more reactive enantiomers) is always somewhat more difficult than of the unaffected substrates (less reactive enantiomers), even with high enantioselectivity. As the desired (*R*)-**4** is derived from the more reactive enantiomer (*S*)-**7**, termination of the reaction at the proper conversion is very important. We then simulated the relationship between conversion and ees of the digested product **4** and unaffected recovery **7** under a certain mathematical model,[16] and Figure 2 predicted ca. 80% conversion as the critical point.

The progress of the actual enzymatic reaction was monitored occasionally by HPLC. After 2 days, we stopped the reaction at 82% conversion, and enantiomerically pure (*R*)-**4** in 82% and (*R*)-**7** of 68.1% ee in 18% were obtained (Scheme 3). In this event, two interesting observations were noted. When starting with (*S*)-**7** of 68.1% ee, the BSEH-catalyzed hydrolysis proceeded with slightly higher enantioselectivity than the value of 73 that had been estimated for the hydrolysis of (±)-**7**. In addition, the reaction proceeded substantially faster with (*S*)-enriched **7**. This acceleration phenomenon should be ascribed to less amounts of (*R*)-**7** which, possessing a K_m value similar to that of (*S*)-**7**, must have worked as a competitive inhibitor against the BSEH.

The combined total yield of enantiomerically pure (*R*)-**4** as described in Schemes 2 and 3 was 74% based on the original starting material, (±)-**7**. With enantiomerically pure (*R*)-**4** being secured in quantity, effort was directed toward its conversion to (*R*)-bicalutamide (**1**) (Scheme 4). Selective oxidation of the diol was performed with TEMPO-mediated oxidation to give **8** (97%),[22] by avoiding any reagents possibly causing the undesired glycol cleavage through a cyclic intermediate by metallic oxidants.[23] For the next amide bond formation between

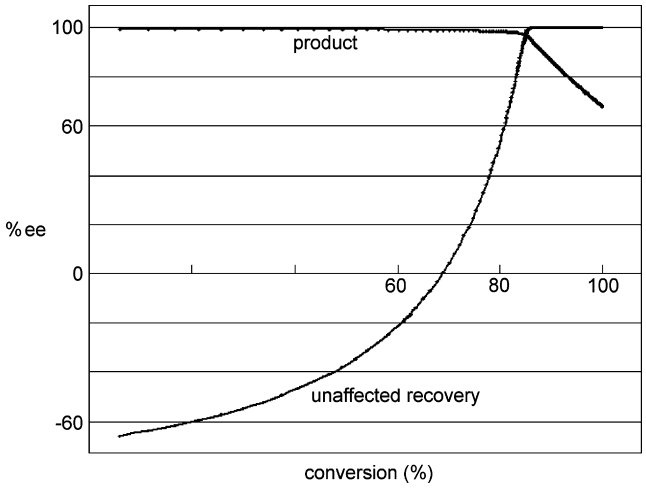
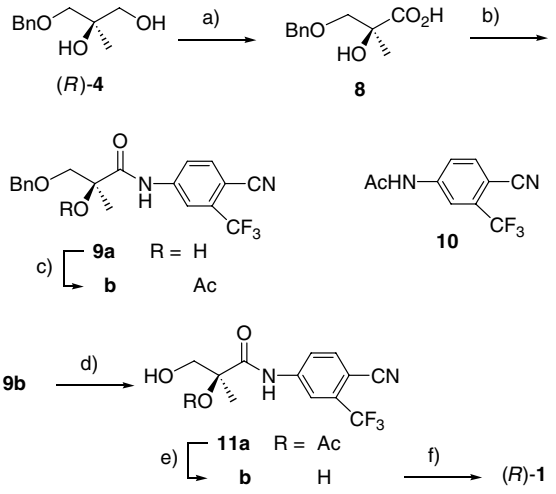
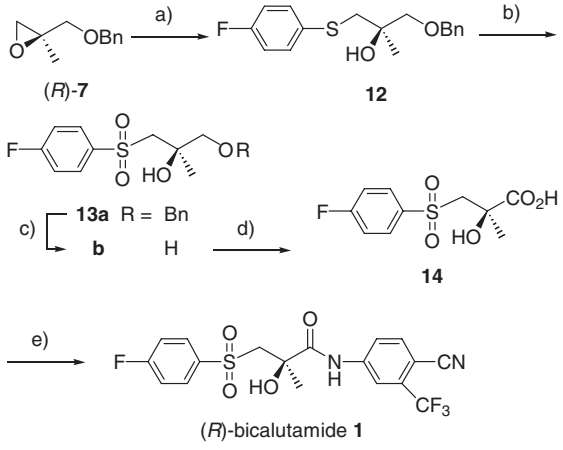


Figure 2. Simulation for the progress of *B. subtilis* epoxide hydrolase-catalyzed hydrolysis of (*S*)-**7** ($E = 73$, ee0 = 68.1%).



Scheme 4. Reagents and conditions: (a) TEMPO, NaClO, $NaClO_2$, MeCN-buffer, 35 °C, 24 h, 97%; (b) $SOCl_2$, THF, **6**, DMAP, room temperature, 5 days; (c) Ac_2O, pyridine, 83% from **8**; (d) DDQ, *hv* (352 nm, 15 W), MeCN, 85%; (e) K_2CO_3, MeOH, 85%; (f) lit.[28]

highly sterically hindered **8** and amine **6** with very low nucleophilicity, activation of α-hydroxy acid **8** was only realized by way of acid chloride[10] in THF. The smooth reaction required excessive amount of amine **6**, and an assistance of DMAP (3 equiv). When this reaction was attempted in *N*,*N*-dimethylacetamide according to the literature procedures, formation of an α-halo acid by-product was detected. As far as this particular amide bond formation was concerned, the conventional reagents for peptide synthesis, such as EDCI-HOBT, did not work. Product **9a** was obtained as an inseparable mixture with **6**, then the crude product was directly acetylated so that acetate **9b** (83% from **8**) was separated from **10** by SiO_2 chromatography.[24] For the deprotection of the *O*-benzyl group in **9b**, DDQ oxidation under UV irradiation conditions[25] was effective, and the desired alcohol **11a** was obtained in 85% yield.[26] By comparison, its exposure to catalytic hydrogenolysis caused side reactions in which the aromatic cyano group was



Scheme 5. Reagents and conditions: (a) Compound **5**, NaH, THF, room temperature, 90 min, 93%; (b) H_2O_2, AcOH, 60 °C, 24 h; (c) H_2, Pd–C, EtOH, room temperature, 48 h, 91% from **12**; (d) TEMPO, NaClO, $NaClO_2$, MeCN-buffer, 35 °C, 24 h, 93%; (e) $SOCl_2$, THF, **6**, room temperature, 5 days, 91%.

reduced to a benzylamine function. Finally, the acetyl protective group was removed to give diol **11b** (85%, 100% ee),[27] which is a known precursor for (*R*)-**1**[28] (Scheme 4).

In conclusion, large-scale preparation of diol (*R*)-**4** as well as epoxide (*R*)-**7** was achieved using an engineered BSEH-catalyzed hydrolation of racemic epoxide, and the product was applied for an expeditious route to (*R*)-bicalutamide (21% overall yield).[29] Last but not the least, a chemoenzymatic method to convert (±)-**7** as a whole to diol (*R*)-**4** was also established, which should serve the synthesis of biologically active compounds and other industrial materials, since (*R*)-**4** can be regarded as a desymmetrized form of 2-methylpropane-1,2,3-triol with its molecular termini being differentiated as a robust benzyl ether.

References and notes

1. Tucker, H.; Crook, J. W.; Chesterson, G. J. *J. Med. Chem.* **1988**, *31*, 954–959.
2. Chen, B.-C.; Zhao, R.; Gove, S.; Wang, B.; Sundeen, J. E.; Salvati, M. E.; Barrish, J. C. *J. Org. Chem.* **2003**, *68*, 10181–10182.
3. Tucker, H.; Chesterson, G. J. *J. Med. Chem.* **1988**, *31*, 885–887.
4. Mukherjee, A.; Kirkovsky, L.; Yao, X. T.; Yates, R. C.; Miller, D. D.; Dalton, J. T. *Xenobiotica* **1996**, *26*, 117–122.
5. McKillop, D.; Boyle, G. W.; Cockshott, I. D.; Jones, D. C.; Phillips, P. J.; Yates, R. A. *Xenobiotica* **1993**, *23*, 1241–1253.
6. Kirkovsky, L.; Mukherjee, A.; Yin, D.; Dalton, J. T.; Miller, D. D. *J. Med. Chem.* **2000**, *43*, 581–590.
7. Marhefka, C. A.; Gao, W.; Chung, K.; Kim, J.; He, Y.; Yin, D.; Bohl, C.; Dalton, J. T.; Miller, D. D. *J. Med. Chem.* **2004**, *47*, 993–998.
8. Nair, V. A.; Mustafa, S. M.; Mohler, M. L.; Fisher, S. J.; Dalton, J. T.; Miller, D. D. *Tetrahedron Lett.* **2004**, *45*, 9475–9477.
9. Nair, V. A.; Mustafa, S. M.; Mohler, M. L.; Yang, J.; Kirkovsky, L. I.; Dalton, J. T.; Miller, D. D. *Tetrahedron Lett.* **2005**, *46*, 4821–4823.
10. James, K. D.; Ekwuribe, N. N. *Tetrahedron* **2002**, *58*, 5905–5908.
11. Hellström, H.; Steinreiber, A.; Mayer, S. F.; Faber, K. *Biotechnol. Lett.* **2001**, *23*, 169–173.
12. (±)-Epoxide (**7**) was prepared on a large scale according to the following procedures: To a soln of benzyl metallyl ether (prepared from benzyl alcohol and metallyl chloride in a conventional manner, 5.00 g, 30.8 mmol) in MeCN (2.5 mL) and EtOH (12.5 mL) was added a soln of $KHCO_3$ (0.925 g, 9.24 mmol) in H_2O_2 (30% in H_2O, 4.78 mL, 61.6 mmol). MeCN was added to the mixture and stirred at room temperature for 24 h. H_2O_2 (30% in H_2O, 1.2 mL, 15.4 mmol) was further added to the mixture and stirred at room temperature for 2 days. The mixture was quenched by the addition of a soln of $Na_2S_2O_3$ (12.5 g) in H_2O (30 mL), and extracted with ice-chilled hexane. The extract was conventionally worked up and purified by SiO_2 chromatography to give **7** (13.9 g, 92%). Its NMR spectrum was identical with that reported previously.[20]
13. Simeó, Y.; Faber, K. *Tetrahedron: Asymmetry* **2006**, *17*, 402–409.

14. Yamaguchi, H.; Shirasaka, N.; Ikunaka, M. (Nagase & Co., Ltd.), Japan, Kokai Tokkyo Koho 2004-349, 377, 2004; *Chem. Abstr.* **2006**, 145, 59218, also orally presented; Yamaguchi, H.; Shirasaka, N.; Sakoda, A.; Ikunaka, M. Development of a useful biocatalyst (epoxide hydrolase) to prepare optically active 1,2-diols. 2F2-42, the 85th annual meeting of Chemical Society of Japan, March 26–29, Yokohama, 2005. Experimental procedures were as follows: Stock cultures of microorganisms were explored from scratch for those capable of (*S*)-selective hydrolysis of (±)-**7**, which led to identification of a wild strain of *B. subtilis* (JCM 10629) as producing an EH of the required stereoselectivity. The gene encoding epoxide hydrolase (*yfhM*) was cloned from the genomic DNA of *B. subtilis* by the standard method. Both amylase promoter and terminator sequences were cloned from the genomic DNA of *Bacillus amyloliquefaciens* NBRC 15535. The amylase promoter, the epoxide hydrolase gene, and the amylase terminator were inserted into an expression vector pUB110 in this order. The competent cells of *B. subtilis* MT-2 (deficient in neutral protease) were transformed with the plasmid vector thus constructed and the clone (dubbed Tamy 2 strain) was then selected which exhibited the epoxide hydrolase activity. For the utilization of amylase promoter, see: Saito, N.; Yamamoto, K. *J. Bacteriol.* **1975**, 121, 848–856.
15. To a cell suspension of *B. subtilis*[14] (19.5 mL) were added glycerol (6.0 mL), (±)-**7** (4.5 g, 25.2 mmol) and stirred at room temperature for 7 days. The progress of the reaction was monitored by HPLC analysis: [Senshu Pack PEGASIL ODS, 0.46 cm × 15 cm; MeOH–H_2O (3:2), 1.0 mL/min], t_R(min) = 3.8 (**4**), 6.8 (**7**). Then the broth was centrifuged (3000 rpm), and the supernatant was saturated with NaCl and mixed with EtOAc. The mixture was stirred for 1 h and filtered through a pad of Celite. The organic layer of the filtrate was separated and the aqueous layer was further extracted with EtOAc. The cell debris precipitated by centrifugation was mixed with acetone (80 mL). The mixture was stirred for 1 h and filtered through a pad of Celite. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue (4.16 g) was charged on a silica gel column (400 mL). Elution with hexane–EtOAc (2:1) afforded (*R*)-**4** (2.25 g, 11.5 mmol, 46%) as a solid and (*R*)-**7** (1.64 g, 9.20 mmol, 37%) as an oil.
Compound (*R*)-**4**: $[\alpha]_D^{27}$ −4.8 (*c* 1.04, CH_2Cl_2); HPLC: 79.0% ee [Chiralcel OD-H, 0.46 cm × 25 cm; hexane–*i*-PrOH (15:1), 0.5 mL/min], t_R(min) = 29.1 [(*S*)-, 10.5%], 31.1 [(*R*)-, 89.5%]. ^{1}H NMR ($CDCl_3$): δ 7.31–7.19 (5H, m), 4.49 (2H, s), 3.58 (1H, dd, *J* = 4.6, 11.0 Hz), 3.45 (1H, d, *J* = 9.1 Hz), 3.40 (1H, dd, *J* = 7.8, 11.0 Hz), 3.36 (1H, d, *J* = 9.1 Hz), 2.71 (1H, s), 2.26 (1H, dd, *J* = 4.6, 7.8 Hz), 1.08 (3H, s). Its NMR spectrum was identical with that reported previously.[20]
Compound (*R*)-**7**: $[\alpha]_D^{27}$ −11.7 (*c* 1.09, MeOH) [lit.[20] $[\alpha]_D^{25}$ −10.4 (*c* 1.26, MeOH)], HPLC: 100% ee [ChiralPak AS-H, 0.46 cm × 25 cm; hexane–*i*-PrOH (90:1), 0.5 mL/min], t_R(min) = 19.3 [(*R*)-, single peak]. No peak ascribable to (*S*)-isomer [t_R(min) = 20.1] was detected. Its NMR spectrum was identical with that of racemic sample.
16. Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.
17. Strauss, U. T.; Felfer, U.; Faber, K. *Tetrahedron: Asymmetry* **1999**, *10*, 107–117.
18. Steinreiber, A.; Hellström, H.; Mayer, S. F.; Orru, R. V. A.; Faber, K. *Synlett* **2001**, 111–113.
19. Orru, R. V. A.; Mayer, S. F.; Kroutil, W.; Faber, K. *Tetrahedron* **1998**, *54*, 859–874.
20. Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2001**, *12*, 1383–1388.
21. A mixture of cell suspension (19.5 mL), glycerol (6.0 mL), and (±)-**7** (4.5 g, 25.2 mmol) was stirred at room temperature for 7 days. Workup and purification provided a crude mixture [4.74 g, (*R*)-**4** (88.3% ee), and (*R*)-**7** (97.9% ee), 47.4:52.6], which was diluted with H_2O (86.4 mL). With an ice-cooling, conc. H_2SO_4 (6.7 mL) was added dropwise, and the resulted mixture was stirred at 0 °C for 10 min and further at room temperature for 30 min. After neutralization, the mixture was extracted and purified in a conventional SiO_2 chromatography to give (*R*)-**4** (4.10 g, 83%, 82.3% ee).
This was dissolved with Et_2O (82 mL), cooled slowly to −30 °C and kept at that temperature for 6 h. Mother liquor was decanted off with suction, and the crystal was rinsed twice with cold Et_2O. The crystal was dried to afford (*R*)-**4** (2.1 g, 52%) recovery, as colorless fine needles, mp 30–31 °C; $[\alpha]_D^{27}$ −7.03 (*c* 0.965, CH_2Cl_2) [lit.[30] $[\alpha]_D$ −6.30 (*c* 0.87, CH_2Cl_2)]; HPLC: 100% ee. *Caution*: when the mixture is kept at a temperature lower than −30 °C for a prolonged period, crystals of (*R*)-**4** would suffer from contamination with (*S*)-**4**.
22. A soln of (*R*)-**4** (510 mg, 2.60 mmol), TEMPO (37.2 mg, 0.238 mmol), MeCN (13 mL), and sodium phosphate buffer (pH 6.7, 0.67 M, 9.7 mL) was heated to 35 °C. First, a portion (20%) of the $NaClO_2$ soln [80% $NaClO_2$ (0.588 g) in H_2O (2.6 mL), 5.20 mmol] and a portion (20%) of the dilute bleach [10% NaOCl (39.2 μL) in H_2O (1.4 mL), 2.0 mol %] were added, and the remainder of the $NaClO_2$ soln and dilute bleach were added simultaneously over 1 h. At 24 h intervals, the same amount of TEMPO, $NaClO_2$ and dilute bleach were added twice to the mixture in the same manner as described above and the stirring was continued at 35 °C for total 48 h. After cooling to room temperature, H_2O (25 mL) was added, and the pH was adjusted to 8.0 with 2.0 M NaOH. The reaction was quenched by the addition of ice-chilled soln of Na_2SO_3 (2.1 g) in H_2O (40 mL), such that the temperature did not exceed 20 °C. The pH of the aqueous layer was adjusted to 9.0, and neutral, non-polar impurities were removed by washing with MTBE (methyl *t*-butyl ether, 3 mL). Acidification and extraction gave **8** (531 mg, 97%) as an oil, $[\alpha]_D^{26}$ −6.9 (*c* 0.805, EtOH), IR (film): 3438, 3064, 3032, 2986, 2880, 1734, 1496, 1454, 1373, 1101, 740, 698 cm^{-1}. ^{1}H NMR (CD_3OD): δ 7.23–7.16 (5H, m), 4.49 (1H, d, *J* = 12.1 Hz), 4.43 (1H, d, *J* = 12.1 Hz), 3.60 (1H, d, *J* = 9.5 Hz), 3.38 (1H, d, *J* = 9.5 Hz), 1.24 (3H, s). ^{13}C NMR (CD_3OD): δ 177.7, 139.3, 129.1, 128.6, 128.5, 77.1, 75.8, 74.4, 22.8. For the TEMPO-mediated oxidation, see: Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564–2566.
23. Plietker, B. *Synthesis* **2005**, 2453–2472.
24. $SOCl_2$ (0.113 mL, 1.56 mmol) was added dropwise under argon to a solution of **8** (32.6 mg, 0.155 mmol) in dry THF (0.160 mL) at 0 °C. The resulting mixture was stirred for 2 h under the same conditions. A solution of **6** (34.6 mg, 0.186 mmol) in dry THF (0.180 mL) was added dropwise to the above solution. The mixture was stirred further for 2 h at 0 °C, then DMAP (56.8 mg, 0.465 mmol) was added. The mixture was stirred at room temperature for 5 days. The conventional workup and acetylation of the residue provided **9b** (54.1 mg, 83%) as an oil, $[\alpha]_D^{23}$ −7.4 (*c* 0.985, EtOH) IR (film): 3337, 3109, 3064, 3031, 2941, 2868, 2230, 1747, 1710, 1589, 1525, 1507, 1430, 1372, 1328, 1240, 1181, 1135, 752, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.80 (1H, s), 8.08 (1H, d, *J* = 1.6 Hz), 7.94 (1H, dd, *J* = 8.2,

1.6 Hz), 7.78 (1H, d, $J = 8.2$ Hz), 7.36–7.27 (5H, m), 4.59 (2H, s), 4.28 (1H, d, $J = 9.6$ Hz), 3.63 (1H, d, $J = 9.6$ Hz), 2.14 (3H, s), 1.65 (3H, s). ^{13}C NMR ($CDCl_3$): δ 169.7, 169.4, 141.6, 136.5, 135.7, 133.7 (q, $^2J_{FC} = 32.3$ Hz), 128.7, 128.4, 127.9, 122.0, 122.0 (q, $^1J_{FC} = 273.7$ Hz), 117.3 (q, $^3J_{FC} = 5.0$ Hz), 115.5, 104.2, 81.2, 74.1, 72.1, 21.6, 20.5. HRMS (EI, 70 eV): calcd for $C_{21}H_{19}F_3N_2O_4$: (M^+): 420.1295; found: m/z 420.1290.

25. Rahim, M. A.; Matsumura, S.; Toshima, K. *Tetrahedron Lett.* **2005**, *46*, 7307–7309.
26. To a soln of **9b** (30.2 mg, 0.0718 mmol) in dry MeCN (11 mL) was added DDQ (24.4 mg, 0.108 mmol) and the mixture was stirred at room temperature for 24 h under irradiation by Toshiba EFD15BLB black light (UV, 352 nm, 15 W). During the reaction, the apparatus and lamp were wrapped with aluminum foil so as to enhance the reflection. The conventional workup and purification afforded **11a** (20.1 mg, 85%), $[\alpha]_D^{21}$ −27.1 (*c* 0.99, EtOH), IR (film): 3446, 3339, 2925, 2858, 2231, 1732, 1613, 1579, 1524, 1429, 1373, 1327, 1234, 1179, 1135, 1052, 759 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 9.12 (1H, s), 8.08 (1H, d, $J = 1.3$ Hz), 7.94 (1H, dd, $J = 8.3$, 1.3 Hz), 7.79 (1H, d, $J = 8.3$ Hz), 4.45 (1H, d, $J = 11.9$ Hz), 4.36 (1H, d, $J = 11.9$ Hz), 3.79 (1H, s), 2.10 (3H, s), 1.50 (3H, s). ^{13}C NMR ($CDCl_3$): δ 172.5, 172.0, 141.2, 135.8, 134.0 (q, $^2J_{FC} = 32.3$ Hz), 121.7, 121.1 (q, $^1J_{FC} = 273.7$ Hz), 117.2 (q, $^3J_{FC} = 5.8$ Hz), 115.4, 104.7, 76.3, 69.6, 23.4, 20.8. HRMS (EI, 70 eV): calcd for $C_{14}H_{11}F_3N_2O_3$: ($M+1^+$): 312.0019; found: m/z 312.0701.
27. Compound **11b**: Mp 131.2–131.5 °C. $[\alpha]_D^{21}$ −42.2 (*c* 0.945, MeOH) [lit.[28] $[\alpha]_D^{18}$ −43.6 (*c* 1.0, MeOH)], IR (film): 3342, 2925, 2854, 2231, 1697, 1612, 1581, 1522, 1429, 1327, 1178, 1134, 1051, 845 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 9.10 (1H, s), 8.09 (1H, d, $J = 2.1$ Hz), 7.92 (1H, dd, $J = 8.4$, 2.1 Hz), 7.78 (1H, d, $J = 8.4$ Hz), 4.14 (1H, d, $J = 11.0$ Hz), 3.57 (1H, d, $J = 11.0$ Hz), 3.40 (1H, s), 2.14 (1H, s), 1.45 (3H, s). ^{13}C NMR ($CDCl_3$): δ 174.1, 141.7, 136.1, 134.3 (q, $^2J_{FC} = 34.0$ Hz), 122.3 (q, $^1J_{FC} = 274.5$ Hz), 122.0, 117.5 (q, $^3J_{FC} = 5.0$ Hz), 115.7, 104.8, 71.7, 67.8, 22.9. HPLC: 100% ee [Chiralcel OD-H, 0.46 cm × 25 cm; hexane–*i*-PrOH (15:1), 0.5 mL/min], t_R(min) = 53.9 [(*S*)-, 100%]. No peak ascribable to (*S*)-isomer [t_R(min) = 57.2] was detected.
28. Soros, B.; Tuba, Z.; Galik, G.; Bor, A.; Demeter, A.; Trischler, F.; Harvath, J.; Brlik, J. WO 2001000608, 2002; *Chem. Abstr.* **2002**, 134, 86040.
29. Alternatively, (*R*)-bicalutamide (**1**) was also synthesized from (*R*)-**7** as in Scheme 5.
    Compound **12**: $[\alpha]_D^{22}$ +5.7 (*c* 1.07, EtOH). IR (film): 3448, 3089, 2862, 1589, 1491, 1369, 1227, 1092, 827, 739, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.38 (2H, ddd, $J = 7.2$, 5.1, 2.0 Hz), 7.35–7.25 (5H, m), 6.94 (2H, ddd, $J = 8.6$, 2.0, 7.2 Hz), 4.42 (2H, s), 3.43 (1H, d, $J = 9.1$ Hz), 3.31 (1H, d, $J = 9.1$ Hz), 3.17 (1H, d, $J = 13.2$ Hz), 3.08 (1H, d, $J = 13.2$ Hz), 2.62 (1H, s), 1.24 (3H, s). ^{13}C NMR ($CDCl_3$): δ 161.6 (d, $^1J_{FC} = 246.3$ Hz), 137.7, 132.1 (d, $^3J_{FC} = 7.5$ Hz), 131.9, 128.3, 127.7, 127.5, 115.9 (d, $^2J_{FC} = 21.6$ Hz), 75.4, 73.3, 72.6, 44.5, 23.8.
    Compound **13a**: $[\alpha]_D^{18}$ −12.3 (*c* 1.12, EtOH). IR (film): 3506, 3105, 2866, 1591, 1495, 1317, 1236, 1146, 1084, 846, 750 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.92 (2H, ddd, $J = 8.5$, 5.0, 2.0 Hz), 7.31 (2H, ddd, $J = 9.2$, 8.5, 2.0 Hz), 7.27–7.17 (5H, m), 4.48 (2H, s), 3.47 (1H, s), 3.47 (1H, d, $J = 14.3$ Hz), 3.46 (2H, s), 3.33 (1H, d, $J = 14.3$ Hz), 3.36 (1H, s), 1.25 (3H, s). ^{13}C NMR ($CDCl_3$): δ 165.6 (d, $^1J_{FC} = 256.2$ Hz), 137.5, 137.1, 130.5 (d, $^3J_{FC} = 10.0$ Hz), 128.3, 127.8, 127.6, 116.5 (d, $^2J_{FC} = 23.2$ Hz), 76.2, 73.4, 71.7, 62.6, 24.8.
    Compound **13b**: Mp 85.0–85.5 °C. $[\alpha]_D^{18}$ −5.2 (*c* 1.05, EtOH). IR (KBr): 3467, 3074, 2945, 1591, 1495, 1454, 1315, 1203, 1144, 837 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.97 (2H, ddd, $J = 6.8$, 5.1, 1.7 Hz), 7.25 (2H, ddd, $J = 8.4$, 6.8, 1.7 Hz), 3.66 (1H, s), 3.62 (3H, m), 3.35 (1H, d, $J = 14.2$ Hz), 3.24 (1H, d, $J = 14.2$ Hz), 2.45 (1H, dd, $J = 6.1$ Hz, 5.9 Hz), 1.42 (3H, s). ^{13}C NMR ($CDCl_3$): δ 165.8 (d, $^1J_{FC} = 256.2$ Hz), 136.5 (d, $^4J_{FC} = 3.3$ Hz), 130.5 (d, $^3J_{FC} = 9.1$ Hz), 116.7 (d, $^2J_{FC} = 22.4$ Hz), 72.8, 69.4, 62.5, 24.6. HRMS (EI, 70 eV): calcd for $C_{10}H_{14}FO_4S$: ($M+H^+$): 249.0595; found: m/z 249.0587.
    Compound **14**: Prisms from hexane–EtOAc, mp 132.0–132.2 °C, $[\alpha]_D^{21}$ −8.7 (*c* 1.04, EtOH). IR (KBr): 3475, 3105, 2997, 1728, 1589, 1491, 1458, 1325, 1284, 1147, 822 cm^{-1}. ^{1}H NMR (CD_3OD): δ 7.97 (2H, ddd, $J = 8.7$, 5.1, 2.1 Hz), 7.29 (2H, ddd, $J = 9.0$, 8.7, 2.1 Hz), 3.84 (1H, d, $J = 14.8$ Hz), 3.65 (1H, d, $J = 14.8$ Hz), 1.44 (3H, s). ^{13}C NMR (CD_3OD): δ 176.8, 167.0 (d, $^1J_{FC} = 253.8$ Hz), 138.7, 132.5 (d, $^3J_{FC} = 10.0$ Hz), 117.0 (d, $^2J_{FC} = 23.2$ Hz), 73.3, 65.0, 27.6.
    Compound (*R*)-**1**: Mp 180–181 °C [lit.[28] 181–182 °C]. $[\alpha]_D^{22}$ −83.2 (*c* 1.04, MeOH) [lit.[10] $[\alpha]_D^{18}$ −82 (*c* 1.0, MeOH)], HPLC: 100% ee [Chiralcel OJ-H, 0.46 cm × 25 cm; hexane–*i*-PrOH (5:4), 0.5 mL/min], t_R(min) = 22.4 [(*R*)-, 100%]. No peak ascribable to (*S*)-isomer [t_R(min) = 27.3] was detected. IR (KBr): 3462, 3340, 3109, 2916, 2231, 1703, 1612, 1581, 1522, 1495, 1431, 1333, 1292, 1142, 845 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 9.07 (1H, s), 7.97 (1H, s), 7.91–7.86 (2H, m), 7.78 (1H, m), 7.13–7.19 (2H, m), 5.03 (1H, s), 3.96 (1H, d, $J = 14.5$ Hz), 3.48 (1H, d, $J = 14.5$ Hz), 1.58 (3H, s). ^{13}C NMR ($CDCl_3$): δ 173.6, 164.7 (d, $^1J_{FC} = 252.1$ Hz), 143.0, 137.0, 136.1, 131.3 (d, $^3J_{FC} = 13.3$ Hz), 131.3 (q, $^2J_{FC} = 31.5$ Hz), 122.8, 122.4 (q, $^1J_{FC} = 273.7$ Hz), 117.4 (q, $^3J_{FC} = 5.0$ Hz), 116.0 (d, $^2J_{FC} = 22.4$ Hz), 115.7, 101.9, 73.1, 63.4, 27.2. Its IR and NMR spectra were identical with those reported previously.[10]
30. Tanner, D.; Somfai, P. *Tetrahedron* **1986**, *42*, 5985–5990.