JOC*Note*

Reversible Carboxamide-Mediated Internal Activation at C(6) of 2-Chloro-4-anilino-1*H*-pyrrolo[2,3-*d*]pyrimidines

Stanley D. Chamberlain, Roseanne M. Gerding, Huangshu Lei, Ganesh Moorthy, Samarjit Patnaik, Anikó M. Redman, Kirk L. Stevens, Joseph W. Wilson, Bin Yang, and J. Brad Shotwell*

GlaxoSmithKline, Oncology R&D, 5 Moore Drive, Research Triangle Park, North Carolina 27709

jbs26900@gsk.com

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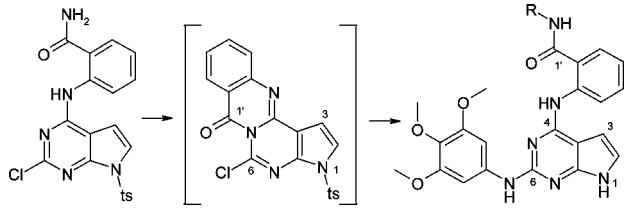
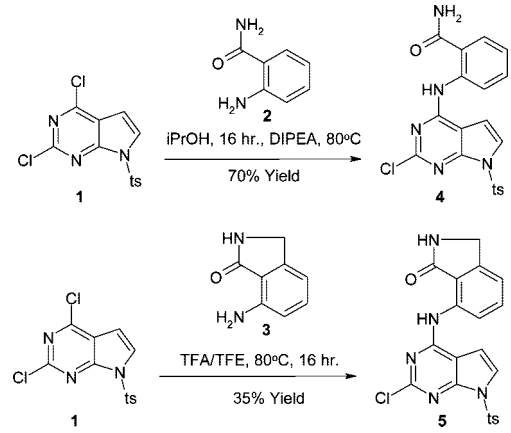


A synthetic route to bisanilino-1*H*-pyrrolo[2,3-*d*]pyrimidines has been discovered, wherein the C(6)-chloride reactivity is necessarily enhanced via reversible acid-catalyzed internal activation of the pyrimidine ring by a C(1′)-carboxamide moiety. Subsequent selective nucleophilic displacements at C(6) and C(1′) constitute a one-pot tandem protocol for the rapid assembly of bisanilino-1*H*-pyrrolo[2,3-*d*]pyrimidines.

Structures possessing aminopyrimidines are remarkably general in their ability to potently inhibit a variety of protein kinases via a direct 2-point interaction with the kinase hinge. Potent inhibition of a number of anticancer/anti-inflammation kinase targets including AurA/B,[1] IGF-1R/IR,[2] FAK,[2] VEGF,[3] ALK,[2] SYK,[4] IKK,[5] and JAK[6] by 2,4-bisanilino pyrimidines is well-documented. The development of this class of inhibitors has been aided by straightforward chemical syntheses wherein 2,4-dichloropyrimidines are versatile starting materials, allowing sequential derivatization of both chlorides via S_NAR displacements with functionalized anilines. We recognized the potential for the corresponding 4,6-bisanilino-1*H*-pyrrolo[2,3-*d*]pyrimidines to bind to kinases in an analogous manner, with a 3-point contact to the kinase hinge, and expected that chemical diversification of known dichloro-pyrrolopyrimidine **1** via sequential chloride displacements would proceed smoothly in analogy to chemistry reported for 2,4-dichloropyrimidines.[1−6] We were especially interested in 1*H*-pyrrolo[2,3-*d*]pyrimidines[2] containing side-chain carboxamides and herein describe our successful synthetic efforts toward this class of potential kinase inhibitors.

SCHEME 1. Synthesis of Carboxamides 4 and 5[7]



Dichloride **1** was prepared according to previous reports[8] and readily derivatized by acid- or base-mediated addition of anilines **2** and **3** to afford C(4)-substituted pyrrolopyrimidines **4** and **5** in reasonable yields (Scheme 1). Exposure of **4** to aniline **6** and hydrochloric acid, quenching with ammonium hydroxide, and subsequent detosylation, afforded C(6) derivative **8** in good yield. In contrast, chloride **5** proved refractory toward acid-catalyzed, electrophilic aromatic substitution, and preparation of **9** using palladium-catalyzed methods proved extremely capricious (Scheme 2).

In general, pyrrolopyrimidines are much more resistant toward S_NAR displacements than corresponding simple pyrimidine substrates, with their reduced electrophilicity apparently a result of the electronic impact of the pendant pyrrole. As such, within

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(5) Wagnon, J.; Nguefack, J.; Jegham, S.; Bosch, M.; Bouaboula, M.; Casellas, P.; Tonnerre, B.; Olsen, J.; Mignani, S. Novel 2,4-Dianilinopyrimidine Derivatives, The Preparation Thereof, Their Use as Medicaments, Pharmaceutical Compositions and, in Particular, as IKK Inhibitors. WO 2007/006926 A2, November 25, 2005.

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(7) TFE = trifluoroethanol.

(8) Gore, P.; Patel, V. K.; Walker, A.; Woodrow, M. Pyrrolopyrimidine Derivatives as Syk Inhibitors and Their Preparation, Pharmaceutical Compositions, and Use in the Treatment of Inflammatory and Allergic Diseases. WO 2007042298 A1, April 19, 2007.

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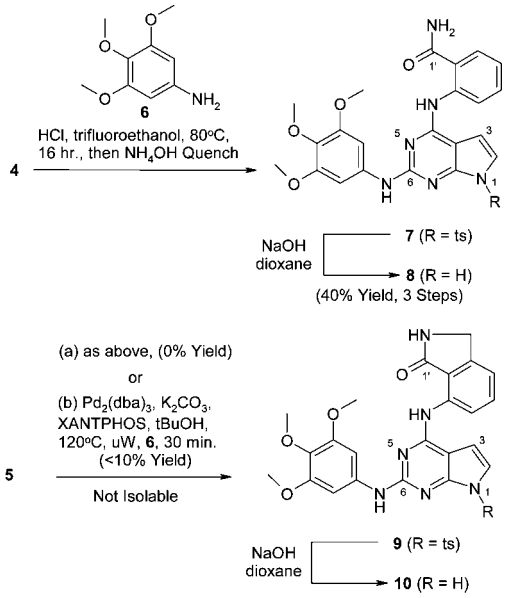
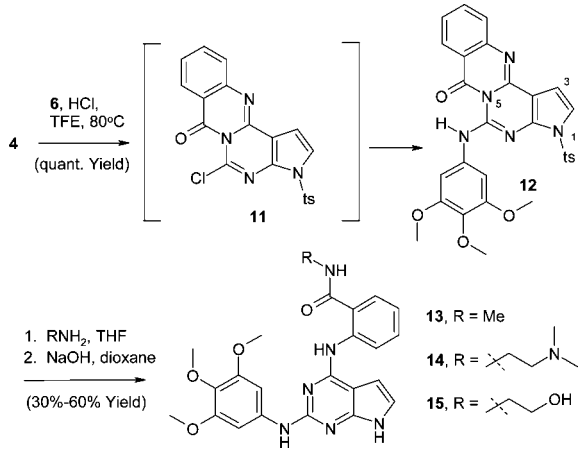
SCHEME 2. Apparent Reduced Reactivity of 5 Toward Chloride Displacements



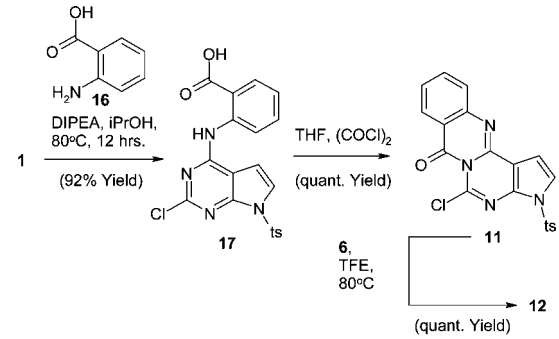
SCHEME 3. Reversible Internal Activation at C(6)



the pyrrolopyrimidine series, we were quite surprised at the reactivity differences between **4** and **5**. Whereas **4** apparently reacts analogously to the related pyrimidines reported elsewhere,[1−6] **5** has a reactivity profile more consistent with other literature reports of pyrrolopyrimidines.[8] In our hands, a number of molecules related to **4**, but lacking a carboxamide moiety at C(1′), proved completely refractory to S_NAR displacements, consistent with the reduced electrophilicity of pyrrolopyrimidines in general, but inconsistent with the reactivity of **4**. Therefore, the reactivity of **4** was an outlier among a variety of similarly substituted pyrrolopyrimidines we investigated and suggested a unique mechanism by which the primary carboxamide moiety (present in **4**) directly participated in the C(6)-chloride displacement.

Analysis of unquenched reacting mixtures by LCMS suggested a discrete intermediate was involved in the conversion of **4** to **7**. Exposure of carboxamide **4** to HCl and aniline **6** at 80 °C for 12 h, followed by isolation prior to quenching with ammonium hydroxide, affords stable and isolable tetracyclic **12** (Scheme 3), wherein displacement of the C(6) chloride has been accompanied by concomitant intramolecular cyclization of the

SCHEME 4. Isolation and Reactivity of Key Intermediate 11



carboxamide at N(5).[9] Interestingly, tetracyclic **12** can be intercepted by a variety of primary amines, in addition to ammonia, to afford the corresponding secondary amide products (**13**−**15**). This constitutes a general route to bisanilino-1*H*-pyrrolo[2,3-*d*]pyrimidines, wherein the reduced reactivity of the C(6) chloride is enhanced via reversible internal activation of the pyrimidine ring by the C(1′) carboxamide, with a concomitant elimination of ammonia and acylation of the N-5 pyrimidine nitrogen.

We postulated that the in situ formation of chloride **11** accounts for the inherent differences in reactivity between **4** and **5** because the constraint inherent in lactam **5** would prevent intramolecular activation by N(5). Also noteworthy, trifluoroethanol proved uniquely efficient in its ability to promote the conversion of **4** → **12**.[10] This suggests a key alcoholysis event could precede the formation of **11**.[11] This further accounts for the loss of reactivity for **5** since the opening of the lactam by trifluoroethanol would leave a high, effective concentration of a primary amino group more disposed toward displacement of a transient trifluoroethyl ester than the N(5) nitrogen.

Aiming to prepare and isolate **11** as a valuable activated synthetic intermediate, we found treatment of dichloride **1** with anthranilic acid under standard conditions, followed by exposure to oxalyl chloride, afforded **11** that is stable and isolable as the HCl salt (Scheme 4).[12] Interestingly, **11** is extremely reactive toward a variety of anilines exclusively at C(6) and afforded the corresponding displacement products in <2 h at 80 °C or upon stirring at room temperature for 16 h. This enhanced reactivity at C(6) is consistent with acid-catalyzed, intramolecular cyclization (i.e., **4** →**11**) functioning as a key step in the one-pot formation of tetracyclic **12** from **4** (Scheme 3).

We envisioned the exploitation of this internal C(6)-chloride activation for the synthesis of **10**, as well as for other molecules lacking a primary carboxamide moiety, would be possible via manipulation of the carboxamide following the activation step.

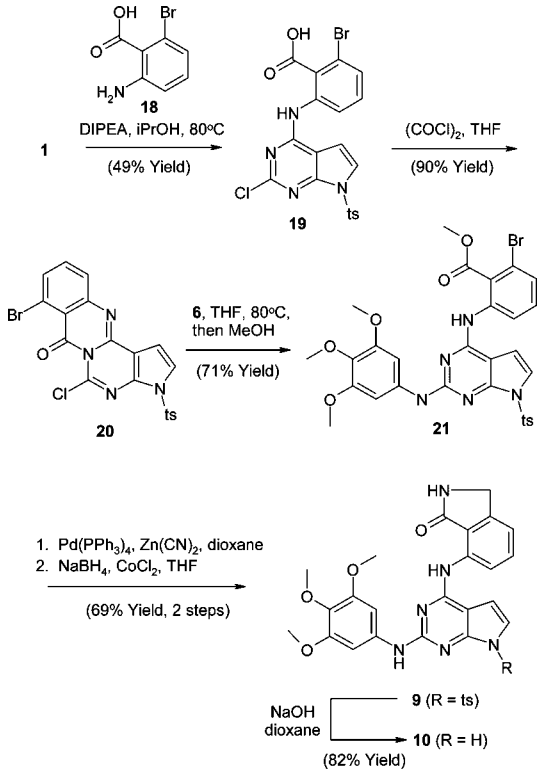
(9) Although this general tetracyclic substructure has appeared in several communications, it has not been exploited as a general means of activating electron-rich pyrimidines or related substrates. See: (a) Vasudevan, A.; Mavandadi, F.; Chen, L.; Gangjee, A. *J. Org. Chem.* **1999**, *64*, 634. (b) Querioz, M.; Begouin, A.; Ferreira, I.; Kirsch, G.; Calhelha, R.; Barbosa, S. *Eur. J. Org. Chem.* **2004**, 3679. (c) El-Bahaie, S.; El-Deeb, A.; Assy, M. *Pharmazie* **1991**, *46*, 26. (d) Abdel-Fattah, A.; Aly, A.; Gad, F.; Hassan, N.; El-Gazzar, A. *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *163*, 1.

(10) Additionally screened were 2-propanol, *tert*-butanol, DMF, and hexafluoroisopropanol.

(11) Products arising from alcoholysis of the amide and ring opening of **11** by trifluoroethanol can sometimes be observed in the reacting mixtures prior to quenching with ammonia or another base.

(12) Additionally, tetracyclic **11** could be isolated by exposure of **4** to HCl in trifluoroethanol and as a component of reaction mixtures quenched prematurely with saturated aqueous sodium bicarbonate.

SCHEME 5. Synthesis of Key Lactam 10



Accordingly, aniline **18** added efficiently to dichloride **1**, and subsequent exposure to oxalyl chloride afforded tetracyclic bromide **20**. Treatment of **20** with trimethoxy aniline **6**, followed by dilution with warm methanol, efficiently promoted tandem C(6)-chloride displacement and subsequent methanolysis to afford ester **21** in good overall yield. With the requisite C(6) aniline in place, cyanation and treatment with cobalt borohydride[13] gave lactam **9** in excellent yield. Basic hydrolysis afforded the target pyrrolopyrimidine **10** (Scheme 5).

In summary, we have developed an efficient protocol for the rapid assembly of a variety of carboxamides containing bisanilinopyrrolopyrimidines (**8**, **10**, and **13**−**15**). The reduced reactivity of the C(6) chloride relative to related pyrimidine substrates has been overcome through reversible internal activation of the pyrrolopyrimidine ring by the C(1′) carboxamide via tetracyclic **11** and **20**. As such, this approach does not rely on an S_NAR displacement at C(6); rather, a tandem intramolecular cyclization/aniline displacement, followed by nucleophilic addition at C(1′), is employed. This allows a means of both amide diversification and restoration of the pyrimidine ring. Careful synthetic design has allowed the exploitation of this reversible internal activation in the context of final molecules not possessing primary carboxamide moieties (e.g., **10**).

Experimental Section

2-({2-Chloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)benzoic Acid (17). A slurry of 2,4-dichloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine **1** (50 g, 146 mmol) and 2-aminobenzoic acid **16** (27.2 g, 175 mmol) in *i*-PrOH (1200 mL) and 30 mL of DIEA were heated to reflux. After 1 h, the solution turned a clear brown color, at which time about 450 mL of volatiles was removed via distillation. The remaining mixture was treated with DIEA (90 mL) and heated to reflux for 16 h. The reaction mixture was then further concentrated by distilling more volatiles off (400 mL over 4 h), then continued heating at reflux overnight. The resulting mixture was cooled to room temperature and concentrated under reduced pressure to obtain a thick oil, which was diluted with EtOAc (1.3 L), then sequentially washed with a 1 N HCl solution (2 × 500 mL) and a saturated $NaHCO_3$ solution (500 mL). Further dilution of the separated organic layer with a saturated NaCl solution (500 mL) led to the formation of a thick precipitate. The entire mixture was filtered, and the solid was washed with Et_2O. The solid was dried overnight in a vacuum oven at 60 °C to obtain 2-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)benzoic acid **17** as a yellow solid (61.63 g, 92%): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.34 (s, 1 H), 8.30 (d, J = 8.2 Hz, 1 H), 7.97 (d, J = 8.4 Hz, 2 H), 7.85−7.93 (m, 1 H), 7.72 (d, J = 3.8 Hz, 1 H), 7.57 (t, J = 7.2 Hz, 1 H), 7.44 (d, J = 8.2 Hz, 2 H), 7.13 (t, J = 7.6 Hz, 1 H), 6.69 (d, J = 4.0 Hz, 1 H), 2.33 (s, 3 H); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm 21.11, 102.38, 105.33, 119.28, 121.96, 123.32, 124.38, 127.73, 130.19, 131.07, 133.66, 133.96, 139.75, 146.28, 150.34, 153.64, 154.08, 169.42; IR (KBr pellet) 3410, 1624, 1576, 1560, 1388, 1284, 1260, 1188, 1164, 1147, 670, 578 cm^{-1}; HRMS *m/e* calcd for $C_{20}H_{16}ClN_4O_4S$ $(M + H)^+$ 443.05753, found 443.05750.

5-Chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[2′,3′:4,5]pyrimido[6,1-*b*]quinazolin-7(3*H*)-one (11). A slurry of 2-({2-chloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)benzoic acid **17** (33.05 g, 71.7 mmol) and THF (1000 mL) was treated with a few drops of DMF and oxalyl chloride (12.55 mL, 143 mmol). The resulting fine slurry was stirred at rt for 3 h, then maintained at ∼5 °C for 17 h, without stirring. The cold slurry was filtered, the solid washed with cold THF, then dried in a vacuum oven at rt to obtain 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[2′,3′:4,5]-pyrimido[6,1-*b*]quinazolin-7(3*H*)-one hydrogen chloride salt **11** as a pale yellow solid (∼34.6 g, quantitative yield ∼100%): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.37 (s, 3H), 7.07 (d, 4.21 Hz, 1H), 7.34 (d, J = 4.21 Hz, 1H), 7.47 (d, 8.06 Hz, 2H), 7.53−7.63 (m, 1H), 7.78−7.90 (m, 1H), 8.00 (d, J = 8.42 Hz, 2H), 8.18 (dd, J = 7.78 Hz, 1.74 Hz, 1H), 9.28 (d, J = 8.42 Hz, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm (single aryl resonance unresolved) 21.12, 93.83, 104.27, 119.97, 121.52, 121.82, 126.61, 127.11, 127.84, 130.05, 134.16, 138.18, 145.49, 145.89, 151.72, 154.23, 158.42; IR ($CDCl_3$ solution) 1723, 1625, 1602, 1387, 1181, 1167, 1157 cm^{-1}; HRMS *m/e* calcd for $C_{20}H_{13}ClN_4O_3S$ $(M + H)^+$ 425.0475, found 425.0475.

3-[(4-Methylphenyl)sulfonyl]-5-{[3,4,5-tris(methyloxy)phenyl]amino}pyrrolo[2′,3′:4,5]pyrimido[6,1-*b*]quinazolin-7(3*H*)-one (12). To a suspension of 5-chloro-3-[(4-methylphenyl)sulfonyl]pyrrolo[2′,3′:4,5]pyrimido[6,1-*b*]quinazolin-7(3*H*)-one HCl salt **11** (3.0 g, 6.50 mmol) in 2,2,2-trifluoroethanol (100 mL) was added 3,4,5-tris(methyloxy)aniline (1.31 g, 7.15 mmol), and the mixture was heated at 80 °C for 2 h. At this time, solvents were removed under reduced pressure to afford 3-[(4-methylphenyl)sulfonyl]-5-{[3,4,5-tris(methyloxy)phenyl] amino}pyrrolo[2′,3′:4,5]pyrimido[6,1-*b*]-quinazolin-7(3*H*)-one HCl salt **12** (4.2 g, 6.91 mmol) as a yellow solid with sufficient purity for direct use in subsequent transformations.

***N*-Methyl-2-[(2-{[3,4,5-tris(methyloxy)phenyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]benzamide (13).** 3-[(4-Methylphenyl)sulfonyl]-5-{[3,4,5-tris(methyloxy) phenyl]amino}pyrrolo[2′,3′:4,5]pyrimido[6,1-*b*]quinazolin-7(3*H*)-one HCl salt **12** (400 mg, 0.658 mmol) was suspended in THF (10 mL) and a solution of 2 M $MeNH_2$ in THF (3.29 mL, 6.58 mmol). After stirring overnight, the reaction mixture was diluted with ethyl acetate and washed with water and a saturated brine solution. Organics were dried over sodium sulfate, and solvents were removed under reduced pressure. The residue was flushed through a SiO_2 plug with 10% MeOH/CH_2Cl_2 to afford intermediate *N*-methyl-2-[(7-[(4-methylphenyl)-sulfonyl]-2-{[3,4,5-tris(methyloxy)phenyl]amino}-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]benzamide (365 mg, 0.606 mmol) as a

(13) Satoh, T.; Suzuki, S. *Tetrahedron Lett.* **1969**, *52*, 4555.

yellow foam (ESIMS $(M + H)^+ = 603$). The residue was dissolved in dioxane (6 mL), and 2 N NaOH (4 mL) was added in a microwave-safe vessel. The reaction was heated in a microwave at 120 °C for 15 min. The reaction was diluted with ethyl acetate, and the organic layer was washed with water and saturated brine solution and dried over sodium sulfate. Solvents were removed under reduced pressure, and the residue was purified by chromatography on SiO_2 to afford *N*-methyl-2-[(2-{[3,4,5-tris(methyloxy)phenyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]benzamide **13** (168 mg, 0.375 mmol, 57% yield, two steps) as a tan solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.83 (d, $J = 4.39$ Hz, 3 H), 3.62 (s, 3 H), 3.76 (s, 6 H), 6.32 (dd, $J = 3.20$, 1.83 Hz, 1 H), 6.98−7.09 (m, 2 H), 7.28 (s, 2 H), 7.42−7.53 (m, 1 H), 7.75 (d, $J = 7.87$ Hz, 1 H), 8.75 (d, $J = 4.58$ Hz, 1 H), 8.87 (s, 1 H), 9.10 (d, $J = 8.42$ Hz, 1 H), 11.34 (s, 1 H), 11.76 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 170.2, 156.1, 153.4, 153.3, 152.7, 141.9, 138.5, 132.5, 132.1, 128.6, 121.0, 120.9, 120.8, 119.4, 99.6, 97.9, 97.1, 60.8, 56.3, 27.0; IR (solid powder) 3410, 3305, 1582, 1509, 1485, 1451, 1413, 1238, 1130, 1003, 831, 754, 696 cm^{-1}; HRMS *m/e* calcd for $C_{23}H_{25}N_6O_4$ $(M + H)^+$ 449.19318, found 449.19302.

Acknowledgment. The authors thank Erich Baum for helpful suggestions during the preparation of the manuscript.

Supporting Information Available: Additional experimental details and spectroscopic characterization for **4**, **5**, **7**−**15**, **17**, and **19**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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