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NEW SYNTHESIS OF SPIRO-BENZOPYRAN AMINO ACIDS BY INTRAMOLECULAR AMIDOALKYLATION

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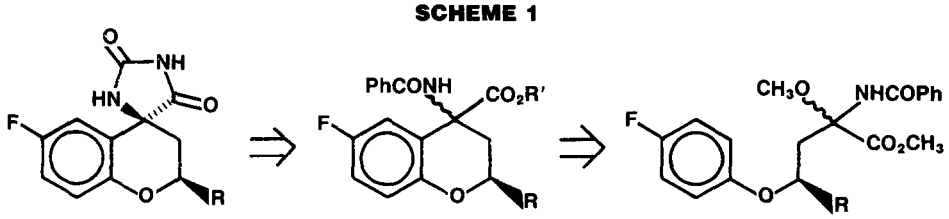
Summary: A new synthesis of spiro-benzopyran amino acids is presented. The key reaction is the intramolecular amidoalkylation of methyl 2-benzamido-4-(4-fluorophenoxy)-2-methoxybutyrate to yield methyl 4-benzamido-2,3-dihydro-6- fluoro-4H-benzopyran-4-carboxylate.

While the amidoalkylation reaction has been used widely for the synthesis of novel amino acids,[1] the Friedel-Crafts amidoalkylation of aromatic substrates has emphasized "glycine cation" equivalents in the preparation of phenylglycines.[2] Amidoalkylation with α-oxidized derivatives of higher amino acids was reported in only two related cases in which either α-acetoxy-[3] or α-methoxy-[4] alanine and phenylalanine derivatives reacted with excess anisole. Furthermore, intramolecular amidoalkylations have been reported previously only where either the nitrogen or carboxylate moiety of the amino acid was part of the newly formed ring.[5]

We have been seeking novel routes to the aldose reductase inhibitor, sorbinil **1**[6] and its homologue **2**[7], and have recently published an efficient synthesis of these based on an amidoalkylation and intramolecular oxazolidin-5-one alkylation to provide intermediates **3a** and **4a**.[8] In this note, a complementary process is described (Scheme 1) which utilizes an intramolecular amidoalkylation to prepare the spiro-amino acid methyl esters **3b** and **4b**. Unlike the earlier process,[8] 1,3-asymmetric induction occurred in the formation of the 2-methyl benzopyran amino acid **4b**, modestly favoring the (2R)(4R)-diastereomer.

SCHEME 1



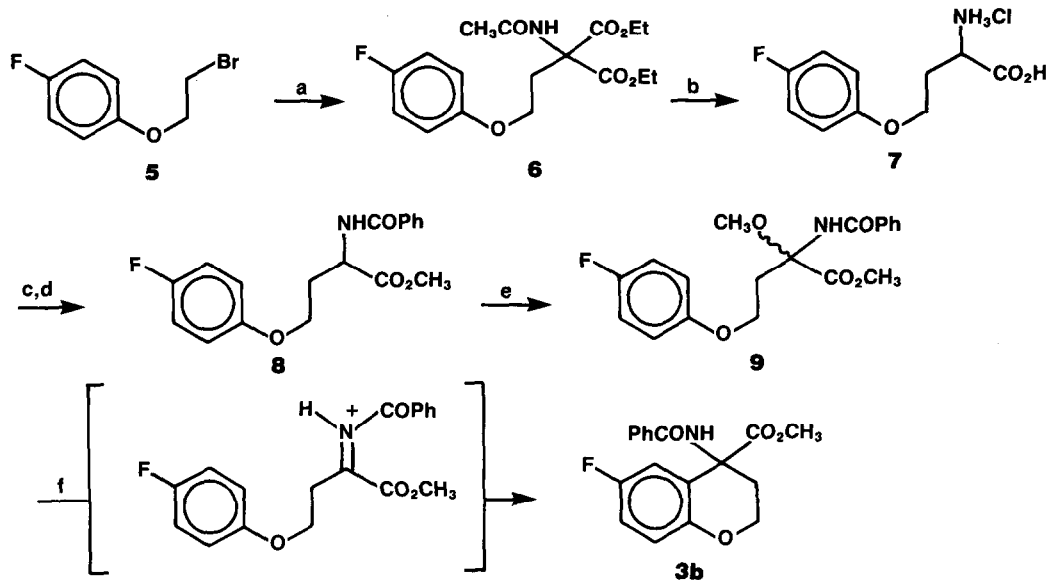
1, R = H
2, R = CH_3

3, R = H
4, R = CH_3
a, R' = H; b, R' = CH_3

9, R = H
11a, R = CH_3

The synthesis of spiro amino acid **3b** is shown in Scheme 2.[9] Diethyl acetamidomalonate[10] was alkylated with 2-(4-fluorophenoxy)ethylbromide **5**[8] and the product hydrolyzed to the crystalline amino acid hydrochloride **7**. Compound **7** provided a useful intermediate for introducing a variety of protecting groups onto the amino acid. For the present study, esterification and benzoylation gave **8**. The α-methoxylation was carried out according to the procedure of Poisel[11] using t-butyl hypochlorite in methanol with sodium methoxide.

SCHEME 2

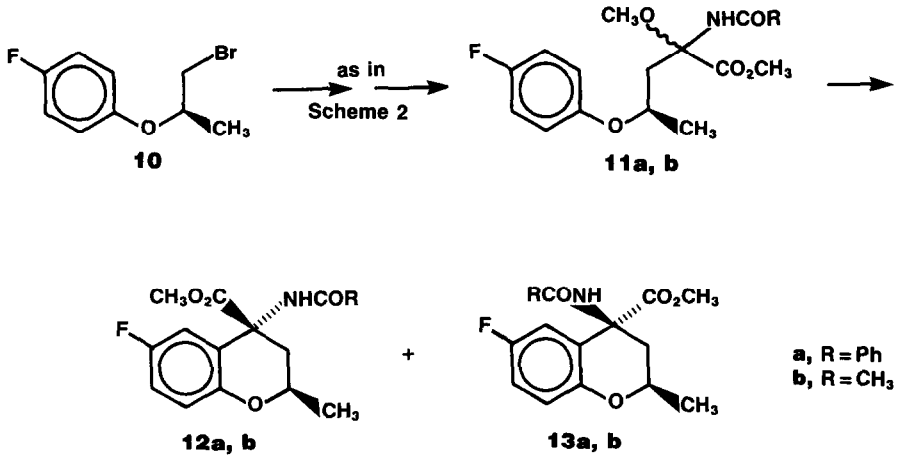


a) diethyl acetamidomalonate, NaH, DMF (60%); b) conc. HCl, reflux (70%); c) $SOCl_2$, MeOH (95%); d) benzoyl chloride, triethylamine, CH_2Cl_2 (80%); e) t-butyl hypochlorite, MeOH, MeONa (71%); f) CH_3SO_3H or $BF_3{\cdot}Et_2O$, $CHCl_3$ (85%).

The intramolecular amidoalkylation proceeded equally well in either neat methanesulfonic acid or in chloroform solution with boron trifluoride etherate;[12] the yield for either method being ca. 85%. Intermediate **3b** can be hydrolyzed to 4-amino-2,3-dihydro-6-fluoro-4H-1-benzopyran-4-carboxylic acid and converted to sorbinil as described previously.[8]

To apply this process to the preparation of **2**, (R)-1-bromo-2-(4-fluorophenoxy)propane **10**[8] was used as the starting material for the process outlined in Scheme 2. The intermediates in this series are mixtures of diastereomers and were purified by chromatography to avoid fractionation; the chemical yields were comparable to those above. Both the acetamido and benzamido amino acid methyl esters were prepared to study the stereochemistry of the intramolecular cyclization. The diastereomeric α-methoxy esters **11a** and **11b** were especially easy to separate by chromatography, although their absolute configurations were not assigned. A variety of acidic reaction conditions were found to give high chemical yields in the intramolecular amidoalkylation and NMR analysis of the crude reaction mixtures provided the diastereomer ratios of the product benzopyran amino acids directly.[13]

The assignment of absolute stereochemistry of **12a** was made by comparing the NMR spectra of the mixture of diastereomers to that of a reference sample of **12**, methyl (4R)-benzamido-2,3-dihydro-6-fluoro-(2R)-methyl-4H-1-benzopyran-4-carboxylate.[14] Each set of cyclization conditions, starting with either a single diastereomer of **11** or the 1:1 mixture of diastereomers, gave the same product ratio and yield. The highest % de was found with benzamide **11a** in methanesulfonic acid at 0°C; giving a 72:28 mixture of **12a:13a**. The same substrate **11a** with either $SnCl_4$ or trimethylsilyl triflate in CH_2Cl_2 at -78°C resulted in a 60:40 ratio of products. The acetamide **11b** in either methanesulfonic acid at 0°C or with TMS triflate in CH_2Cl_2 at -78°C gave an identical 2:1 ratio of **12b** to **13b**. In both amide series, it was the (2R)(4R)-diastereomer **12** which predominated while diastereomer **13**, the (2R)(4S)-precursor to **2**, was the minor product.



Having shown that 1,3 stereochemical control in the intramolecular amidoalkylation was possible with the synthesis of 2-methyl benzopyran amino acids, the asymmetric synthesis of **1** by using chiral auxiliaries on the amino acid moiety in the intramolecular amidoalkylation is being studied.

Acknowledgement. The assistance of Mark L. Elliott for the preparation of the intermediates in Scheme 2 is gratefully acknowledged.

References and Footnotes

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9. Satisfactory infrared, mass and NMR spectral data was obtained on each new compound. The reactions have not been optimized.
10. Snyder, H.R.; Shekleton, J.F.; Lewis, C.D. *J. Amer. Chem. Soc.* 1945, **67**, 310.
11. Poisel, H. *Chem. Ber.* 1977, **110**, 942.
12. Both reactions are started at 0°C and warmed to room temperature. In the methanesulfonic acid reaction, ice was added to precipitate the product as a solid. This material was sufficiently pure for further reactions.
13. NMR diagnostic signals in $CDCl_3$ at 250 MHz: **12a**, δ 4.28 (m, 1), 3.82 (s, 3), 2.94 (dd, J = 14 and 2 Hz, 1), 2.60 (dd, J = 14 and 12 Hz, 1), 1.445 (d, J = 6Hz, 3). **13a**, δ 4.62 (m, 1), 3.78 (s, 3), 3.09 (dd, J = 14 and 2Hz, 1), 2.00 (dd, J = 14 and 12 Hz, 1), 1.437 (d, J = 6Hz, 3).
14. Reaction of the less polar amino acid ester (2R)(4R)-18 from ref. 8 with benzoyl chloride and triethylamine in CH_2Cl_2 provided the reference sample.

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