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Syntheses of 5- and 6-[2,3]-dihydrobenzofuran β-amino acids

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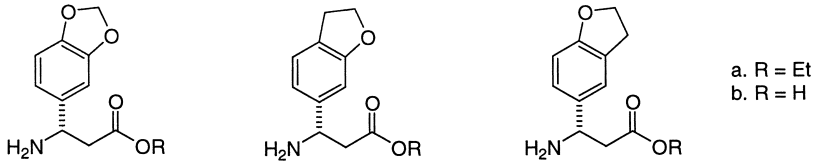
Abstract

Efficient stereoselective syntheses of 5- and 6-[2,3]-dihydrobenzofuran β-amino acids are described. These 3-aryl β-amino acids are aspartic acid mimetics that are structurally related to known benzodioxole systems. In many cases, the benzodioxole can inhibit and induce cytochrome P-450; neither of these dihydrobenzofuran β-amino esters is a potent inhibitor of several human P-450 enzymes.

β-Amino acids are constituents of many naturally-occurring peptides, terpenes and macrolides. As synthetic intermediates, β-amino acids serve as important precursors to β-lactams. In the course of synthesizing novel RGD (Arg-Gly-Asp) peptidomimetics containing 3-aryl-β-amino acids, we[1] and others[2] have investigated the utility of 3-[5-(benzo-1,3-dioxole)]-β-alanine **1** as an aspartic acid mimetic. While incorporation of β-amino acid **1** into RGD peptidomimetics can lead to potent integrin receptor antagonists, the benzodioxole moiety in **1** has shown a propensity to irreversibly bind to cytochrome P-450 isozymes via formation of a metallocarbene complex between the dioxymethylene and the heme functions.[3] Because of the potential metabolic lability of the benzodioxole bicycle, we were interested in designing syntheses of the dihydrobenzofuran β-alanines **2** and **3** as isosteric replacements for **1**. Presumably, deletion of one of the two oxygen atoms of the benzodioxole would prevent formation of P-450 carbene complexes. In this paper, we describe efficient syntheses of the dihydrobenzofuran aspartic acid replacements **2a** and **3a**, and evaluate their potential to inhibit cytochrome P-450.



1 **2** **3**

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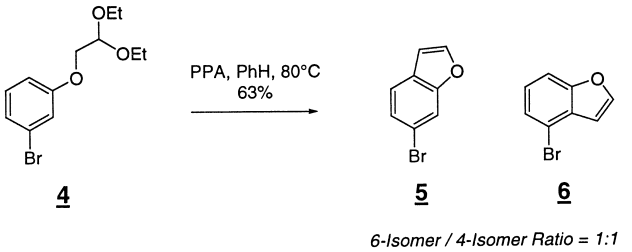
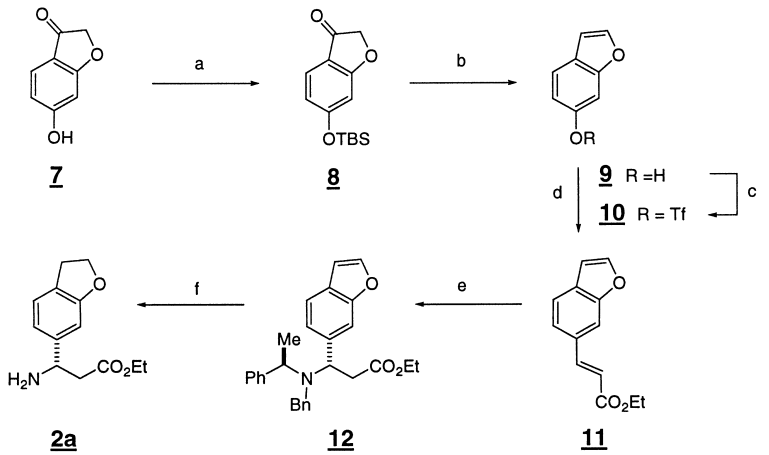
We planned to synthesize β-amino acid esters **2a** and **3a** by a diastereoselective heteroconjugate addition of (*R*)-(+)-*N*-benzyl-α-methylbenzylamine to the β-benzofuranyl acrylates in accordance with the Davies protocol (vide infra).[4] This strategy required the syntheses of both the 5- and 6-substituted benzofurans. Initially, we attempted to prepare the 6-bromobenzofuran **5** by cyclodehydration of the 3-bromophenoxyacetaldehyde acetal **4** with polyphosphoric acid in refluxing benzene (Scheme 1).[5] This led to an inseparable mixture (ratio 1:1) of the 6- and 4-bromobenzofurans. The use of other Lewis acids (BF_3–OEt_2, BCl_3, $TiCl_4$) led to decomposition of **4** and none of the desired cyclization products.



Scheme 1.

An alternative strategy for the selective synthesis of the 6-substituted benzofuran was pursued (Scheme 2). Silylation of commercially available 6-hydroxybenzofuranone[6] **7** gave **8** with minimal formation of the undesired enol silane.[7] Reduction of the benzofuranone with diisobutylaluminum hydride provided the intermediate 3-hydroxy-6-silyloxy-[2,3]-dihydrobenzofuran, which was heated in aqueous HCl/THF to effect dehydration of the benzylic hydroxyl group and subsequent desilylation to give 6-hydroxybenzofuran **9**. Phenol **9** was transformed to the triflate **10** under standard conditions. Heck coupling between **10** and ethyl acrylate with catalytic $Pd(Ph_3P)_2Cl_2$ provided the 3-(6-[2,3]-dihydrobenzofuran)-2-propenoic acid ethyl ester **11**. Heteroconjugate addition of (*R*)-(+)-*N*-benzyl-α-methylbenzylamine via the Davies procedure afforded **13** with



Scheme 2. Conditions: (a) TBSCl, Et_3N, MeCN, 93%; (b) *i*Bu_2AlH, CH_2Cl_2, –78°C, then HCl/H_2O/THF, 80%; (c) N-$PhNTf_2$, Et_3N, CH_2Cl_2, 96%; (d) ethyl acrylate, $Pd(Ph_3P)_2Cl_2$, Et_3N, DMF, 90°C, 62%; (e) *R*-(+)-benzyl-α-methylbenzylamine, *n*-BuLi, THF, –78°C, 72%; (f) $Pd(OH)_2$, $AcOH/H_2O$/EtOH, H_2 (1 atm), then $HCl/EtOAc/CH_2Cl_2$, 75%

excellent diastereoselectivity (>95:5).[8] We have found the Davies procedure to be a highly practical method for the diastereoselective synthesis of 3-aryl-β-amino acids. Hydrogenolysis of the benzyl groups of **13** with Pearlman's catalyst occurred with concomitant furan reduction to give the desired β-amino acid **2a**.[9] Alternatively, partial reduction of **13** under transfer hydrogenation conditions (1,4-cyclohexadiene, Pd/C, AcOH) effected debenzylation of the amine **13** without saturation of the [2,3]-benzofuran.

Synthesis of the corresponding 5-[2,3]-dihydrobenzofuran β-amino acid **3a** was accomplished by an analogous synthetic sequence commencing with commercially available 5-benzofuran carboxaldehyde.[10]

By our measurements (shown in Table 1), benzodioxole **1a** is an inhibitor of human CYP3A4 (IC_{50} = 800 nM). As hoped, dihydrobenzofuran β-amino esters **2a** and **3a** display diminished inhibitory potency for several human P-450 enzymes (CYP3A, CYP2C9, CYP2D6) compared to **1a**.[11]

Table 1
Inhibition of human recombinant P-450 isozymes

	(IC50, μM)		
Compound	CYP3A4	CYP2C9	CYP2D6
1a	0.8	7.4	1.1
2a	29.3	> 100	18.4
3a	71.3	>100	65.7

Efficient syntheses of the isomeric β-amino esters **2a** and **3a** have been described. Oxygen atom deletion from benzodioxole **1** provides isosteric dihydrobenzofuran β-amino esters **2a** and **3a** as aspartic acid mimetics that are not potent P-450 inhibitors. Benzofuran β-alanines **2** and **3** should have considerable utility in the syntheses of new integrin antagonists.

Acknowledgements

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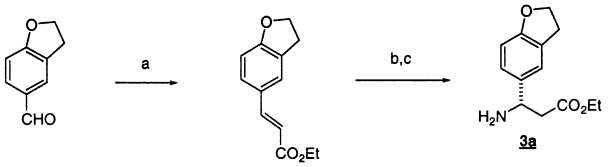
7. Silylation of the phenolic oxygen in **8** allows dissolution of **9** in organic solvents. Without protection, the metal alkoxide derived from deprotonation of **8** is highly insoluble.
8. The stereoassignment of **12** as the (*S*)-diastereomer is based on the Davies precedent (see Ref. 3).
9. Data for ester **2a** (HCl salt): $[\alpha]_D^{25}$ +9.4 (*c* 0.02; MeOH); ^{1}H NMR (300 MHz, MeOD) δ 7.27 (d, J = 7.5 Hz, 1H), 6.89 (dd, J = 7.5, 1.8 Hz, 1H), 6.84 (d, J = 1.8 Hz, 1H), 4.59 (m, 3H), 4.15 (q, J = 7.5 Hz, 2H), 3.20 (t, J = 8.4 Hz, 2H), 2.99 (m, 2H), 1.21 (t, J = 7.5 Hz, 3H) ppm.
10. Commercially available 5-benzofuran carboxaldehyde (Maybridge Chemical Company) was (a) olefinated (carboethoxytriphenylphosphorane, 95%), followed by (b) heteroconjugate addition (*R*-(+)-benzyl-α-methylbenzylamine, *n*-BuLi, THF, 51%), and (c) hydrogenolysis ($Pd(OH)_2$, H_2, 91%) to provide ester **3a**.



Data for ester **3a** (HCl salt): $[\alpha]_D^{25}$ +5.10 (*c* 0.05; MeOH); ^{1}H NMR (300 MHz, MeOD) δ 7.29 (s, 1H), 7.14 (dd, J = 8.1, 1.5 Hz, 1H), 6.73 (d, J = 8.1 Hz, lH), 4.55 (t, J = 8.7 Hz, 2H), 4.52 (m, 1H), 4.12 (q, J = 7.5 Hz, 2H), 3.24 (t, J = 8.7 Hz, 2H), 2.92 (m, 2H), 1.19 (t, J = 7.5 Hz, 3H) ppm.

11. Compounds **1a**, **2a** and **3a** were incubated with 5–10 pmol of human recombinant CYP3A4, -2C9 and -2D6 in phosphate buffer (pH 7.4) containing an NADPH-generating system and isozyme-selective fluorogenic probes. The probe substrates included 7-benzyloxy-4-(trimethyl)-coumarin at 20 μM for CYP3A4, 7-benzyloxy-4-(trimethyl)-coumarin at 50 μM for CYP2C9 and 3-[2-(*N*,*N*-diethyl-*N*-methylamino)ethyl]-7-methoxy-4-methylcoumarin at 1 μM for CYP2D6. The substrate concentrations correspond to the K_m for the respective isozyines. The reactions were carried out so that product formation was linear with protein concentration and incubation time at 37°C, and terminated by adding 75 μl of 80% acetonitrile/20% 0.5 M Tris. The fluorescent products were quantitated with a SPECTRAmax® Gemini Dual-Scanning Microplate Spectrofluorometer (Molecular Devices, Sunnyvale, CA) and the IC_{50} values obtained from a four-parameter logistic curve plotted with Data Assistant (Microsoft Excel®).