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Palladium-Mediated Intramolecular Aryl Amination on Furanose Derivatives: An Expedient Approach to the Synthesis of Chiral Benzoxazocine Derivatives and Tricyclic Nucleosides

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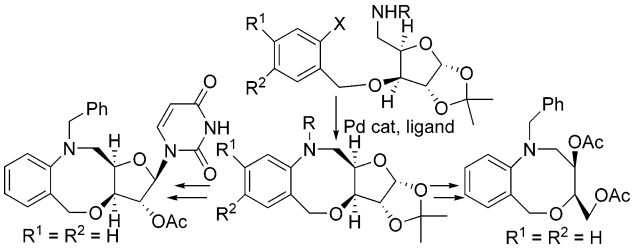

Pd-catalyzed intramolecular arylamination on sugar derivatives has been accomplished by using bulky biaryl phosphine ligands. An application of this methodology on a variety of D-glucose-derived substrates, **2a**−**f**, led to the synthesis of highly functionalized cis-fused tricyclic oxazocines, **3a**−**e**. The products could subsequently be transformed to the optically active benzoxazocine derivative **4** and tricyclic nucleoside **6**. This is the first example of the synthesis of eight-membered rings via intramolecular cycloamination of furanose derivatives, which provides a very useful method for the catalytic synthesis of medium-ring heterocycles.

The abundance of medium rings incorporating oxygen or nitrogen atoms in medicinally interesting compounds[1] continues to ensure that they are important synthetic targets for organic chemists.[2,3] For example, the benzoxazocine ring is often present in pharmaceutical agents as a core structural motif. Synthetic routes to medium-ring heterocycles involving direct ring closure are often slow and hampered by unfavorable enthalpies and entropies of the reaction. A few reported approaches for the construction of the oxazocine ring are based on the cyclization of bromoallenes bearing oxygen nucleophilic functionalities in the presence of a Pd(0) catalyst,[4] ring-closing metathesis,[5] or Pd(0)-induced ring cyclization.[6] The above methodologies either require a relatively lengthy sequence of reactions or furnish low yields of the reaction products. As a part of our research program related to the synthesis of benzannulated medium-ring ethers[7] or amines,[8] we planned to synthesize eight-membered rings bearing both oxygen and nitrogen atoms because of their expected useful biological activities.[9] Interest in the use of the easily accessible carbohydrates from the chiral pool for the synthesis of optically active heterocycles has also been growing rapidly.[10] In a continuation of our interest in the carbohydrate-based synthesis of medium-ring heterocycles, we felt that the use of the chiron approach,[11] along with the application of

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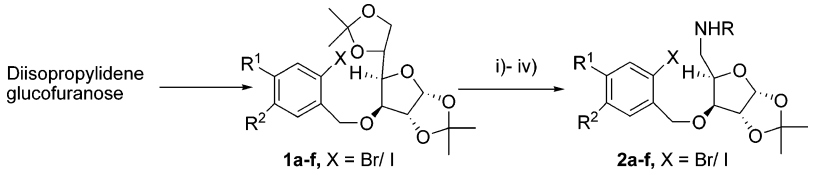
SCHEME 1. Construction of *O*-Bromo/Iodo Benzylated Sugar Amines 2a−f[a]



[a] Reagents and conditions: (i) 70% AcOH (v/v), rt, overnight; (ii) aq $NaIO_4$, MeOH, rt, 45 min; (iii) RNH_2 (1.2 equiv), anhydrous CH_2Cl_2, MS (4 Å), rt, 12 h, N_2; (iv) $NaBH_4$, dry MeOH, rt, 3 h.

intramolecular C−N ring closure between aromatic bromides or iodides and an aliphatic amine, offers a better and more convenient alternative to the synthesis of benzoxazocine derivatives in optically pure form.

Over the past few years much effort has gone into developing palladium-catalyzed aryl-amination chemistry.[12] The initial work by Hartwig and Louie[13a] and Buchwald and Wolfe[13b] focused on the intermolecular amination of aryl bromides or iodides to give substituted anilines. More recently, this aryl-amination chemistry has undergone optimization, particularly with the development of new ligand systems,[14] and an intramolecular version has been utilized for the synthesis of heterocyclic compounds.[15]

In this paper, we describe a facile conversion of D-glucose to tricyclic sugar-annulated benzoxazocine derivatives in chiral form. Cleavage of the sugar ring of these tricyclic derivatives provides a convenient route for entry into chiral, functionalized benzoxazocines.

The possibility of converting the intermediate furanose derivatives to nucleoside analogues is an added attraction. It should be mentioned that the design of conformationally restricted nucleosides as monomers in oligonucleotide analogues and as potent antiviral agents[16] has attracted considerable attention recently. Anticipating better biological activities, nucleosides with bi- and tricyclic carbohydrate moieties[17,18] have been synthesized to restrict the conformational flexibility of the nucleoside into conformers, which are ideal for nucleic acid recognition. Herein, we report the synthesis of a new tricyclic nucleoside analogue in which the furanose ring is linearly cis fused with a benzoxazocine moiety. The present communication deals with the scope of the aryl-amination reaction on sugar derivatives for developing functionalized chiral benzoxazocine derivatives and tricyclic nucleosides incorporating an eight-membered ring.

TABLE 1. Preparations of Sugar Amines 2a−f

		1a-f → 2a-f					
Entry	Substrate	R	R_1	R_2	X	Product	Yield(%)
1	**1a**	$PhCH_2$-	H	H	Br	**2a**	65
2	**1b**	$(CH_3)_2CH$-	H	H	Br	**2b**	75
3	**1c**	$PhCH_2$-	OCH_3	OCH_3	Br	**2c**	70
4	**1d**		H	H	Br	**2d**	80
5	**1e**		H	OCH_3	Br	**2e**	85
6	**1f**	$PhCH_2$-	H	H	I	**2f**	67

The starting material, 1,2:5,6-di-*O*-isopropylidene glucofuranose, was smoothly converted to the *O*-2-bromo/iodo benzylated sugar amines, **2a**−**f**, through the intermediate *O*-(2-bromobenzyl) glucofuranosides, **1a**−**e**,[7a] and *O*-(2-iodo-benzyl) glucofuranoside, **1f**. Selective removal of the 5,6-*O*-isopropylidene moiety from the benzylated products, **1a**−**f**, was smoothly effected with 70% aqueous HOAc at 25 °C, and the resulting diol on $NaIO_4$ oxidation, imine formation with aliphatic amines, and subsequent $NaBH_4$ reduction in MeOH afforded the desired amines, **2a**−**f**, in good yields (Scheme 1; Table 1). The spectral data of **2a**−**f** are in excellent agreement with the assigned structures.

Our initial goal was to explore the synthesis of benzoxazocine-annulated furanose derivatives **3a**−**e** from **2a**−**f** through Pd-catalyzed intramolecular cycloamination reactions in the presence of bases and ligands**.** After considering several phosphine ligands, we chose to pursue the conditions reported by Buchwald et al.[19] Entry 1 of Table 2 clearly indicates that the reaction under these conditions failed to provide the desired compound, **3a**. We next applied other conditions reported in the literature[20] (entry 2, Table 2) to effect intramolecular

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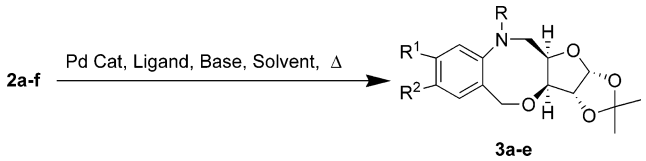
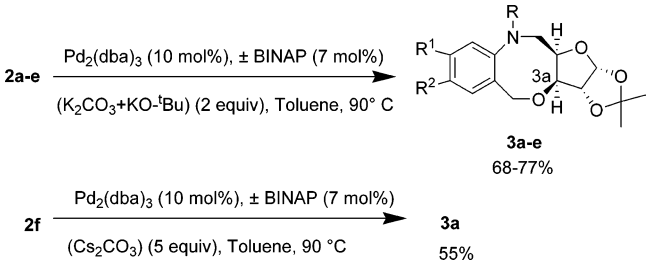
TABLE 2. Optimization of the Intramolecular Palladium Catalyzed Cycloamination Reaction



entry	substrate	base	catalyst	ligand	solvent	product	yield (%)
1	**2a**	K_2CO_3 + KO-*t*Bu	$Pd(PPh_3)_4$	no ligand	toluene	**3a**	nr[a]
2	**2a**	KO-*t*Bu	$Pd(OAc)_2$	±BINAP	toluene	**3a**	30[b]
3	**2a**	K_2CO_3 + KO-*t*Bu	$Pd_2(dba)_3$	±BINAP	DMF	**3a**	20[c]
4	**2a**	K_2CO_3 + KO-*t*Bu	$Pd_2(dba)_3$	±BINAP	toluene	**3a**	75[d]
5	**2a**	K_2CO_3 + KO-*t*Bu	$Pd_2(dba)_3$	±BINAP	toluene	**3a**	50[e]
6	**2a**	K_2CO_3 + KO-*t*Bu	$Pd_2(dba)_3$	Ph_3P	toluene	**3a**	5[f]
7	**2b**	K_2CO_3 + KO-*t*Bu	$Pd_2(dba)_3$	±BINAP	toluene	**3b**	74[d]
8	**2c**	K_2CO_3 + KO-*t*Bu	$Pd_2(dba)_3$	±BINAP	toluene	**3c**	68[d]
9	**2d**	Cs_2CO_3	$Pd_2(dba)_3$	±BINAP	toluene	**3d**	65[g]
10	**2d**	K_2CO_3 + KO-*t*Bu	$Pd_2(dba)_3$	±BINAP	toluene	**3d**	77[d]
11	**2e**	K_2CO_3 + KO-*t*Bu	$Pd_2(dba)_3$	±BINAP	toluene	**3e**	70[d]
12	**2f**	Cs_2CO_3	$Pd_2(dba)_3$	±BINAP	toluene	**3a**	55[g]

[a] Reaction conditions: 10 mol % $Pd(PPh_3)_4$, no ligand, 2.0 equiv K_2CO_3, 2.0 equiv KO-*t*Bu, toluene (10 mL/mmol substrate), 90 °C, 24 h, nr = no reaction. [b] Reaction conditions: 2 mol % $Pd(OAc)_2$, 4 mol % ±BINAP, 2.0 equiv KO-*t*Bu, toluene (10 mL/mmol substrate), 90 °C, 24 h. [c] Reaction conditions: 10 mol % $Pd_2(dba)_3$, 7 mol % ±BINAP, 2.0 equiv K_2CO_3, 2.0 equiv KO-*t*Bu, DMF (10 mL/mmol substrate), 105 °C, 16 h. [d] Reaction conditions: 10 mol % $Pd_2(dba)_3$, 7 mol % ±BINAP, 2.0 equiv K_2CO_3, 2.0 equiv KO-*t*Bu, toluene (10 mL/mmol substrate), 90 °C, 16 h. [e] Reaction conditions: 10 mol % $Pd_2(dba)_3$, 10 mol % ±BINAP, 2.0 equiv K_2CO_3, 2.0 equiv KO-*t*Bu, toluene (10 mL/mmol substrate), 90 °C, 18 h. [f] Reaction conditions: 10 mol % $Pd_2(dba)_3$, 10 mol % Ph_3P, 2.0 equiv K_2CO_3, 2.0 equiv KO-*t*Bu, toluene (10 mL/mmol substrate), 90 °C, 24 h. [g] Reaction conditions: 10 mol % $Pd_2(dba)_3$, 7 mol % ±BINAP, 5.0 equiv Cs_2CO_3, toluene (10 mL/mmol substrate), 90 °C, 16 h.

SCHEME 2. Synthesis of cis-Fused Furobenzoxazocines



cyclization, but this effected the transformation in only 30% yield. However, application of the more recently disclosed reagents [$Pd_2(dba)_3$/±BINAP/KO-*t*Bu + K_2CO_3][15e] gave the desired cyclic products **3a**−**e** in 68−77% yield (Scheme 2).

The assigned structures of the products **3a**−**e** were based on spectroscopic data. The stereochemistries of H-**3a** (δ 4.30−4.45, d, J = 3.0 Hz) and other protons were derived by a comparison of the J values with those of similar products prepared by us.[7a]

Because we did not encounter any example of an intramolecular cycloamination to prepare oxazocine rings and the reported condition for benzazepine analogues did not efficiently provide access to the desired ring systems, we sought to explore further the scope of this reaction (Table 2).

Evaluations of ligands and palladium sources showed that the best conditions for the reaction were $Pd_2(dba)_3$ as the palladium source, ±BINAP as the ligand, KO-*t*Bu with K_2CO_3 as the base, and toluene as the solvent. A stoichiometric ratio of catalyst/ligand [10 mol % $Pd_2(dba)_3$/7 mol % ±BINAP] should be used in all cases. The use of excess ligand furnished a low yield of the desired product, **3a** (entry 5, Table 2). Loadings of catalyst less than 10 mol % were also less effective. A combination of K_2CO_3 (2.0 equiv) and KO-*t*Bu (2.0 equiv) worked best as the base component. The use of a weak base[21] like Cs_2CO_3 (5 equiv) gave a slight lowering of the yield (entry 9, Table 2). However, this worked better when the iodo substrate **2f** was used (entry 12, Table 2).

The feasibility of synthesizing benzoxazocines and tricyclic nucleoside analogues from the annulated sugar derivatives could be realized using **3a** (Scheme 3). Thus, **3a** was converted to the functionalized benzoxazocine **4** through a sequence of reactions involving the removal of the 1,2-*O*-isopropylidene group with 4% H_2SO_4 (v/v) in CH_3CN/H_2O (3:1), $NaIO_4$ cleavage of the diol, $NaBH_4$ reduction of the carbonyl group, and acetylation. The formation of **4** was deduced from the appearance of four methylene carbon signals at δ 59.2, 59.8, 63.8, and 77.3 in its ^{13}C NMR spectrum. As an application of our methodology, a nucleobase could be successfully installed on **3a** by cleavage of the acetonide group, acetylation to form the anomeric mixture of diacetates **5**, and reaction with 2,4-bis(trimethylsilyloxy)uracil in the presence of TMS−OTf in CH_3CN at room temperature. The presence in each case of two doublets at δ 5.65, 7.44 (J = 8.1 Hz) and a broad singlet at 8.89 (olefin and NH protons of uracil, respectively) in the ^1H NMR of **6** confirmed the presence of nucleobase in the product. The assignment of the structure **6** was further supported by ^1H−^1H COSY results. Anchimeric assistance by the neighboring acetoxy group directs the incoming nucleobase to the β face,[22] forming the nucleoside derivative **6**.

In conclusion, it has been demonstrated that a Pd-catalyzed intramolecular arylamination reaction can be applied to carbohydrate-derived substrates to synthesize tricyclic furobenzoxazocines. The key step in this synthesis exploits recent advancements in the area of palladium catalysts on sugar

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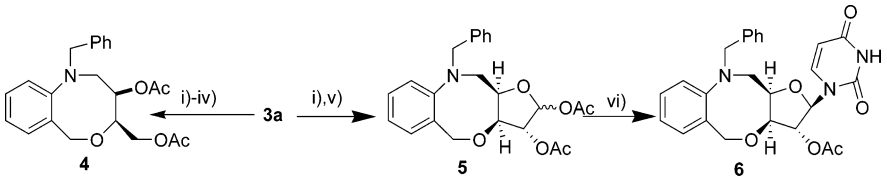
SCHEME 3. Conversion of 3a to Benzoxazocine Derivatives and a Modified Nucleoside[a]



[a] Reagents and conditions: (i) 4% H_2SO_4 (v/v), acetonitrile/water (3:1), rt, 12 h; (ii) aq $NaIO_4$, MeOH, rt, 45 min; (iii) $NaBH_4$, anhydrous MeOH, rt, 3 h; (iv) Ac_2O, pyridine, rt, 12 h, overall yield, 60%; (v) Ac_2O, pyridine, rt, 12 h, 90%; (vi) 2,4-bis-(trimethylsilyloxy)uracil, TMS−OTf, anhydrous acetonitrile, rt, 5 h, N_2, 60%.

derivatives to form benzofused oxazocines. Overall, the best conditions for this reaction are $Pd_2(dba)_3$ as the catalyst, ±BINAP as the ligand, KO-*t*Bu with K_2CO_3 as the base, and toluene as the solvent. The reaction worked on a variety of D-glucose-derived substrates, as shown in Table 2, and can be explored to synthesize tricyclic nucleoside analogues incorporating the oxazocine core. This simple protocol is capable of being extended to many other carbohydrate-derived precursors, leading to a unity of structural types.

Experimental Section

General Procedure for the Cycloamination Reaction of 2a and 2f. To a solution of amine **2a** (1 mmol) in dry toluene (10 mL/mmol substrate) were added bases KO-*t*Bu (224 mg, 2 equiv) and K_2CO_3 [276 mg, 2 equiv; or Cs_2CO_3 (5 equiv) for **2f** (1 mmol)], Pd-catalyst (10 mol %), and ±BINAP (7 mol %), and the reaction mixture was heated at 90 °C for 16 h under an argon atmosphere. After the disappearance of the starting amine (TLC), the crude reaction mixture was passed through a silica bed and then extracted with CH_2Cl_2 (4 × 25 mL). The organic layer was washed with water (4 × 25 mL) and dried, and the solvent was evaporated under reduced pressure. The crude mass was purified by flash chromatography over silica gel to furnish the cyclized product **3a**.

(2*R*,3*R*,3a*S*,11a*R*)-10-Benzyl-2,3-isopropylidenedioxy-3,3a,5,-10,11,11a-hexahydro-2*H*-furo[3,2-*c*][1,5]benzoxazocine (3a). Pale yellow solid; mp 116 °C; yield 75% (eluent, light petroleum/ethyl acetate, 7:1); $[\alpha]^{25}_D$ +108.7 (*c* 2.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.26 (s, 3H), 1.29 (s, 3H), 3.14 (dd-like, 1H), 3.26 (dd, J = 14.5, 5.2 Hz, 1H), 3.78−3.84 (m, 1H), 4.23 (d, 1H, J = 13.1 Hz), 4.37 (d, 1H, J = 3.0 Hz), 4.44 (d, 1H, J = 13.2 Hz), 4.58 (d-like, 2H), 4.90 (d, 1H, J = 12.9 Hz), 5.78 (d, 1H, J = 3.6 Hz), 6.93−7.38 (m, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.5, 26.8, 58.7, 59.3, 77.8, 79.8, 85.2, 89.4, 105.0, 111.3, 119.1, 122.6, 127.3, 2 × 128.4, 2 × 128.8, 129.1, 130.7, 133.1, 139.2, 154.8. IR ν_{max} (KBr): 2922, 1749, 1492, 1240, 1078, 1010 cm^{-1}. EIMS: *m*/*z* 367 (M^+, 70%). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.73; H, 6.98; N, 3.65.

(3*R*,4*R*)-3-Acetoxy-4-acetoxymethyl-1-benzyl-1,3,4,6-tetrahydro-2*H*-benzo[*c*][1,5]oxazocine (4). Compound **3a** (1 mmol) was dissolved in CH_3CN-H_2O (3:1) containing 4% H_2SO_4, and the mixture was stirred at room temperature for 12 h. The acidic solution was neutralized with solid $NaHCO_3$ at 0 °C and filtered, and the filtrate was evaporated in a vacuum. The residue was extracted with ethyl acetate (6 × 25 mL), and the combined organic layers were dried and concentrated under vacuum. The colorless residue was dissolved in a minimum volume of methanol and treated with aqueous $NaIO_4$ (256 mg, 1.2 mmol, dissolved in 3 mL of water) at 0 °C with stirring for 45 min at room temperature. The usual workup followed using a $NaBH_4$ reduction of the crude in dry methanol (20 mL), which afforded the diol. This was dissolved in dry pyridine (5 mL), treated with Ac_2O (0.5 mL), and stirred at room temperature for 12 h. Pyridine was evaporated from the reaction mixture under reduced pressure, and the product was extracted with $CHCl_3$ (6 × 25 mL). The combined organic layers were washed successively with cold aqueous HCl (1% v/v, 2 × 30 mL) and water (3 × 50 mL) and then dried. The solvent was evaporated under vacuum. The crude mass was purified by silica gel flash chromatography to afford the diacetate **4** as colorless oil: overall yield, 60% (eluent, light petroleum/ethyl acetate); $[\alpha]^D_{25}$ +68.43 (*c* 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.87 (s, 3H), 2.04 (s, 3H), 3.04 (dd, 1H, J = 13.7, 9.0 Hz), 3.20 (dd, 1H, J = 13.9, 5.2 Hz), 3.89−3.94 (m, 1H), 4.17 (d-like, 2H), 4.38 (d-like, 3H), 4.65 (d, 1H, J = 13.0 Hz), 4.95 (d, 1H, J = 13.0 Hz), 7.00−7.41 (m, 9H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 20.7, 20.9, 59.2, 59.8, 63.8, 72.0, 77.3, 81.0, 120.1, 123.7, 127.6, 2 × 128.6, 2 × 129.1, 129.2, 130.6, 134.7, 138.8, 154.5, 170.1, 170.8. IR ν_{max} (liquid film): 1741, 1493, 1450, 1371, 1233, 1044 cm^{-1}. ESIMS: *m*/*z* 384 (MH^+), 406 (MNa^+). Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.70; H, 6.40; N, 3.45.

(2*R*,3*R*,3a*S*,11a*R*)-3-Acetoxy-10-benzyl-2-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-3,3a,5,10,11,11a-hexahydro-2*H*-1,4-dioxa-10-aza-benzo[*a*]cyclopenta[*e*]cycloocten (6). 2,4-Bis-(trimethylsilyloxy)uracil was prepared by refluxing a mixture of uracil (336 mg, 3.0 mmol) and trimethyl silyl chloride (2 drops) dissolved in hexamethyl disilazane (5 mL) under N_2 for 10 h. The residue, obtained after evaporation of the solvent in vacuum, was dissolved in dry CH_3CN (5 mL) and added to a solution of diacetate compound **5** (411 mg 1.0 mmol) in dry CH_3CN (5 mL) and TMS−OTf (0.5 mL). The mixture was stirred at room temperature under N_2 for 5 h. TLC showed the completion of the reaction. The solution was neutralized with solid $NaHCO_3$ and water (3 drops), and the solvent was evaporated under vacuum. The gummy material was extracted with $CHCl_3$ (3 × 25 mL), and the organic part was washed with brine solution (3 × 25 mL), dried, and concentrated under vacuum. The crude product was purified by flash chromatography over neutral alumina to afford **6** as a sticky liquid (247 mg): yield, 60% (eluent, light petroleum/ethyl acetate, 1:1); $[\alpha]^D_{25}$ +98.69 (*c* 3.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.12 (s, 3H), 3.31−3.35 (m, 2H), 3.65−3.69 (m, 1H), 4.27 (d, 1H, J = 13.2 Hz), 4.36 (d, 1H, J = 3.5 Hz), 4.48 (d, 1H, J = 13.2 Hz), 4.63 (d, 1H, J = 12.9 Hz), 5.01 (d-like, 2H), 5.65 (d, 1H, J = 8.1 Hz), 5.90 (d, 1H, J = 2.2 Hz), 7.03−7.37 (m, 9H), 7.44 (d, 1H, J = 8.1 Hz), 8.89 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.6, 53.4, 58.8, 77.6, 81.1, 82.0, 87.7, 87.9, 102.8, 119.5, 123.0, 127.5, 2 × 128.5, 2 × 128.7, 129.4, 130.9, 132.9, 138.9, 140.2, 150.2, 154.3, 163.1, 169.4. IR ν_{max} (liquid film): 3206, 1749, 1692, 1601, 1455, 1377, 1227 cm^{-1}. ESIMS: *m*/*z* 464 (MH^+), 486(MNa^+). Anal. Calcd for $C_{25}H_{25}N_3O_6$: C, 64.79; H, 5.44; N, 9.07. Found: C, 64.52; H, 5.23; N, 8.98.

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Supporting Information Available: Experimental procedures for **1f**, **2a**−**f**, **3b**−**e**, and **5**; ^1H and ^{13}C NMR data for **1f**, **2a**−**f**, **3b**−**e**, and **5**; and NMR spectra files for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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