Novel Synthesis of the Aldose Reductase Inhibitor Sorbinil via Amidoalkylation, Intramolecular Oxazolidin-5-one Alkylation, and Chymotrypsin Resolution

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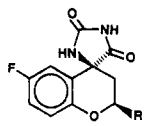
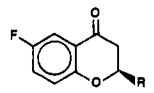
A new synthesis of the aldose reductase inhibitors sorbinil (1) and its 2(*R*)-methyl homologue **2** is presented. The amidoalkylation of 2-(4′-fluorophenoxy)ethyl halides **6** with *N*-benzoyl-α-hydroxyglycine yielded *N*-benzoyl-5-fluoro-2-(2-haloethoxy)phenylglycines **10**. The *N*-benzoyl amino acid group was dehydrated to oxazolidin-5-one **11** and underwent subsequent intramolecular spiroalkylation to 2,3-dihydro-6-fluorospiro[4*H*-1-benzopyran-4,4′-2-phenyloxazolidin]-5-one (**12**) in high yield upon treatment with acetic anhydride and either triethylamine or potassium carbonate. Acidic hydrolysis of oxazolidin-5-one **12** provided the desired racemic spiro amino acid *rac*-**5**, completing a three-step insertion of a glycine moiety. The methyl ester of *rac*-**5** was resolved by stereospecific hydrolysis with α-chymotrypsin and converted to (*S*)-**1** with potassium cyanate in acetic acid. The method was extended to (2*R*,4*S*)-**2** by utilizing (*S*)-ethyl lactate as the source of chirality at C-2.

Sorbinil, (4*S*)-2,3-dihydro-6-fluorospiro[4*H*-1-benzopyran-4,4′-imidazolidine]-2′,5′-dione (**1**), is of potential therapeutic interest because it may prevent or alleviate the chronic complications of diabetes mellitus due to its ability to inhibit the enzyme aldose reductase.[1] It is currently in clinical trials.

Sorbinil has been obtained by brucine resolution[2] of the racemic hydantoin precursor *rac*-**1** and by asymmetric synthesis.[3] Both methods required 2,3-dihydro-6-fluoro-4*H*-1-benzopyran-4-one (**3**) and introduced the amino acid functionality through either Bucherer–Bergs[4] [$(NH_4)_2CO_3$, KCN] or Strecker[5] [HCN, (*S*)-2-phenethylamine] reactions. Similarly, the recently described 2(*R*)-methyl homologue **2** of sorbinil was prepared in racemic form from 2,3-dihydro-6-fluoro-2-methyl-4*H*-1-benzopyran-4-one (*rac*-**4**). Resolution of *rac*-**2** as its *N*-methylcinchonidinium salt provided the 2*R*,4*S* isomer **2**.[6]



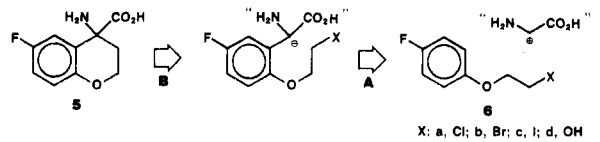
1 (R = H)
2 (R = CH_3)



3 (R = H)
rac-**4** (R = CH_3)

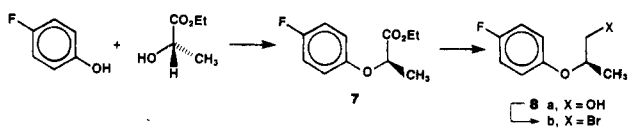
With a view to avoiding the use of cyanides in the preparation of kilogram quantities of **1**, we have examined other approaches to a potentially useful intermediate, 4-amino-2,3-dihydro-6-fluoro-4*H*-1-benzopyran-4-carboxylic acid (**5**). Our strategy was based on the retrosynthetic analysis shown in Scheme I and required a glycine moiety which can be reacted alternatively as an electrophile (transformation A) and then as an intramolecular nucleophile (transformation B).[7] This paper describes the successful use of *N*-acyl-α-hydroxyglycines[8] to fulfill this role and the conversion of **5** to (*S*)-**1**. Also, (2*R*,4*S*)-**2** was synthesized by this method and used (*S*)-ethyl lactate as the source of the 2(*R*)-methyl group.

Scheme I

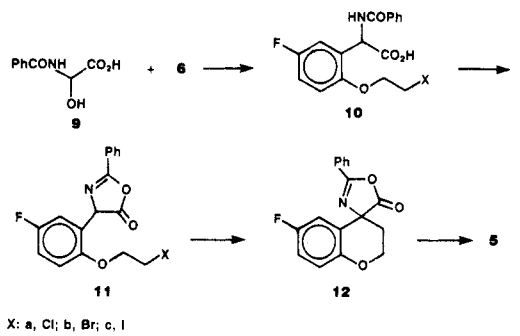


X: a, Cl; b, Br; c, I; d, OH

Scheme II



Scheme III



X: a, Cl; b, Br; c, I

Results and Discussion

2-(4-Fluorophenoxy)ethyl chloride (**6a**) and the bromide (**6b**) were prepared according to Marvel and Tanenbaum[9] from 4-fluorophenol, ethylene dihalide, and aqueous sodium hydroxide. The iodide (**6c**) was prepared in two steps. 4-Fluorophenol and ethylene carbonate were heated in the presence of catalytic potassium fluoride[10] to form 2-(4-fluorophenoxy)-ethanol (**6d**) in quantitative yield. **6d** was reacted with triphenylphosphonium diiodide in *N*,*N*-dimethylformamide (DMF) affording **6c**. (*R*)-1-Bromo-2-(4-fluorophenoxy)propane (**8b**) required three steps (Scheme II). 4-Fluorophenol and (*S*)-ethyl lactate were

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(2) Sarges, R.; Bordner, J.; Dominy, B. W.; Peterson, M. J.; Whipple, E. B. *J. Med. Chem.* **1985**, *28*, 1716.

(3) Sarges, R.; Howard, H. R.; Kelbaugh, P. R. *J. Org. Chem.* **1982**, *47*, 4081.

(4) Ware, E. *Chem. Rev.* **1950**, *46*, 403.

(5) Patel, M. S.; Worsley, M. *Can. J. Chem.* **1970**, *48*, 1881. Harada, K.; Okawara, T. *J. Org. Chem.* **1973**, *38*, 707.

(6) Kawakami, Y.; Nagai, Y.; Ono, H.; Ueda, K.; Sato, T.; Tanaka, S. *Heterocycles* **1984**, *21*, 583. *rac*-**2** was a mixture of 2*R*,4*S* and 2*S*,4*R* diastereomers isolated from the Bucherer–Bergs reaction.

(7) A conceptually similar approach to ring annellation based on sulfones as 1,1-dipoles has been described. See: Trost, B. M.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 7260.

(8) (a) Zoller, U.; Ben-Ishai, D. *Tetrahedron* **1975**, *31*, 863. (b) Schouteeten, A.; Christidis, Y.; Mattioda, G. *Bull. Soc. Chim. Fr.* **1978**, 248.

(9) Marvel, C. S.; Tanenbaum, A. L. *Organic Syntheses*; Wiley: New York, 1944; Collect. Vol. 1, p 436.

(10) Strege, P. E. U.S. Pat. 4341905.

0022-3263/87/1952-3587$01.50/0

condensed under Mitsunobu conditions[11] giving (*R*)-ethyl 2-(4-fluorophenoxy)propionate (**7**). This ester was reduced with lithium aluminum hydride in tetrahydrofuran (THF), and the resulting alcohol (**8a**) was treated with triphenylphosphonium dibromide in DMF to yield **8b**. The optical purity (97% ee) and absolute configuration (2*R*) of **8b** were determined by conversion to **2**.[6]

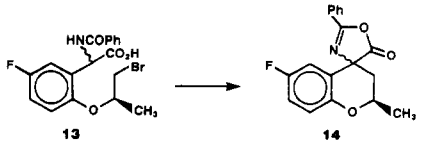
The overall conversion of **6** to the racemic spiro amino acid **5** is shown in Scheme III. The synthesis of phenylglycines by amidoalkylation has been reviewed by Zaugg.[12] Most of our studies used *N*-benzoyl-α-hydroxyglycine[8a] as the reagent for this reaction with the 2-(4-fluorophenoxy)ethyl halides **6**, although *N*-acetyl-α-hydroxyglycine[8b] was effective also (vide infra). All the amidoalkylations were carried out in methanesulfonic acid at room temperature and were complete after several hours but could be left longer for convenience with no adverse effect. Pouring the acidic solution slowly into stirring ice water gave the *N*-benzoyl phenylglycines **10** as solids in yields ranging between 83% and 95%. The products were pure enough for the next reaction and typically contained 1–2% benzamide and traces of residual **6**. No indication of the other possible regioisomer was seen. The optically active **8b** gave a 1:1 mixture of diastereomers (**13**).

The most challenging step in this strategy was the intramolecular carbanionic alkylation. The chemistry of amino acid α-anions has been an area of great interest recently.[13] The successful methods must provide for protection of both functional groups of the amino acid as well as enhancing the acidity of the α-proton. Often imine derivates of the nitrogen have been used but most require strong bases for the generation of the α-anion and low temperatures. Our substrates had the additional complications that protection and activation of the amino acid moiety had to be done in the presence of the alkylating group and that 2-phenoxyethyl halides are known to react sluggishly with nucleophiles and are prone to side reactions, especially elimination of HX in the presence of strong bases.[14] Steglich and co-workers[15] have demonstrated that the protected amino acid equivalents oxazolidin-5-ones could be readily alkylated with benzylic halides in the presence of diisopropylethylamine, but with simple alkyl iodides (methyl and ethyl) the yield was only 32%. Nevertheless, **10b** was converted to oxazolidin-5-one **11b** by heating in methylene chloride with 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate.[16] **11b** was isolated in 78% yield as a yellow solid in reasonable purity but converted slowly to more polar materials upon prolonged storage at room temperature. We were delighted to find that treatment of **11b** with 1 equiv of diisopropylethylamine gave rapid and complete conversion to the spiro oxazolidin-5-one **12**, one spot by TLC, which was isolated as an orange oil in 60% yield. The structure of **12** was proven by spectral data and further chemical conversions.

Since our primary interest was to produce kilogram quantities of spiro amino acid **5** and as structures related to **11b** were known to undergo side reactions readily,[17] we decided to investigate the conditions required for spiroalkylation further, hoping to avoid prolonged handling or isolation of **11b**. Initially, it was found that refluxing a solution of **10b** with several equivalents of acetic anhydride, the traditional reagent for this dehydration, in a wide range of nonprotic organic solvents (CH_2Cl_2, tetrahydrofuran, EtOAc, 1,2-dichloroethane) for 6–18 h caused conversion of **10b** to **11b**. Treatment of the cooled solution with 2 equiv of triethylamine (TEA) in DMF gave satisfactory cyclizations although those reactions that were heated overnight to complete dehydration did show the presence of some side products prior to the addition of the base. Also, intramolecular cyclization in the absence of DMF was not complete in these solvents. We found then that simple addition of TEA to **10b** and acetic anhydride in DMF at room temperature caused rapid, complete dehydration to **11b** followed by spiroalkylation with little evidence of side products. This observation led to two procedures suitable for large scale use.

In procedure A, a slurry of **10b** in DMF (3 mol/L) with acetic anhydride (1.5 equiv) was treated with neat triethylamine (2 equiv) in a slow stream. Partway through the addition, solution was achieved and TLC analysis of an aliquot showed formation of **11b**. Toward the end of TEA addition, crystallization of triethylammonium bromide occurred. A mild exotherm was seen during the course of the base addition. Starting with 2.6 kg of **10b**, addition of TEA required 45 min during which time the reaction temperature reached 55 °C. After the reaction was held at 45–50 °C for an additional 30 min, **12** was isolated via solvent extraction in 90% yield in good purity. For procedure B, a slurry of **10b** in acetone (0.6 mol/L) with acetic anhydride (1.5 equiv) was treated with 2 equiv of solid potassium carbonate in one portion. The same stepwise formation of **11b** and conversion to **12** occurred with a mild exotherm over several hours; the alkylation step was slower in this solvent. Filtration of the solids gave a product solution from which **12** was isolated in similar yield and quality as above by evaporation of the acetone.

Several variables in the intramolecular alkylation were studied qualitatively. The effects of changing the leaving group X and introducing steric hindrance in the side chain were examined. Both bromide **10b** and iodide **10c** were found to give comparable yields and quality of **12** under either procedure A or B. Using procedure A, the chloroethyl ether **10a** required heating of the reaction mixture and gave **12** in a lower yield along with side products. Using procedure B, the side products became predominant with **10a**. In the synthesis of **2**, the presence of an α-methyl group in bromo ether **13** slowed the rate of the reaction, but both procedures gave similar yields. No diastereoselectivity was found in the spiro-alkylation and roughly a 1:1 mixture of the diastereomers *rac*-**14** was observed.

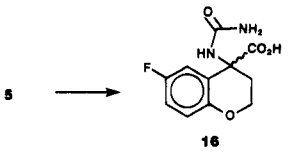


13 **14**

Hydrolysis of **12** to **5** was accomplished in a mixture of concentrated HCl and formic acid at reflux. The intermediate N-benzoyl spiro amino acid usually precipitated from the solution upon warming and slowly redissolved at reflux. **5** has been isolated as its hydrochloride, taken directly to a methyl ester (**15**) by treatment with methanol and thionyl chloride according to Brenner,[18] or reacted at

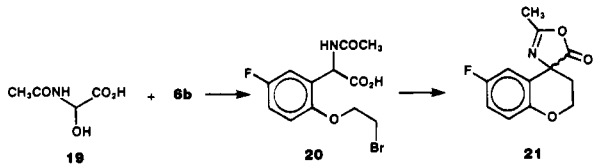
(11) Mitsunobu, O. *Synthesis* **1981**, 1.
(12) Zaugg, H. E. *Synthesis* **1984**, 85.
(13) O'Donnell, M. J.; Bennett, W. D.; Polt, R. L. *Tetrahedron Lett.* **1985**, *26*, 695, ref 1.
(14) Stork, G.; McElvain, S. M. *J. Am. Chem. Soc.* **1946**, *68*, 1053 and ref 6.
(15) Kubel, B.; Gruber, P.; Hurnaus, R.; Steglich, W. *Chem. Ber.* **1979**, *112*, 128.
(16) Hoyng, C. F.; McKenna, M.; Novak, K. *Synth. Commun.* **1980**, *10*, 761.
(17) Gotthardt, H.; Huisgen, R.; Bayer, H. O. *J. Am. Chem. Soc.* **1970**, *92*, 4340. Turch, J. I.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 397.
(18) Brenner, M.; Huber, W. *Helv. Chim. Acta* **1953**, *36*, 1109.

neutral pH with sodium cyanate to provide ureido acid **16** as a readily isolable solid.[19] The latter method was a convenient way to assess the overall yield for the process.



This was found to be as high as 75% for conversion of **10b** to **16** on a 5-g scale. The conversion of the chloride **10a** to **16** via procedure A gave a 45% overall yield on a 10-g scale. Overall yields of 55–60% were more typical with kilogram quantities of **10b**. Similarly for the synthesis of **2**, the 2(*R*)-methyl homologue **14** was hydrolyzed as above to amino acid *rac*-**17** and converted to its methyl ester (*rac*-**18**). *rac*-**18** was isolated as a mixture of two diastereomers, 2*R*,4*S* and 2*R*,4*R*. These could be separated by medium pressure liquid chromatography over silica gel.

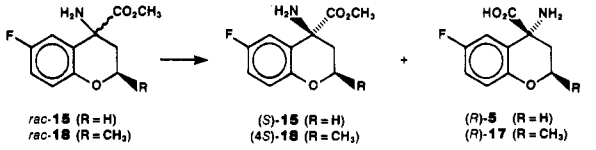
N-Acetyl-α-hydroxyglycine (**19**) was used also for the synthesis of **5**. Although Mattioda[8b] has reported **19** as a low melting crystalline monohydrate, in our hands it was isolated as an oil from the reaction of acetamide and glyoxylic acid in acetone. Amidoalkylation of **6b** with **19**



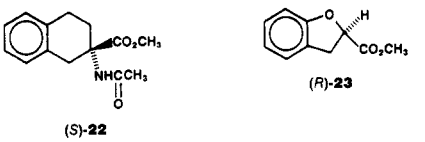
in methanesulfonic acid at room temperature gave *N*-acetyl-2-(2-bromoethoxy)-5-fluorophenylglycine (**20**) in 56% yield. The spiroalkylation was carried out according to procedure A and the resulting oxazolidin-5-one **21** was partially hydrolyzed with aqueous sodium hydroxide to provide the N-acetyl derivative of **5** in 60% yield. Further acid hydrolysis gave the hydrochloride of **5** in 88% yield.

The next stage of this new synthesis of sorbinil was the stereoselective, enzymatic hydrolysis of the spiro amino acid ester *rac*-**15**. α-Chymotrypsin is an enzyme involved in the hydrolysis of aromatic amino acid residues in peptides and both its mechanism of action and chemical applications have been well studied.[20] The substrate specificity of chymotrypsin has been rationalized by a model for the active site which features four bonding loci.[21] The two most important interactions are at the reactive carboxylate group which must bind with a suitable orientation for hydrolysis and at the hydrophobic site which is responsible for aromatic amino acid specificity. At a third site, the amido function of amino acid substrates can hydrogen bond to help orient the carboxylate moiety, while the final region is one of limited volume which excludes large groups. The optimal substrates for the enzyme are N-acyl derivatives of (*S*)-phenylalanine. Resolution of other amino acid esters include a spiro analogue of phenylalanine (**22**)[22] and α-methylphenylalanine methyl ester[23] which have been described recently. All amino acid res-

Scheme IV



olutions result in the selective hydrolysis of the *S* amino acid ester. In contrast, the chymotrypsin hydrolysis of



rac-**15** was found to selectively hydrolyze the *R* isomer (Scheme IV). This result was consistent with the stereoselectivity seen for some non-amino acid ester substrates such as **23** where the interaction of the lipophilic moiety with the enzyme oriented the carboxylate group for selective hydrolysis of the *R* isomer.[21b] Examination of Dreiding models indicated that (4*R*)-**15** most closely mimicked the interactions of the known non-amino acid substrates with the enzyme at the two major bonding sites, while the α-amino group resided at the volume restricted site, rather than at the hydrogen-bonding locus. The rate of hydrolysis was slow (unoptimized) but synthetically useful and was performed on multigram quantities. For the synthesis of **2**, only the mixture of diastereomers (*rac*-**18**), 2*R*,4*S* and 2*R*,4*R*, was exposed to the enzyme, where again the 4*R* isomer was selectively hydrolyzed (Scheme IV). Since we have found by NMR that these two diastereomers were comformationally rigid, it was the isomer with an equatorial carboxylate which underwent hydrolysis. We have not tried the enzymatic resolution of the mixture of the enantiomers (2*R*,4*S*)- and (2*S*,4*R*)-**18**.

The resolved esters (4*S*)-**15** and (2*R*,4*S*)-**18** were converted to the desired hydantoins by treatment with excess potassium cyanate in acetic acid.[24] This reaction was run at room temperature for 18 h, while the formation of the intermediate ureido ester was monitored by TLC. Heating the reaction mixture caused complete conversion to the hydantoins **1** and **2**, respectively.

Experimental Section

Melting points were determined on a Thomas Hoover capillary melting point apparatus and were uncorrected. NMR spectra were obtained on either a Varian EM-360 (60 MHz) or a Brucker WM 250 (250 MHz) spectrometer in deuteriochloroform ($CDCl_3$) or dimethyl sulfoxide-d_6 (Me_2SO-d_6), with tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin-Elmer 283B spectrophotometer. Mass spectra were determined with a Finnigan 4510 mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by the Analytical Chemistry Department, Pfizer Central Research. α-Chymotrypsin-Type II was purchased from Sigma Chemical Co.

2-(4-Fluorophenoxy)ethyl chloride (6a) and 2-(4-fluorophenoxy)ethyl bromide (6b) were prepared according to Marvel and Tanenbaum[8] from 4-fluorophenol and the appropriate ethylene dihalide.

6a: 66% yield, as a colorless oil; NMR ($CDCl_3$, 60 MHz) δ 7.0 (m, 4), 4.2 (t, 2), 3.8 (t, 2).

6b: 86% yield; mp 58–60 °C; NMR ($CDCl_3$, 60 MHz) δ 7.1 (m, 4), 4.3 (t, 2), 3.7 (t, 2). Anal. Calcd for C_8H_8BrFO: C, 43.84; H, 3.65. Found: C, 44.03; H, 3.70.

2-(4-Fluorophenoxy)ethyl Iodide (6c). 4-Fluorophenol (112 g, 1 mol), ethylene carbonate (90 g, 1 mol), and potassium fluoride (2 g, 0.034 mol) were heated slowly with stirring to 160 °C and

(19) Cue, B. W.; Moore, B. S. U.S. Pat. 4 435 578.
(20) Jones, J. B.; Beck, J. F. In Techniques of Chemistry, Vol. 10, *Applications of Biochemical Systems in Organic Chemistry*; Jones, J. B., Sih, C. J., Perlman, D., Eds.; John Wiley and Sons: New York, 1977; Chapter 4.
(21) (a) Cohen, S. G.; Schultz, R. M.; Weinstein, S. Y. *J. Am. Chem. Soc.* **1966**, *88*, 5315. (b) Pattabiraman, T. N.; Lawson, W. B. *J. Biol. Chem.* **1972**, *247*, 3029.
(22) Matta, M. S.; Rohde, M. F. *J. Am. Chem. Soc.* **1972**, *94*, 8573.
(23) Anantharamaiah, G. M.; Roeske, R. W. *Tetrahedron Lett.* **1982**, *23*, 3335.
(24) Read, W. T. *J. Am. Chem. Soc.* **1922**, *44*, 1746.

held at that temperature until gas evolution ceased.[9] The mixture was cooled to room temperature providing essentially a quantitative yield of 2-(4-fluorophenoxy)ethanol (**6d**). Iodine (134.5 g, 0.53 mol) was added in six equal portions to a solution of triphenylphosphine (139 g, 0.53 mol) in benzene (1.5 L) over 1 h. The resultant mixture was stirred for 2 h and then pyridine (79 mL, 0.98 mol) was added. To this was added dropwise a solution of **6d** (50 g, 0.32 mol) in benzene (250 mL), and the reaction was stirred at room temperature for 18 h. Methanol was added and solids were removed by filtration. The benzene filtrate was washed with water (500 mL), 10% sodium bisulfite (500 mL), water (500 mL), 1 N HCl (2 × 500 mL), and brine (200 mL). The benzene was evaporated in vacuo and **6c** crystallized from hexanes as a white solid; 78 g, 92% yield; mp 41–43 °C; NMR ($CDCl_3$, 60 MHz) δ 7.0 (m, 4), 4.2 (t, 2), 3.4 (t, 2).

(*R*)-Ethyl 2-(4-Fluorophenoxy)propionate (7). 4-Fluorophenol (7.5 g, 0.067 mol), (*S*)-ethyl lactate (7.9 g, 0.067 mol), and triphenylphosphine (18.75 g, 0.067 mol) in 100 mL of tetrahydrofuran (THF) were treated dropwise with a solution of diethyl azodicarboxylate (12.5 g, 0.067 mol) in 50 mL of THF. After 18 h at room temperature, the solvent was evaporated in vacuo and a mixture of ether (150 mL) and hexanes (150 mL) was added. The solids that precipitated were removed by filtration and the filtrate was washed with 1 N NaOH (2 × 50 mL), water (50 mL), and brine (50 mL). The solution was dried over $MgSO_4$. Evaporation gave **7** as an oil which was distilled in vacuo, 10.2 g, 72% yield: bp 90–92 °C (0.7mm); $[\alpha]_D$ +37.4° (*c* 2.148, $CHCl_3$); IR ($CHCl_3$) 1748 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 7.0 (m, 4), 4.8 (q, 1), 4.3 (q, 2), 1.6 (d, 3), 1.3 (t, 3). Anal. Calcd for $C_{11}H_{13}FO_3$: C, 62.26; H, 6.13. Found: C, 62.25; H, 6.22.

(*R*)-2-(4-Fluorophenoxy)propanol (8a). Compound **7** (27.3 g, 0.129 mol) was reduced with lithium aluminum hydride (3.8 g, 0.1 mol) in THE, giving **8a** as an oil in 94% yield: bp 85–95 °C (0.6 mm); $[\alpha]_D$ −33.0° (*c* 2.125, MeOH); NMR ($CDCl_3$, 60 MHz) δ 7.1 (m, 4), 4.4 (m, 1), 3.8 (d, 2), 1.3 (d, 3).

(*R*)-1-Bromo-2-(4-fluorophenoxy)propane (8b). Bromine (19.8 g, 0.124 mol) was added dropwise to a solution of **8a** (20 g, 0.118 mol) and triphenylphosphine (32.4 g, 0.128 mol) in DMF (50 mL) with the temperature held below 25 °C by cooling. After being stirred at room temperature for 18 h, the solution was diluted with ethyl acetate (500 mL) and was washed with water (3 × 200 mL), saturated $NaHCO_3$ (150 mL), water (150 mL), and brine (75 mL). The organic solution was dried over $MgSO_4$ and evaporated in vacuo to a slurry. This was diluted with hexanes (250 mL) and stirred for 0.5 h. The solids were collected and the filtrate was evaporated to give **8b** as an oil in 80% yield, 22.2 g: bp 83–85 °C (0.15 mm); $[\alpha]_D$ −10.2° (*c* 2.258, MeOH); NMR ($CDCl_3$, 60 MHz) δ 7.1 (m, 4), 4.5 (m, 1), 3.5 (m, 2), 1.4 (d, 3); mass spectrum, *m/e* 233/231 (M^+). Anal. Calcd for $C_9H_{10}BrFO$: C, 46.35; H, 4.29. Found: C, 46.36; H, 4.26.

***N*-Benzoyl-2-(2-bromoethoxy)-5-fluorophenylglycine (10b).** *N*-Benzoyl-α-hydroxyglycine[8a] (156 g, 0.8 mol) was added in portions as a solid to a mechanically stirred solution of **6b** (188.5 g, 0.86 mol) in methanesulfonic acid (620 mL) with the temperature <35 °C. The solid slowly dissolved over 1–2 h. At this point, the reaction can be worked up or left for a longer time without loss of yield. The thick reaction solution was poured into stirred ice water, precipitating **10b** as an off-white solid. The product was filtered, washed with water and ethanol, and dried in vacuo, 310 g, 95% yield. This material was suitable for the next reaction and contained a small amount of benzamide (1–2 %) and traces of **6b**. Recrystallization from methanol gave analytical material: mp 232.5–234 °C dec; IR (KBr) 3568–2400 (br), 1744 (s), 1730 (s), 1632 (s), 1605 (s) cm^{-1}; NMR ($CDCl_3$/Me_2SO-d_6, 60 MHz) δ 8.9 (d, 1), 8.0 (m, 2), 7.55 (m, 3), 7.2 (m, 3), 6.1 (d, 1), 4.4 (t, 2), 3.8 (t, 2); mass spectrum, *m/e* 395.9 (M^+), 351 ($M^+ - CO_2H$). Anal. Calcd for $C_{17}H_{15}BrFNO_4$: C, 51.56; H, 3.82; N, 3.54. Found: C, 51.42; H, 3.96; N, 3.64.

The following compounds were prepared by the same procedure as **10b**:

***N*-Benzoyl-2-(2-chloroethoxy)-5-fluorophenylglycine (10a)**: 92% yield; mp 221–224 °C; NMR (Me_2SO-d_6, 60 MHz) δ 9.0 (d, 1, J = 7 Hz), 8.1 (m, 2), 7.8–7.1 (m, 6), 6.2 (d, 1, J = 7 Hz), 4.4 (m, 2), 4.0 (m, 2); mass spectrum, *m/e* 354/352 (M^+). Anal. Calcd for $C_{17}H_{15}ClFNO_4$: C, 58.09; H, 4.31; N, 3.99. Found: C, 57.56; H, 4.38; N, 3.81.

***N*-Benzoyl-2-(2-iodoethoxy)-5-fluorophenylglycine (10c)**: 88% yield; mp 229–232 °C dec; IR (KBr) 3432 (s), 1745 (s), 1632 (s), 1576 (s), 1530 (s), 1498 (s) cm^{-1}; NMR (Me_2SO-d_6, 60 MHz) δ 9.05 (d, 1), 8.2–7.0 (m, 8), 6.3 (d, 1), 4.4 (t, 2), 3.6 (t, 2); mass spectrum, *m/e* 444 (M^+), 398 ($M^+ - H_2CO_2$). Anal. Calcd for $C_{17}H_{15}FINO_4$: C, 46.09; H, 3.42; N, 3.16. Found: C, 46.07; H, 3.52; N, 3.07.

(*R*,*S*)-*N*-Benzoyl-2-((2*R*)-1-bromopropoxy)-5-fluorophenylglycine (13): 83% yield; mp 203–210 °C; NMR (Me_2SO-d_6, 60 MHz) δ 8.9 (t, 1), 8.2–7.1 (m, 8), 6.1 (d, 2), 4.7 (m, 1), 3.7 (d, 2), 1.3 (dd, 3). Anal. Calcd for $C_{18}H_{17}BrFNO_4$: C, 52.73; H, 4.18; N, 3.42. Found: C, 52.78; H, 4.22; N, 3.40.

***N*-Acetyl-2-(2-bromoethoxy)-5-fluorophenylglycine (20).** Acetamide (2.07 g, 0.035 mol) and glyoxylic acid monohydrate (3.86 g, 0.042 mol) were stirred in acetone (35 mL) overnight and then evaporated to an oil which resisted crystallization. This was dissolved in methanesulfonic acid (13 mL) with **6b** (4.35 g, 0.02 mol). After 18 h at room temperature, the mixture was poured into ice water, and the product was collected by filtration and dried in vacuo, 3.8 g, 56% yield: mp 170–178 °C; IR (KBr) 3367 (s), 1731 (s), 1595 (s), 1536 (s), 1502 (s) cm^{-1}; NMR (Me_2SO-d_6, 60 MHz) δ 8.6 (d, 1), 7.3 (m, 3), 5.9 (d, 1), 4.5 (t, 2), 3.9 (m, 2), 2.0 (s, 3); mass spectrum, *m/e* 334/336 (M^+).

4-[2-(2-Bromoethoxy)-5-fluorophenyl]-2-phenyloxazolidin-5-one (11b). 10b (16.26 g, 0.04 mol) and *N*-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (18.6 g, 0.044 mol) were refluxed in CH_2Cl_2 (500 mL) for 4 h. The cooled reaction mixture was filtered and washed with water and brine. After drying over $MgSO_4$, the CH_2Cl_2 was evaporated in vacuo, affording the product as a yellow solid in 78% yield: mp 122–126 °C; IR (CH_2Cl_2) 1825 (s), 1650 (s), 1500 (s) cm^{-1}.

2,3-Dihydro-6-fluorospiro[4*H*-1-benzopyran-4,4′-2′-phenyloxazolidin]-5′-one (12). Spiroalkylation Procedure A. A suspension of **10b** (2.35 kg, 6 mol) in dry DMF (1.8 L) was treated with acetic anhydride (1.22 kg, 11.9 mol) in one portion. The resulting mixture was cooled to 20 °C in a 10 °C water bath while triethylamine (1.22 kg, 12 mol) was added slowly over 40 min. During the course of the addition, the reaction mixture became a solution and shortly thereafter, toward the end, crystallization of triethylamine hydrobromide occurred. During the addition, the temperature of the reaction rose slowly to 55 °C and then fell to 40 °C. The reaction was warmed to 50 °C for 0.5 h to insure completion. Toluene (6 L) and water (6 L) were added to the cooled reaction mixture and the layers were separated. The organics were washed with water (3 × 3 L) and dried over $MgSO_4$. Evaporation of the solvent in vacuo gave **12** as an amber oil in 75–95% yield. This was suitable for use in the next step: IR (CH_2Cl_2) 1825 (s), 1819 (s), 1651 (s), 1492 (s) cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 8.2 (m, 2), 7.8 (m, 3), 7.0 (m, 2), 6.7 (m, 1), 4.5 (m, 2), 2.3 (t, 2); mass spectrum, *m/e* 297 (M^+), 269 ($M^+ - CO$), 253 ($M^+ - CO_2$).

(4*R*,*S*)-2,3-Dihydro-6-fluoro-2(*R*)-methylspiro[4*H*-benzopyran-4,4′-2′-phenyloxazolidin]-5′-one (14). Spiroalkylation Procedure B. (*R*,*S*)-*N*-Benzoyl-2-((2*R*)-1-bromopropoxy)-5-fluorophenylglycine (**13**) (25 g, 0.06 mol) was suspended in acetone (100 mL) and treated with acetic anhydride (9.2 g, 0.09 mol) and potassium carbonate (16.85 g, 0.122 mol). The resulting mixture was stirred at room temperature overnight at which time TLC showed complete conversion. The solids were removed by filtration and washed with acetone. The combined acetone solutions were evaporated in vacuo to give the desired product as an orange oil; 17 g, 90% yield. This was suitable for use in the hydrolysis reaction: NMR ($CDCl_3$, 60 MHz) δ 8.2 (m, 2), 7.7 (m, 3), 7.1 (m, 2), 6.7 (m, 1), 4.7 (m, 1), 2.4–2.0 (m, 2), 1.5 (m, 3).

4-Acetamido-2,3-dihydro-6-fluoro-4*H*-1-benzopyran-4-carboxylic Acid (*N*-acetyl-5). 20 was treated according to procedure A. The crude spirooxazolidinone (**21**) was isolated as an oil: NMR ($CDCl_3$, 60 MHz) δ 7.1 (m, 2), 6.7 (m, 1), 4.4 (m, 2), 2.4–1.8 (m, 5). This was refluxed for 2 h in 3 N NaOH (6 mL). Acidification of the cooled reaction mixture precipitated the desired product, 0.7 g, 60% from **20**: mp 229–234 °C; mass spectrum, *m/e* 253 (M^+), 209 ($M^+ - CO_2$).

4-Amino-2,3-dihydro-6-fluoro-4*H*-1-benzopyran-4-carboxylic Acid, Hydrochloride (5). 12 (37.4 g, 0.126 mol) was dissolved in formic acid (125 mL) and concentrated HCl (100 mL)

and the mixture was heated at reflux for 6 h. During the initial heating a precipitate formed which slowly redissolved. The cooled reaction was diluted with water (250 mL) and twice extracted with CH_2Cl_2 and filtered. The aqueous filtrate was evaporated in vacuo, giving the crude amino acid hydrochloride. This was recrystallized from acetone/ether. Yields were 60–85%: mp 266–267 °C dec; IR (KBr) 3650–2300 (br), 1731 (s), 1497 (s) cm^{-1}. Anal. Calcd for $C_{10}H_{10}FNO_3$·HCl: C, 48.50; H, 4.48; N, 5.66. Found: C, 48.37; H, 4.51; N, 5.54. Similar hydrolysis of 4-acetamido-2,3-dihydro-6-fluoro-4*H*-1-benzopyran-4-carboxylic acid (*N*-acetyl-**5**) gave **5** in 88% yield.

(4*R*,*S*)-Amino-2,3-dihydro-6-fluoro-2(*R*)-methyl-4*H*-1-benzopyran-4-carboxylic Acid (*rac*-18). *rac*-**14** (3 g, 0.01 mol) was refluxed in a mixture of formic acid (10 mL) and concentrated HCl (10 mL). The reaction was evaporated to dryness and the residue dissolved in water and extracted twice with ether. The aqueous layer was adjusted to pH 5 with 1 N NaOH and evaporated to a solid. Recrystallization from acetone gave *rac*-**18**, 1 g, 46% yield: mp 229–233 °C; IR (KBr) 1624 (s), 1564 (s), 1489 (s), 1444 (m) cm^{-1}; NMR (D_2O, 250 MHz) δ 7.25–6.9 (m, 3), 4.35 (m, 0.5), 2.7–2.28 (m, 2), 1.5 (d, 1.5), 1.48 (d, 1.5).

2,3-Dihydro-6-fluoro-4*H*-ureido-1-benzopyran-4-carboxylic Acid (16).[19] Crude **5**·HCl (0.12 mol) was dissolved in water (100 mL) and 6 N NaOH added to give pH 6. Sodium cyanate (16.4 g, 0.25 mol) was added in one portion and the reaction stirred overnight at room temperature. The reaction was filtered to remove a haze and the solution was then acidified to pH 3 with 6 N HCl to precipitate **16** as a white solid, which was dried in vacuo; 24.32 g, 76% yield from **10b**: mp 189–191 °C dec; IR (KBr) 3466 (s), 3382 (s), 1721 (s), 1645 (s), 1562 (s), 1537 (s), 1496 (s) cm^{-1}.

Methyl (4*R*,*S*)-amino-2,3-dihydro-6-fluoro-4*H*-1-benzopyran-4-carboxylate (*rac*-15) was prepared from **5** (15 g, 0.17 mol) according to Brenner[18] with thionyl chloride (9 mL) in methanol (75 mL) and crystallized from ether as the hydrochloride, 18 g, 97% yield, mp 200–202 °C dec. This was dissolved in water (60 mL) and extracted into ethyl acetate after adjusting the aqueous solution to pH 10. The organics were dried over $MgSO_4$, evaporated in vacuo, and crystallized from hexanes, 11.7 g, 73% yield: mp 64–65.5 °C; NMR ($CDCl_3$, 60 MHz) δ 7.0 (m, 3), 4.4 (m, 2), 3.8 (s, 3), 2.8–2.3 (m, 1), 2.1–1.7 (m and s (NH_2), 3). Anal. Calcd for $C_{11}H_{12}FNO_3$: C, 58.66; H, 5.37; N, 6.22. Found: C, 58.48; H, 5.24; N, 6.08.

In a similar manner was obtained methyl (4*R*,*S*)-amino-2,3-dihydro-6-fluoro-2(*R*)-methyl-4*H*-1-benzopyran-4-carboxylate (*rac*-**18**) as an oil in 51% yield from **14**: IR ($CHCl_3$) 2947 (w), 1732 (s), 1484 (s), 1425 (s) cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 7.5–8.3 (m, 3), 4.6 (m, 1), 3.8 (s, 3), 2.65–1.65 (m, 4), 1.5 and 1.4 (dd, 3); mass spectrum, *m/e* 239 (M^+), 180 ($M^+ - CO_2CH_3$). A sample was analyzed as its *d*-di(*p*-toluoyl)tartaric acid salt from ethyl acetate. Anal. Calcd for $C_{32}H_{32}FNO_{11}$: C, 61.44; H, 5.12; N, 2.24. Found: C, 61.15; H, 5.21; N, 2.04.

Methyl (4*S*)-Amino-2,3-dihydro-6-fluoro-4*H*-1-benzopyran-4-carboxylate ((*S*)-15). *rac*-**15** (11.5 g, 0.051 mol) was dissolved in 0.125 N sodium chloride solution (100 mL) by the addition of 6 N HCl to pH 5. α-Chymotrypsin (0.75 g) was added to the mixture. After stirring at 20 °C for several hours, hydrolysis commenced and the pH was maintained at pH 5 by a pHstat (0.5 N NaOH). When 0.5 molar equiv had been taken up hydrolysis ceased (48 to 60 h). The reaction was acidified to pH 2 and stirred for 3 h with activated carbon (1 g) and then filtered and extracted with ethyl acetate. The aqueous layer was adjusted to pH 10 with 6 N NaOH and extracted with ethyl acetate (3 × 100 mL). The resolved ester was recovered from the organic solution as a colorless oil, 4.17 g, 36% yield: $[\alpha]_D$ +51.2° (*c* 0.64, $CHCl_3$); spectral data identical with racemic. Similar treatment of *rac*-**18** gave (4*S*)-**18** in 38% yield as a colorless oil: $[\alpha]_D$ +132.2° (*c* 0.69, $CHCl_3$); NMR ($CDCl_3$, 60 MHz) δ 7.4–6.8 (m, 3), 4.8–4.2 (m, 1), 3.8 (s, 3), 2.5/2.3 (dd, 1), 2.1 (s, 2), 1.8 (d, 1), 1.35 (d, 3).

Sorbinil (1). (*S*)-**15** (4.17 g, 0.019 mol) and sodium cyanate (2.55 g, 0.0392 mol) were stirred in glacial acetic acid (40 mL) at room temperature for 24 h. The solution was heated to 90 °C for 3 h, cooled, and concentrated to a low volume. Addition of water precipitated **1**, which was crystallized from 2-propanol, 2.58 g, 61% yield: mp 240–241 °C; $[\alpha]_D$ +54.1° (*c* 0.9, MeOH) [lit.[2] $[\alpha]_D$ +54.0° (MeOH)].

In the same manner, (2*R*,4*S*)-**18** (1.84 g, 0.0077 mol) and sodium cyanate (1.0 g, 0.015 mol) gave **2** in 79% yield: mp 231–234 °C (from acetone/hexanes); $[\alpha]_D$ +212.2° (*c* 0.55, MeOH) [lit.[25] $[\alpha]_D$ +226.3° (MeOH)]; NMR (Me_2SO-d_6, 250 MHz) δ 8.4 (s, 1), 7.1 (dt, 1), 6.9 (m, 2), 4.8 (m, 1), 3.4 (br s, 1), 2.3 (d, 1), 1.85 (t, 1), 1.35 (d, 3); mass spectrum, *m/e* 250 (M^+), 207 (M^+ – HNCO).

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Phenacyl-Directed Alkylation of Imidazoles: A New Regiospecific Synthesis of 3-Substituted L-Histidines

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A new strategy for regiospecific imidazole alkylation of suitably protected histidines is described wherein a phenacyl group serves as a protecting group of the distal imidazole nitrogen atom. Alkylation of *N*-BOC-1-phenacyl-L-histidine methyl ester at N(3), followed by reductive removal of the phenacyl group from N(1) of the resulting imidazolium intermediate with zinc and acetic acid offers an efficient and flexible route to 3-substituted L-histidines.

Introduction

The frequent location of a histidine residue at catalytic sites of enzymes as well as the essential presence of histidine in certain peptide hormones has led us to investigate modified versions of the natural amino acid which when incorporated in peptides or modified peptides might afford enzyme inhibitors or hormone antagonists. Our initial studies led to the synthesis of 3-substituted histidines by alkylation of *N*,1-bis(BOC)histidine methyl ester (**1**) with alkyl and aryl sulfonates (Scheme I).[1] Although this route provides a wide variety of 3-substituted histidines, it has limitations. Secondary alkyl groups and certain benzyl groups with multiple electron-donating functions cannot be installed at N(3) by this method. We reasoned that part of the difficulty in these cases is that the BOC-protected imidazole, being a very poor nucleophile, requires highly

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