JOC Article

Palladium-Catalyzed Regioselective Hydrodebromination of Dibromoindoles: Application to the Enantioselective Synthesis of Indolodioxane U86192A

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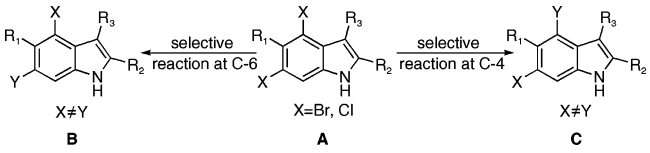
A novel approach to the selective preparation of 4-bromoindoles was developed via $Pd(OAc)_2$/*rac*-BINAP catalytic reactions. A variety of 4,6-dibromoindoles were transformed to 4-bromoindoles with high regioselectivity. This methodology, along with C−N and C−O bond-forming reactions developed in our laboratory, was applied to the enantioselective synthesis of indolodioxane U86192A, an antihypertensive agent.

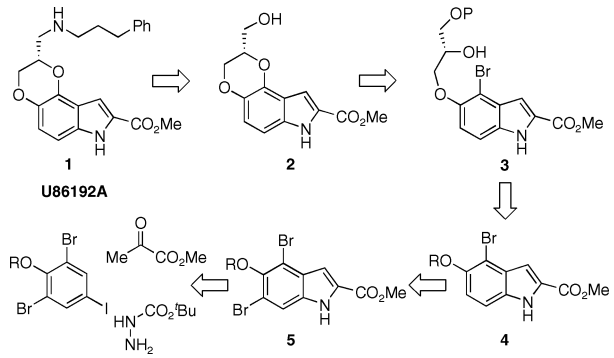
The Fischer indole synthesis has been one of the most versatile methods for the preparation of indoles for over 100 years, and its variations have continually improved on its drawbacks.[1] However, preparation of 4- or 6-substituted or 4,5-disubstituted indoles, which appear in an important class of alkaloids,[2] via the Fischer synthesis is still a significant challenge due to the regiochemical ambiguity occurring during the [3,3]-sigmatropic rearrangement, an integral step in this process.[1a,b] A variety of traditional[3−6] and palladium-catalyzed methods[7−10] have been developed to construct the pyrrole ring using an annelative method from properly substituted aromatic precursors. These methods have the disadvantage in that they require specifically polyfunctionalized benzenes, which are often difficult or expensive to make.

The conceptual outline for our approach is outlined in Scheme 1. It involves the synthesis of intermediate **A**,

SCHEME 1



SCHEME 2. Retrosynthetic Analysis for the Synthesis of Indolodioxane U86192A



in which the substituents at C-4 and C-6 are identical. To access, in a selective manner, B and/or C, regioselective transformations that proceed with high selectivity must be developed. Herein, we describe our first realization of this approach that is a highly selective route to 4-bromo-5-substituted indoles.[12] In addition, we use the method, in combination with other processes recently developed in our laboratory, as the keystones of an asymmetric synthesis of indolodioxane U86192A (Scheme 2, **1**), a compound with interesting antihypertensive activity.[20]

Results and Discussion

Palladium-Catalyzed Regioselective Hydrodebromination of Dibromoindoles. As a prototypical example of **A**, we prepared a series of 4,6-dibromoindoles in a one-pot process via the chemoselective (I vs Br) Cu-catalyzed coupling of symmetric dibromoaryliodides and

(1) (a) Robinson, B. *The Fischer Indole Synthesis*; John Wiley and Sons: Chichester, 1982. (b) Hughes, D. L. *Org. Prep. Proced. Int.* **1993**, *25*, 609. (c) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251.

(2) (a) Raffauf, R. F.*A Handbook of Alkaloids and Alkaloid-containing Plants;* Wiley-Interscience: New York, 1970. (b) Rahman, A. *Indole Alkaloids*; Harwood Academic Publisher: Amsterdam, 1998. (c) Manske, R. H. F.; Holmes, H. L. *The Alkaloids: The Ergot Alkaloids*; Academic Press: New York, 1965; Vol. 8, p 725.

(3) For reviews on indole syntheses, see: (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (b) Sundberg, R. J. *Indoles*; Academic Press: San Diego, 1996.

(4) (a) Madelung, W. *Chem. Ber.* **1912**, *45*, 1128. (b) Houlihan, W. J.; Parrino, V. A.; Uike, Y. *J. Org. Chem.* **1981**, *46*, 4511. (c) Wacker, D. A.; Kasireddy, P. *Tetrahedron Lett.* **2002**, *43*, 5189.

(5) (a) Reissert, A. *Chem. Ber.* **1897**, *30*, 1030. (b) Izumi, T.; Soutome, M.; Miura, T. *J. Heterocycl. Chem.* **1992**, *29*, 1625. (c) Butin, A. V.; Stroganova, T. A.; Lodina, I. V.; Krapivin, G. D. *Tetrahedron Lett.* **2001**, *42*, 2031.

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(9) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.

(10) Soderberg, B. C.; Schriver, J. A. *J. Org. Chem.* **1997**, *62*, 5838.

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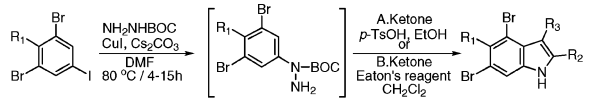
TABLE 1. One-Pot Preparation of 4,6-Dibromoindoles[a]



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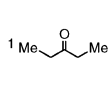
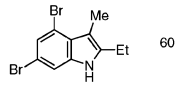
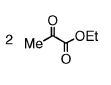
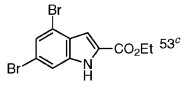
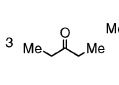
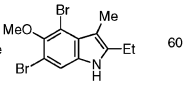
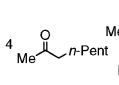
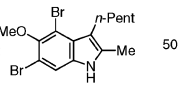
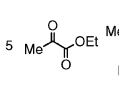
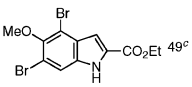
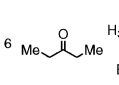
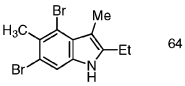
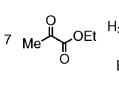
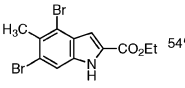
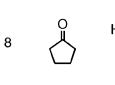
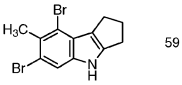
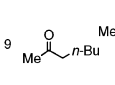
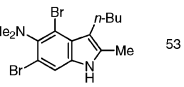
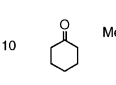
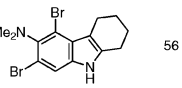
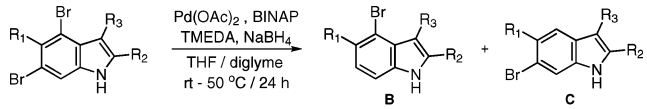
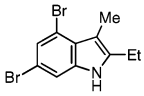
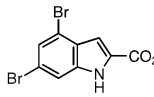
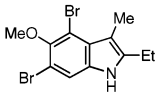
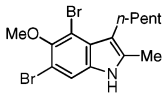
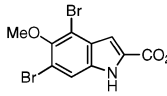
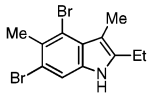
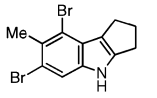
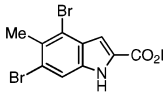
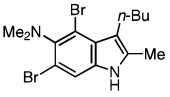
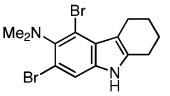
1			60
2			53[c]
3			60
4			50
5			49[c]
6			64
7			54[c]
8			59
9			53
10			56

[a] Reaction conditions: Cu-catalyzed couplings; 1.0 equiv of dibromoaryl iodide, 1.2 equiv of *tert*-butylcarbazate, 5 mol % of CuI, 1.4 equiv of Cs_2CO_3, and DMF (4 mL/mmol of dibromoaryl iodide). Fischer indole cyclization: (A) 1.0 equiv of ketone, 1.6 equiv of *p*-TsOH·H_2O, EtOH, 90 °C or (B) 1.5 equiv of ketone, 2 mL of Eaton's reagent, CH_2Cl_2,[16] 45 °C. [b] Isolated yields for two steps (average of two runs) of compounds estimated to be >95% pure as determined by ^{1}H NMR and combustion analysis. [c] For the cyclization to the indole, method B was used.

TABLE 2. Regioselective Hydrodebromination of 4,6-Dibromoindoles



Entry	Indole	Yield (%)[b] B	Yield (%) C
1		(no selectivity)	
2		(no selectivity)	
3		86	----
4		85	----
5		87	----
6			79 ----
7			81 ----
8			84 ----
9			74 ----
10			73 ----

[a] Reaction conditions: 1.0 equiv of 4,6-dibromoindole, 5 mol % of $Pd(OAc)_2$, 5.5 mol % of *rac*-BINAP, 1.5 equiv of TMEDA, 1.0−1.05 equiv of $NaBH_4$ (1.0 M solution in diglyme), THF. [b] Isolated yields (average of two runs) of compounds estimated to be >95% pure as determined by ^{1}H NMR and combustion analysis.

tert-butylcarbazate,[13] followed by Fischer indolization (Table 1). As can be seen from the results presented in Table 1, a variety of polysubstituted 4,6-dibromo-5-substituted indoles can be produced. The method employed, which utilizes a variation of that described in our prior report,[14] provides easy access to aryl hydrazines generated in situ without the need for the preparation and isolation in a separate step.[15]

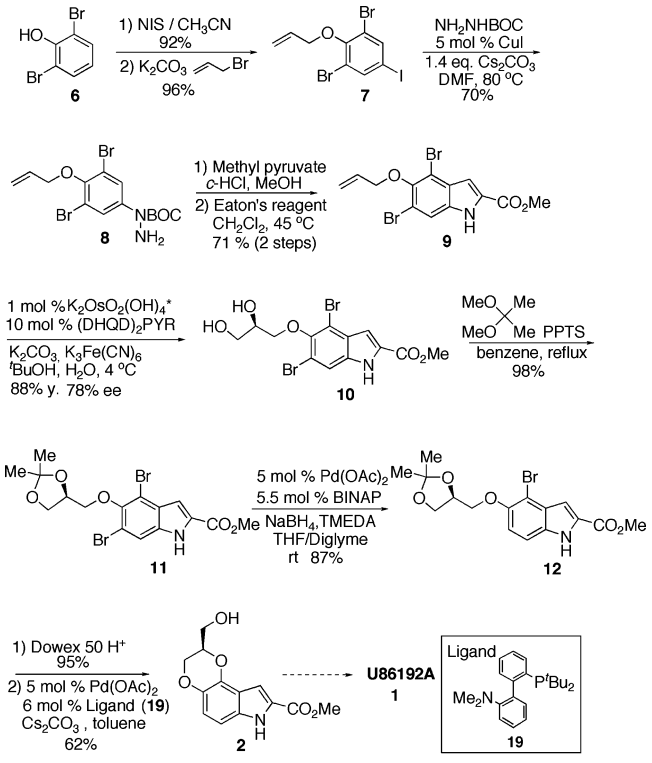
With 4,6-dibromoindoles in hand, we decided to examine their regioselective hydrodebromination.[17] Our preliminary attempts, utilizing ammonium formate and Pd/C, a widely used dehalogenation protocol,[18] revealed that initial hydrodebromination was occurring at C-6. However, the first formed 4-bromoindoles (**B**) reacted faster than **A**. To find a means to overcome this problem, we screened various catalytic systems to discover one that would effect selective debromination. This included many Pd-catalyzed reduction systems with phosphine ligands including PPh_3, DPPE, DPPF, Xantphos, and BINAP, along with several stoichiometric reductants. After some experimentation, we found that selective debromination could be effected using catalytic $Pd(OAc)_2$/*rac*-BINAP and $NaBH_4$ as the stoichiometric reductant in the presence of TMEDA as a base.[19] These reaction conditions were then applied to the dibromoindoles (Table 2) that we had prepared. Dibromoindoles with no substituent at C-5 (entries 1 and 2) were reduced with no regioselectivity. A mixture of the two regioisomeric bromides (~1:1) with 25−35% of the doubly debrominated indoles was observed. On the other hand, substrates with C-5 substituents (entries 3−10) were transformed with high regioselectivity to 4-bromoindoles **B**. In these cases, 3−10% of doubly debrominated products, which were easily separable by chromatography, were formed. The selectivity of the reduction process appears to be largely controlled by steric factors. Electronic effects, however, also seem to play a role in the observed regioselectivity. For example, while the lack of a substituent at C-3 renders the bromide at C-4 less sterically differentiated from that at C-6, an electron-withdrawing group at C-2 (entries 5 and 8) compensates and a high level regioselectivity is seen.

Application to the Enantioselective Synthesis of Indolodioxane U86192A. As an application of this methodology, a concise route to indolodioxane U86192A (**1**) has been developed. U86192A is a potent antihypertensive agent among the derivatives of the nonnatural hybrid of three 5-HT_{1A} receptor binding molecules: 5-hydroxytryptamine, spiroxatrine, and pindolol.[20] We envisioned forming the dioxolane ring of **1** using Pd-catalyzed C−O bond-forming methodology developed in our group (Scheme 2).[21] Using this process, a key intermediate (**2**),

(11) Another approach to prepare 4-substituted indoles involves the direct introduction of a substituent at 4-position via thallation/palladation or lithiation. Both are limited to indoles with specific directing functional groups at the 3-position, however, and use of toxic metals such as thallium detracts from the synthetic utility. Thallation/palladation: (a) Somei, M.; Amari, H.; Makita, Y. *Chem. Pharm. Bull. Jpn*. **1986**, *34*, 3971. (b) Somei, M.; Ewasa, E.; Yamada, F. *Heterocycles* **1986**, *24*, 3065. Lithiation: (a) Iwao, M. *Heterocycles* **1993**, *36*, 29. (b) Chauder, B.; Larkin, A.; Snieckus, V. *Org. Lett*. **2002**, *4*, 815.

(12) After the methodological portion of this work was complete, two papers that describe the preparation of 4,7- or 5,7-disubstituted indoles from 4,7- or 5,7-dibromoindoles via a selective lithium−bromine exchange reaction appeared. (a) Li, L.; Martins, A. *Tetrahedron Lett*. **2003**, *44*, 689. (b) Li, L.; Martins, A. *Tetrahedron Lett*. **2003**, *44*, 5987.

SCHEME 3. Synthesis of Indolodioxane U86192A (I)



* Conditions for asymmetric dihydroxylation

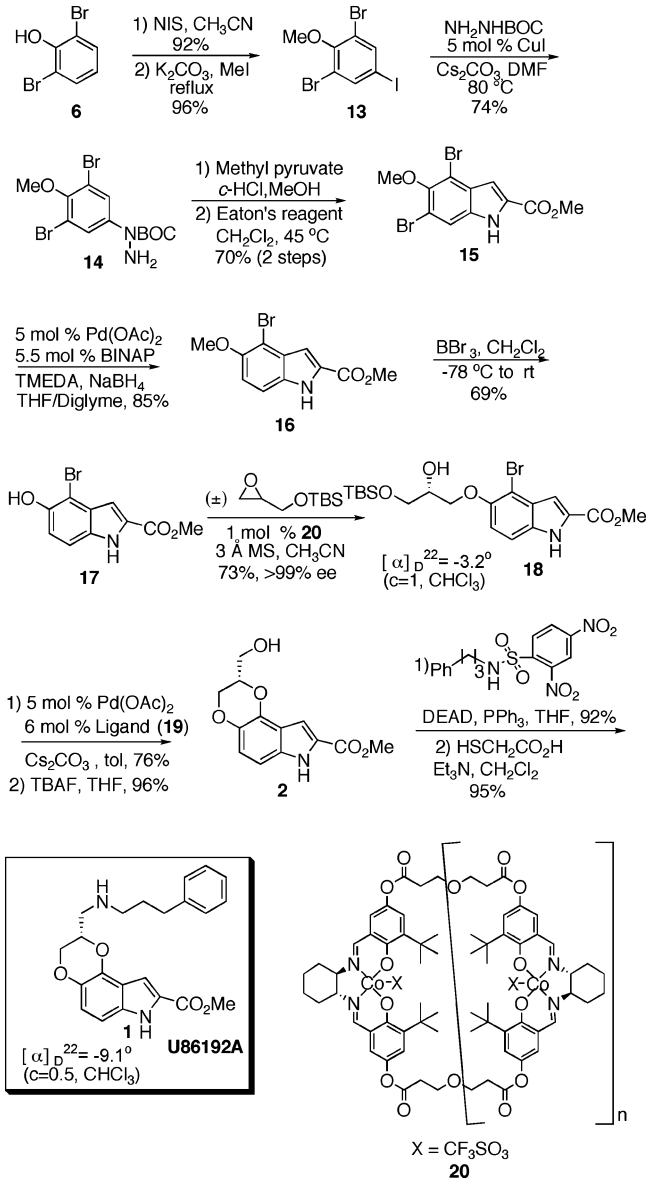
Ligand	Cat $K_2OsO_2(OH)_4$	Reaction time	Yield (%)	ee (%)
10 mol % $(DHQD)_2PHAL$	5 mol %	1day	80	58
10 mol % $(DHQD)_2AQN$	2 mol %	3 days	79[a]	81
10 mol % $(DHQD)_2PYR$	1 mol %	3 days	88	78

[a] Yield based on the recovered S.M. (69% Conversion)

which has previously been converted to (±)-**1**, should be accessible from **3**. Compound **3**, in turn, would derive from **4** (R = H) via alkylation of the phenol with an (*S*)-glycidol equivalent. The bromide **4** would arise from selective reduction of dibromide **5**. Intermediate **5**, in turn, would derive from the components shown via the Fischer indolization method described earlier.

Our initial approach to **1** is shown in Scheme 3. Beginning with 2,6-dibromophenol, allyl ether **7** was prepared via conventional chemistry. The Cu-catalyzed

SCHEME 4. Synthesis of Indolodioxane U86192A (II)



formation of the *N*-aryl *N*-Boc hydrazide proceeded to give **8** in 70% yield. This was then used in the Fischer protocol; in this instance, condensation of **8** with methyl pyruvate was carried out under acidic conditions. The crude hydrazone intermediate, after drying under vacuum, was treated with Eaton's reagent (P_2O_5 in methanesulfonic acid) to give indole (**9**) in 71% yield (two steps). This was then subjected to Sharpless asymmetric dihydroxylation,[22] and the results are as shown. The best compromise between isolated yield and enantioselectivity was found using 10 mol % $(DHQD)_2PYR$ and 1 mol % $K_2OsO_2(OH)_4$ in $^tBuOH/H_2O$ for 3 days at 4 °C. In this way, an 88% yield of diol **10** (78% ee) was isolated. Conversion of the diol **10** to the acetonide followed by regioselective reduction produced **12** in 85% overall yield. Deprotection of **12** produced an intermediate diol that

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could be converted to (**2**) using our previously reported method for intramolecular C−O bond formation.[21]

While we were pleased at having demonstrated that a route that combined both C−N and C−O bond-forming processes with our preparation of 4,5-disubstituted indoles could be used to access **1**, we were disappointed with the level of enantioselectivity that was realized in the Sharpless asymmetric dihydroxylation step. Thus, we embarked on a second, related route, to **1**. As shown in Scheme 4, the initial steps of this second synthetic path were similar to that of the first one, save that a methoxy group at 5-position was used instead of an allyloxy. In this way, **15**, the analogue of **9** was prepared. Its selective debromination followed by demethylation produced bromophenol **17**. This set the stage for the key stereochemical process in the synthesis. Jacobsen's phenolic kinetic resolution (PKR) was utilized with **17** and racemic glycidol TBS ether. Previous incarnations of PKR could not handle bromophenol substrates.[23a] Fortunately, a second generation oligomeric cobalt salen catalyst (**20**) was recently developed by Jacobsen's group.[23c] Application of **20** provided a 73% yield of the differentially protected diol **18** that had an ee of >99%.[24] Application of our C−O bond-forming procedure[21] followed by removal of the TBS group produced (*S*)-**2** in 73% yield. While (±)-**2** had previously been converted to (±)-**1**, the transformation occurred in modest yield.[20] We chose to utilize a Mitsunobu reaction which, after removal of the protecting group on nitrogen using Fukuyama conditions,[25] gave (*S*)-**1** in 88% yield. The overall yield for our synthesis of (*S*)-**1** was 12.5%,[26] which compares favorably to the previous synthesis that gave (±)-**1** in 10.7% overall yield.

Conclusion

In summary, we have developed a novel approach to the selective preparation of 4-substituted indoles. The method, a variation of the Fischer indole synthesis, allows for the preparation of a variety of 2,3,4,5-substituted indoles from aryl halides. The method should be applicable with a number of different functional groups X (Scheme 1) and for a number of different transformations. We have applied this process along with C−N and C−O bond-forming reactions developed in our laboratory for an enantioselective synthesis of (*S*)-U86192A.

Experimental Section

All nonaqueous reactions were run in oven-dried glassware under an argon atmosphere unless otherwise stated. Yields reported in Table 1 and 2 are isolated and an average of two independent runs. The Co-Salen oligomer (**19**) was obtained from Professor Eric N. Jacobsen and Mr. David White (Harvard University). All other reagents were purchased from commercial sources and used without further purification. A detailed description is given in the Supporting Information.

General Procedure for One-Pot Preparation of 4,6-Dibromoindoles (Table 1). An oven-dried resealable Schlenk tube was charged with dibromoaryl iodide (1.00 mmol), *tert*-butylcarbazate (158 mg, 1.20 mmol), CuI (14.3 mg, 9.50 mmol), and Cs_2CO_3 (455 mg, 1.40 mmol). The Schlenk tube was evacuated and backfilled with Ar. Anhydrous DMF (4 mL) was added, and the reaction mixture was stirred at room temperature for 10 min and heated at 80 °C (preheated oil bath) until the dibromoaryl iodide was consumed as determined by GC analysis. The reaction mixture was allowed to cool to room temperature and diluted with ether (∼20 mL) and water (∼40 mL). The aqueous phase was extracted with ether (∼20 mL × 2), and the combined ethereal layers were washed with water and brine and dried over Na_2SO_4. The solvent was removed in vacuo, and the crude aryl hydrazide was used directly for the Fischer indole cyclization without purification. The crude aryl hydrazide, ketone (1.00 mmol), and *p*-TsOH·H_2O (304 mg, 1.60 mmol)[27] were dissolved in EtOH (8 mL), and the solution was stirred at 100 °C (preheated oil bath) until the aryl hydrazide was consumed as determined by TLC analysis. After the reaction mixture was allowed to cool to room temperature, EtOH was removed under vacuum. The reaction mixture was diluted with EtOAc (∼ 30 mL) and neutralized with saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc (∼25 mL × 2), and the combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated under vacuum. Purification of the crude product by column chromatography afforded the analytically pure indole product.

General Procedure for Regioselective Hydrodebromination of 4,6-Dibromoindoles (Table 2). An oven-dried Schlenk tube was charged with 4,6-dibromoindole (0.500 mmol), $Pd(OAc)_2$ (5.60 mg, 0.0250 mmol), and *rac*-BINAP (17.0 mg, 0.028 mmol). The Schlenk tube was evacuated and backfilled with Ar, and anhydrous THF (1 mL) was added. The reaction mixture was stirred for 20 min at room temperature. TMEDA (113 μL, 0.750 mmol) and additional THF (1 mL) were added, and the reaction mixture was stirred for 20 min at room temperature. $NaBH_4$ (0.5 M solution in diglyme, 1.05 mL, 0.525 mmol) was slowly added, and the reaction mixture was stirred at room temperature or 50 °C (preheated oil bath) for 24 h. After the reaction mixture was allowed to cool to room temperature, it was diluted with EtOAc (∼2 mL). The resulting heterogeneous mixture was then filtered through a pad of silica gel eluting with EtOAc. The filtrate was concentrated, and purification of the concentrated filtrate by column chromatography afforded the desired product.

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Supporting Information Available: General experimental procedures and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) Spectroscopic data for **1** were consistent with that previously reported in ref 19.

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