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Cu-Catalyzed N-Arylation of Oxazolidinones: An Efficient Synthesis of the κ-Opioid Receptor Agonist CJ-15161†

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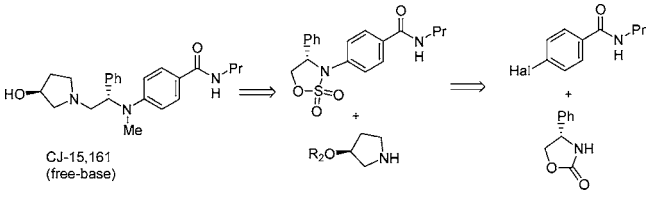

An efficient method for intermolecular N-arylation of oxazolidinones using catalytic copper in the presence of a bidentate ligand is reported. The conditions allow the use of copper and can be used to prepare enantiopure *N*-aryl β-amino alcohols. A short, scalable synthesis of CJ-15,161 is also reported. The required amines were obtained from the precursor α-amino acids or, more conveniently, from the corresponding 1,2-amino alcohols.

Cross-coupling is one of the most straightforward and general bond-forming methods. However, until a few decades ago, its development had been surprisingly sluggish. In particular, cross-coupling methodology to form C−X (X = N or other heteroatom) bonds is limited compared to analogous C−C bond-forming processes such as Suzuki, Stille, and Negishi coupling reactions, largely as as result of the sensitivity of functional groups to the harsh coupling conditions (e.g., presence of strong base, nucleophilic amine, high reaction temperature, etc.). Direct N-arylation with aryl halides is an attractive alternative to classical S_NAr reactions for introduction of nitrogen-containing functionalities in target molecules. Consequently, several recent reports have appeared in the literature with improved reaction conditions.[1] However, more work still needs to be done to improve the efficiency of this process for practical application.

Buchwald[2] and Hartwig[1b] have independently demonstrated the generality of Pd-catalyzed N-arylation involving amides and have extended this chemistry to acyclic carbamates.[3] Recently, Buchwald has further improved the scope of traditional Cu-catalyzed cross-couplings under Goldberg-type conditions.[4] Traditionally these involved stoichiometric copper reagents in a high-boiling solvent at high temperature. These reactions can now be performed using catalytic copper (<1−10 mol %) in the presence of a bidentate amine ligand,[4b] and a weak base (e.g., K_3PO_4 or K_2CO_3). These conditions tolerate many functional groups that are known to be problematic in palladium-catalyzed coupling reactions and provide a cost-effective and practical method for N-arylation. Recently, our laboratory was interested in N-arylation of oxazolidinones,[5] and we reported a method[6] involving a Pd-catalyzed C−N cross-coupling process between aryl chlorides and oxazolidinones that provided a convergent access to such systems in a relatively few number of steps. These derivatives could also be used as surrogates to produce a diverse array of enantiopure β-amino alcohols for further synthetic manipulation. We became interested in this area in the course of developing a fundamentally different synthetic strategy (Scheme 1) to a potential κ receptor agonist, CJ-15,161, that would present synthetic advantages as well as ensure our proprietary freedom to operate in this area.

The limitations of the original synthetic route to **10** (CJ-15,-161) included poor regioselectivity during the epoxide ring opening, processing a mixture of regioisomers, low overall yield, and the noncrystalline nature of the intermediates. The above

† Dedicated with respect to the memory of Professor U. R. Ghatak.

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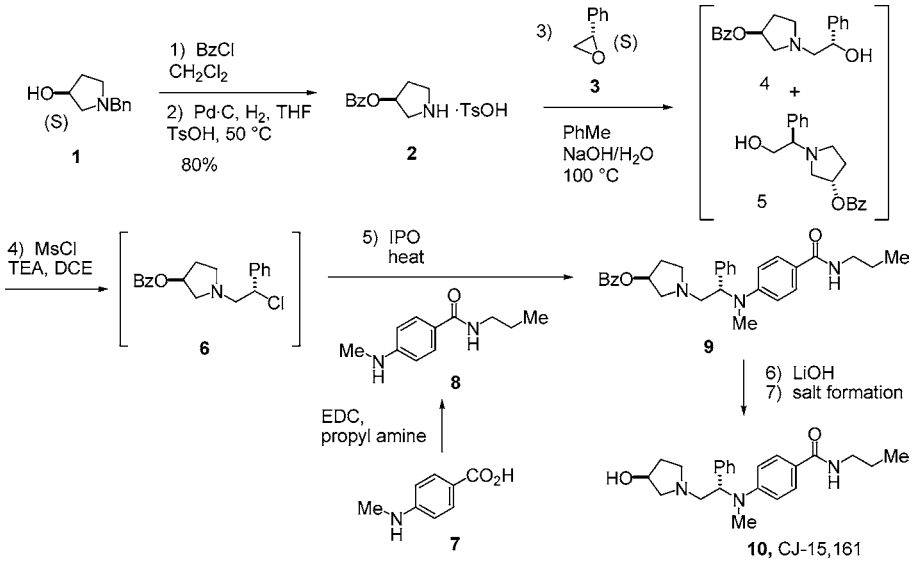
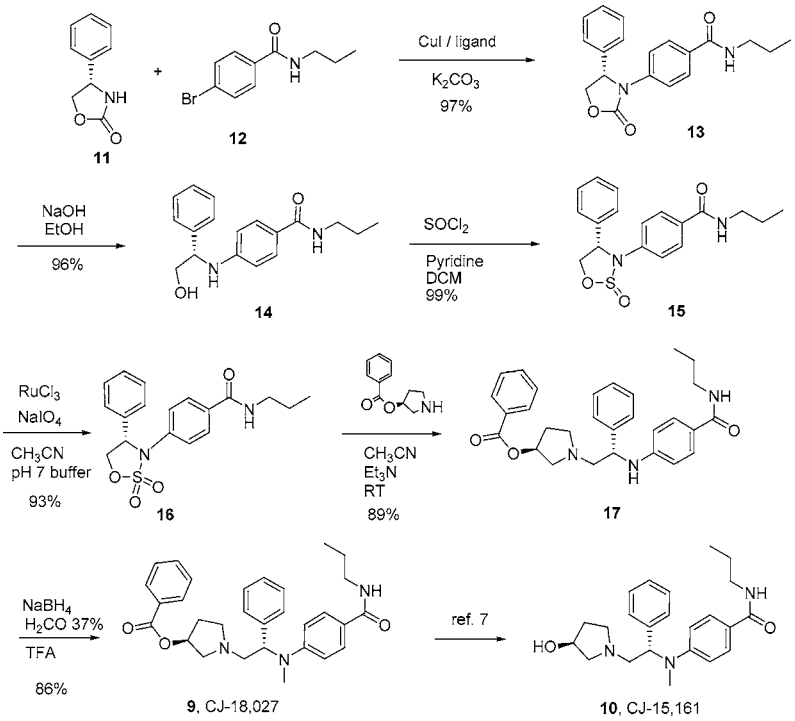
SCHEME 1. Original Route to CJ-15,161



SCHEME 2. Formal Synthesis of 10 Involving Cu-Catalyzed Aryl Amination



process, however, was made more efficient during a recent bulk campaign. A notable improvement was the ability to obtain crystalline **9** (Scheme 1).[7a] A synthesis of the penultimate intermediate **9**, which explores an alternative disconnection, a palladium-mediated C−N bond-forming step, has also been reported from our laboratories (Scheme 2).[7b] We herein report a mild, practical, and scalable synthetic method for N-arylation of oxazolidinone in general using relatively efficient (cost, operation) Cu-catalyzed conditions. This method has been successfully applied and elaborated to the synthesis of a *κ*-opioid receptor agonist (*κ*-ORA) CJ-15,161, leading to a process more amenable to large scale.

After some initial experiments, the reaction of oxazolidinones with ArX (X = Br, I) in the presence of catalytic Cu was demonstrated to be fairly general, and the results are summarized in Table 1. The coupled N-arylated oxazolidinones were obtained in high yield in most of the cases. Interestingly, the reaction turned out to be less sensitive to the electronic nature of the substituent of the substrate aryl halides compared to Pd-catalyzed coupling conditions. Also, the oxidation state of the copper catalyst (0, 1, or 2) proved not to be as important as is usually thought. The mechanism of this process is not well established. It is possible that the addition of a bidentate amine ligand not only helps solubilize copper salts but also promotes

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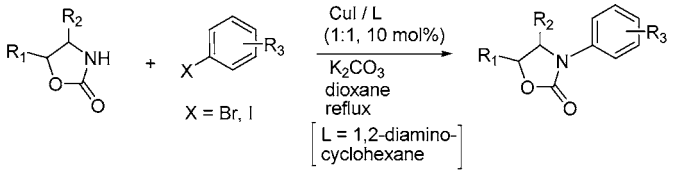
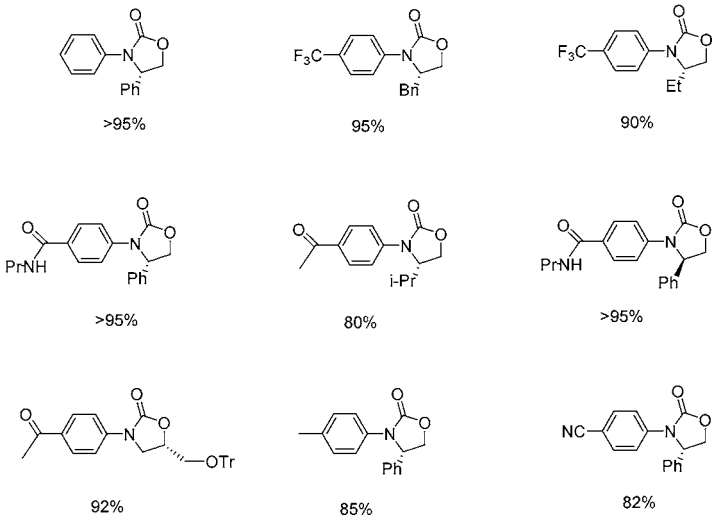
TABLE 1. Examples of Cu-Catalyzed N-Arylation of Oxazolidinones with Aryl Bromides[a]





[a] Reactions were performed in dioxane at 100−110 °C (bath temperature) under nitrogen. Yields refer to an average of two runs. The isolated compounds are 95−99% pure as judged by NMR and HPLC analysis. For physical characterization data of *N*-aryloxazolidinones, see ref 6.

the copper (I)/(II) disproportionation and stabilizes the active copper (I) species.

The application of this protocol has been demonstrated by the synthesis of CJ-15,161 as shown in Scheme 2. The key step in the synthesis was the coupling of the *p*-amido aryl bromide (**12**) with the oxazolidinone **11**. Hydrolytic deprotection of the *N*-aryl oxazolidinone **13** in ethanolic NaOH gave the amino alcohol **14**. Efficient conversion of **14** to **9** involved dual protection/activation involving oxathiazolidinone **16** and nucleophilic ring opening of **16** to the 1,2-diamine **17** with pyrrolidinol benzoate ester derivative, followed by reductive methylation.

In summary, we have developed efficient conditions for the Cu-catalyzed *N*-arylation of oxazolidinones and a formal synthesis of CJ-15,161 involving Cu-catalyzed aryl amination as the key step. The direct amination of an amide-containing aryl halide was an interesting aspect of this strategy. Efficient preparation of the substrate amine by dual protection/activation involving oxathiazolidinone formation is another notable feature of the synthetic scheme.

Experimental Section

General Methods. Reagents and solvents were obtained commercially and used without further purification. Reactions were carried out under dry nitrogen atmosphere. Chemical shifts in ^{1}H and ^{13}C NMR spectra are expressed in ppm relative to the internal solvent peak.

General Procedure for the Preparation of *N*-Aryl Oxazolidinones. Representative Procedure for 4-(2-Oxo-4-phenyl-oxazolidin-3-yl)-*N*-propyl-benzamide (13). (*S*)-(+)-4-Phenyl-oxazolodin-2-one[6a] (**11**, 50.0 g, 306.5 mmol), 4-bromo-*N*-propyl-benzamide (**12**, 74.19 g, 306.4 mmol), CuI (5.86 g, 30.8 mmol), and K_2CO_3 (84.84 g, 613.8 mmol) were charged in a N_2-purged flask. A solution of 1,2-diaminocyclohexane (3.70 mL, 30.8 mmol) and dioxane (310 mL) was added to the solids. The white mixture was heated to reflux overnight. After being cooled to 45 °C the reaction mixture was filtered through a pad of Celite. Residual solids on the pad were washed with warm dichloromethane. The combined filtrates were concentrated under reduced pressure and suspended in a saturated NH_4Cl solution. After stirring overnight, solids were recovered by filtration and dried to yield 96.30 g (97%) of the oxazolidinone **13** as light brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, 2H, J = 8.7 Hz), 7.46 (d, 2H, J = 8.7 Hz), 7.37−7.26 (m, 5H), 6.22 (br t, 1H), 5.43 (dd, 1H, J = 8.7, 5.8 Hz), 4.80 (t, 1H, J = 8.7 Hz), 4.21 (dd, 1H, J = 8.3, 5.8 Hz), 3.36 (q, 2H, J = 6.6 Hz), 1.59 (m, 2H), 0.94 (t, 3H, J = 7.5 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1 (C), 155.9 (C), 139.7 (C), 138.0 (C), 130.8 (C), 129.7 (CH), 129.2 (CH), 128.0 (CH), 126.3 (CH), 120.0 (CH), 70.1 (CH_2), 60.4 (CH), 42.0 (CH_2), 23.0 (CH_2), 11.7 (CH_3). Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 69.87; H, 6.16; N, 8.53.

4-(2-Hydroxy-1-phenyl-ethylamino)-*N*-propyl-benzamide (14). A suspension of oxazolidinone **13** (500 mg, 1.54 mmol) in 12.5 N NaOH (0.19 mL, 2.38 mmol) and EtOH (1 mL) was heated to 50 °C for 30 min. The mixture was cooled to room temperature and concentrated. The resulting solid was suspended in 14:1 water/dichloromethane and stirred for 4 h. Solids were recovered by filtration and dried, affording 441 mg (96%) of the aminol **14** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.46 (m, 2H), 7.33−7.25 (m, 5H), 6.45−6.41 (m, 2H), 5.97 (br t, 1H), 5.05 (d, 1H, J = 4.6 Hz), 4.50−4.46 (m, 1H), 3.95 (ddd, 1H, J = 11.2, 6.6, 4.2 Hz), 3.78−3.72 (m, 1H), 3.37−3.32 (m, 2H), 2.69 (t, 1H, J = 6.4 Hz), 1.57 (m, 2H), 0.93 (t, 3H, J = 7.5 Hz). ^{13}C NMR (101 MHz, DMSO-D6) δ 166.8 (C), 151.1 (C), 142.3 (C), 129.0 (CH), 128.9 (CH), 127.6 (CH), 127.5 (CH), 122.4 (C), 112.3 (CH), 66.6 (CH_2), 59.9 (CH), 41.4 (CH_2), 23.3 (CH_2), 12.1 (CH_3). Anal. Calcd

for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.46; H, 7.44; N, 9.48.

4-(2-Oxo-4-phenyl-[1,2,3]oxathiazolidin-3-yl)-*N*-propyl-benzamide (15). Thionyl chloride (200 μL, 2.75 mmol) and anhydrous pyridine (3.4 mL, 42.04 mmol) were added to dichloromethane (3.7 mL) at 0 °C. A suspension of aminol **14** (500 mg, 1.68 mmol) in DCM (24 mL) was added dropwise. The funnel was rinsed with dichloromethane (12 mL), and the resulting mixture was warmed slowly to room temperature. After stirring for 1 h 15 min, water and MTBE were added. Layers were separated. The aqueous layer was extracted with MTBE. The combined organic layers were washed with brine, dried over K_2CO_3, filtered, and concentrated to give 575 mg (99%) of compound **15** as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.60 (m, 2H), 7.37−7.29 (m, 3H), 7.26−7.22 (m, 2H), 7.01−6.98 (m, 2H), 6.07 (br t, 1H), 5.36 (dd, 1H, J = 8.3, 6.6 Hz), 5.29 (dd, 1H, J = 3.3, 6.6 Hz), 4.52 (dd, 1H, J = 8.3, 3.3 Hz), 3.35 (m, 2H), 1.58 (m, 2H), 0.93 (t, 3H, J = 7.5 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0 (C), 141.8 (C), 137.1 (C), 129.5 (CH), 129.1 (C), 128.9 (CH), 128.8 (CH), 126.5 (CH), 117.8 (CH), 78.1 (CH_2), 61.3 (CH), 41.9 (CH_2), 23.1 (CH_2), 11.7 (CH_3). Anal. Calcd for $C_{18}H_{20}N_2O_3S$: C, 62.77; H, 5.85; N, 8.13; S, 9.31. Found: C, 62.72; H, 5.82; N, 8.03; S, 9.25.

4-(2,2-Dioxo-4-phenyl-[1,2,3]oxathiazolidin-3-yl)-*N*-propyl-benzamide (16). Ruthenium(III) chloride hydrate (420 mg, 2.03 mmol) was added to a solution of compound **15** (10.0 g, 29.04 mmol) in dichloromethane (58 mL) and acetonitrile (58 mL) at 0 °C. The mixture was stirred for 10 min before addition of sodium periodate (9.94 g, 46.46 mmol) and a pH 7 buffer solution (58 mL). The mixture was stirred for 20 min, warmed to room temperature, and filtered through a pad of Celite. The residual solids on the Celite pad were rinsed with dichloromethane. The combined filtrates were diluted with water, and the separated aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give 9.78 g (93%) compound **16** as a beige solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67−7.64 (m, 2H), 7.41−7.34 (m, 5H), 7.20−7.16 (m, 2H), 6.10 (br t, 1H), 5.42 (t, 1H, J = 7.1 Hz), 4.95 (dd, 1H, J = 9.1 and 6.6 Hz), 4.51 (dd, 1H, J = 8.7, 7.9 Hz), 3.38−3.33 (m, 2H), 1.59 (m, 2H), 0.94 (t, 3H, 7.1 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9 (C), 138.3 (C), 134.7 (C), 131.7 (C), 129.8 (CH), 129.8 (CH), 128.7 (CH), 127.0 (CH), 119.9 (CH), 73.2 (CH_2), 62.4 (CH), 42.0 (CH_2), 23.0 (CH_2), 11.7 (CH_3). Anal. Calcd for $C_{18}H_{20}N_2O_4S$: C, 58.98; H, 5.59; N, 7.77; S, 8.90. Found: C, 58.92; H, 5.54; N, 7.53; S, 8.86.

Benzoic Acid 1-[2-Phenyl-2-(4-propylcarbamoylphenylamino)-ethyl]-pyrrolidin-3-yl Ester (17). Triethylamine (1.55 mL, 11.10 mmol) was added to a slurry of benzoic acid pyrollidin-3-yl-ester hydrochloride (2.52 g, 11.10 mmol) and compound **16** (2.00 g, 5.55 mmol) in acetonitrile (20 mL) at room temperature. After 1 h 40 min, 1 N aqueous hydrochloric acid (25 mL) was added, and the resulting mixture was stirred for 15 min. Water was added, and the acetonitrile was evaporated under reduced pressure. This aqueous solution was extracted repeatedly with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was adsorbed on silica and filtered through silica gel with 80% EtOAc/Hexanes (500 mL, first fraction) and 2% Et_3N/EtOAc (800 mL, second fraction). The second fraction filtrate was concentrated under reduced pressure to give 2.34 g (89%) of compound **17** as a white foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07−8.04 (m, 2H), 7.61−7.45 (m, 5H), 7.38−7.23 (m, 5H), 6.50−6.47 (m, 2H), 5.90 (br t, 1H, J = 5.6 Hz), 5.46 (br s, 1H), 5.43−5.38 (m, 1H), 4.33 (dd, 1H, J = 10.8, 3.7 Hz), 3.35 (qd, 2H, J = 7.1, 1.3 Hz), 3.07 (dd, 1H, J = 10.8, 6.2 Hz), 2.96−2.88 (m, 2H), 2.81−2.78 (m, 1H), 2.61 (dd, 1H, J = 12.2, 4.4 Hz), 2.57−2.52 (m, 1H), 2.36 (m, 1H), 2.06−1.99 (m, 1H), 1.57 (m, 2H), 0.93 (t, 3H, J = 7.5 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6 (C), 166.6 (C), 150.7 (C), 142.1 (C), 133.4 (CH), 130.4 (C), 129.8 (CH), 129.0 (CH), 128.7 (CH), 128.5 (CH), 127.7 (CH), 126.5 (CH), 123.6 (C), 113.4 (CH), 74.9 (CH), 63.0 (CH_2), 60.1 (CH_2), 57.0 (CH), 52.5 (CH_2), 41.8 (CH_2), 32.2 (CH_2), 23.3 (CH_2), 11.7 (CH_3). Anal. Calcd for $C_{29}H_{33}N_3O_3$: C, 73.86; H, 7.05; N, 8.91. Found: C, 73.79; H, 7.15; N, 8.86.

Benzoic Acid 1-{2-[Methyl-(4-propylcarbamoyl-phenyl)-amino]-2-phenyl-ethyl}-pyrrolidin-3-yl Ester (9). Sodium borohydride (80 mg, 2.12 mmol) and trifluoroacetic acid (2.65 mL) were stirred at room temperature for 20 min. The solution was cooled to 0 °C before addition of DCM (2.65 mL), compound **17** (500 mg, 1.06 mmol), and formaldehyde (37 wt % in H_2O, 158 μL, 2.12 mmol). The mixture was stirred at 0 °C for 90 min, warmed to room temperature, basified with NaOH (1 M), and stirred vigorously for 15 min. Layers were separated. The aqueous layer was extracted repeatedly with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with 60% EtOAc/2% Et_3N/hexanes to yield 443 mg (86%) of **9** (CJ-18,027) as a white foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99−7.97 (m, 2H), 7.66−7.62 (m, 2H), 7.58−7.53 (m, 1H), 7.45−7.41 (m, 2H), 7.34−7.25 (m, 5H), 6.83−6.79 (m, 2H), 5.95 (br t, 1H), 5.36−5.32 (m, 1H), 5.17−5.14 (m, 1H), 3.41−3.36 (m, 2H), 3.11−3.08 (m, 2H), 2.96 (dd, 1H, J = 10.6, 6.0 Hz), 2.89−2.84 (m, 5H), 2.31−2.23 (m, 1H), 1.96−1.89 (m, 1H), 1.61 (q, 2H, J = 7.5 Hz), 0.96 (t, 3H, J = 7.5 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6 (C), 166.6 (C), 152.8 (C), 142.2 (C), 133.2 (CH), 130.5 (C), 129.8 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 127.6 (CH), 127.2 (CH), 122.4 (C), 112.0 (CH), 74.9 (CH), 60.6 (CH), 60.4 (CH_2), 57.6 (CH), 53.1 (CH_2), 41.8 (CH_2), 32.6 (CH_3), 32.2 (CH_2), 23.3 (CH_2), 11.8 (CH_3). Anal. Calcd for $C_{30}H_{35}N_3O_3$: C, 74.20; H, 7.26; N, 8.65. Found: C, 74.33; H, 7.31; N, 8.59.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **9** and **13**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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