Synthesis of 1-Hydroxy-Substituted Pyrazolo[3,4-*c*]- and Pyrazolo[4,3-*c*]quinolines and -isoquinolines from 4- and 5-Aryl-Substituted 1-Benzyloxypyrazoles

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1-Hydroxypyrazolo[3,4-*c*]quinoline (**22**), 1-hydroxypyrazolo[4,3-*c*]quinoline (**21**), 1-hydroxypyrazolo-[3,4-*c*]isoquinoline (**20**), and 1-hydroxypyrazolo[4,3-*c*]isoquinoline (**19**) were prepared from 1-benzyloxypyrazole (**6**), establishing the pyridine B-ring in the terminal step. The pyridine ring of pyrazoloquinolines **14** and **18** was formed via cyclization of a formyl group at C-4 or C-5 and an amino group of a 2-aminophenyl substituent at C-5 or C-4 in 1-benzyloxypyrazole. The pyridine ring of pyrazoloisoquinolines **5** and **9** was created via cyclization of a formyl group in a 2-formylphenyl substituent at C-4 or C-5 with an iminophosphorane group installed at C-5 or C-4 of 1-benzyloxypyrazole by lithiation followed by reaction with tosyl azide and then with tributylphoshine utilizing the Staudinger/aza-Wittig protocol. The 2-aminophenyl and the 2-formylphenyl substituent were introduced at C-5 or C-4 by regioselective metalation followed by transmetalation to the pyrazolylzinc halide and subsequent palladium-catalyzed cross-coupling with 2-iodoaniline or 2-bromobenzaldehyde. The order of reactions and use of protecting groups in the individual sequences have been optimized. The 1-benzyloxy-substituted pyrazoloquinolines and isoquinolines thus obtained were debenzylated by strong acid to the corresponding 1-hydroxy-substituted pyrazoloquinolines and isoquinolines **19**−**22**.

Introduction

The parent ring systems of the four isomeric tricyclic *N*-hydroxy-substituted pyrazolo[4,3-*c*]isoquinoline (**19**), pyrazolo[3,4-*c*]isoquinoline (**20**), pyrazolo[4,3-*c*]quinoline (**21**), and pyrazolo[3,4-*c*]quinoline (**22**) are known, usually as N-1 or N-2 substituted derivatives.[1] Structural analogues of **19**−**22** have been studied for their biological activity as benzodiazepine antagonists,[1a] acetylcholinesterase inhibitors,[1j] interleukin 1 antagonists,[1h] and anti-inflammatory agents.[1e,h,l,m] Ability to displace specific flunitrazepam binding,[1g] as well as antimalarial, antiallergic, and antiviral activities,[1l,m] has also been investigated. The known synthetic sequences usually involve formation of the pyrazole ring, typically via a hydrazine condensation at a late stage of the sequence.[1a,h,j,l] To our knowledge, a general, easily extensible technology for the construction of all four members **19**−**22** of this structural family via the pyridine B-ring closure starting from a substituted pyrazole has not been yet described. No 1-hydroxy-substituted derivatives of ring systems **19**−**22** have been reported. The herein presented syntheses of **19**−**22** start from 1-benzyloxypyrazole (**6**), which can be regioselectively metalated and arylated by cross-coupling reactions in a highly flexible manner.[2,3] Further, the annelation protocols developed for the construction of **5**, **9**, **14**, and **18** should provide an easy access to diverse derivatives of **19**−**22**, e.g., using substituted 2-iodoanilines or 2-bromobenzaldehydes in the cross-coupling step. Possibly, extending these novel ring closing tactics will also enable development of versatile routes to other important classes of condensed N-heteroaromatics. In that respect, the strategy to produce **20** is particularly relevant, due to the close structural resemblance of 1-hydroxypyrazolo[4,3-*c*]quinoline (**20**) to the highly efficient peptide coupling reagent HOAt.[4]

Results and Discussion

Retrosynthetic Analysis. The synthetic approach to the target structures **19**−**22** is outlined in Scheme 1. The

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(1) For illustrative examples of syntheses of these structural classes, see: (a) Cecchi, L.; Colotta, V.; Melani, F.; Palazzino, G.; Filacchioni, G.; Martini, C.; Giannaccini, G.; Lucacchini, A. *J. Pharm. Sci.* **1989**, *78*, 437 (ring system **19**). (b) Nikolyukin, Y. A.; Dulenko, L. V.; Dulenko, V. I. *Khim. Geterotsikl. Soedin.* **1990**, *26*, 1092. (c) Bogza, S. L.; Nikolyukin, Y. A.; Dulenko, V. I. *Khim. Geterotsikl. Soedin.* **1994**, *30*, 1290 (ring system **20**). (d) Staskun, B. *J. Org. Chem.* **1961**, *26*, 2791. (e) Katner, S. A. U.S. Patent 3890324, 17 Jun 1975; *Chem. Abstr.* **1975**, *83*, 1641169b. (f) Gál, M.; Fehér, Ö.; Tihanyi, E.; Horváth, G.; Jerkovich, G. *Tetrahedron* **1982**, *38*, 2933. (g) Melani, F.; Cecchi, L.; Palazzino, G.; Filacchoni, G.; Martini, C.; Pennacchi, E.; Lucacchini, A. *J. Med. Chem.* **1986**, *29*, 291. (h) Skotnicki, J.; Gilman, S. C.; Steinbaugh, B. A.; Musser, J. H. U.S. Patent 4748246, 31 May 1988; *Chem. Abstr.* **1988**, *109*, 110425u. (i) Daou, B.; Soufiaoui, M. *Tetrahedron* **1989**, *45*, 3351. (j) Sicker, D. *J. Heterocycl. Chem.* **1992**, *29*, 275. (k) Gatta, F.; Del Giudice, M. R.; Pomponi, M.; Marta, M. *Heterocycles* **1992**, *34*, 991. (l) Mekheimer, R. *Pharmazie* **1994**, *49*, 486. (m) Hassan, A. A.; Mekheimer, R.; Mohamed, N. K. *Pharmazie* **1997**, *8*, 589 (ring system **21**). (n) Nagarajan, K.; Shah, R. K. *Indian J. Chem.* **1992**, *31B*, 316 (ring system **22**).

(2) Kristensen, J.; Begtrup, M.; Vedsø, P. *Synthesis* **1998**, 1604.

(3) Felding, J.; Kristensen, J.; Bjerregaard, T.; Sander, L.; Vedsø, P.; Begtrup, M. *J. Org. Chem.* **1999**, *64*, 4196.

(4) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397.

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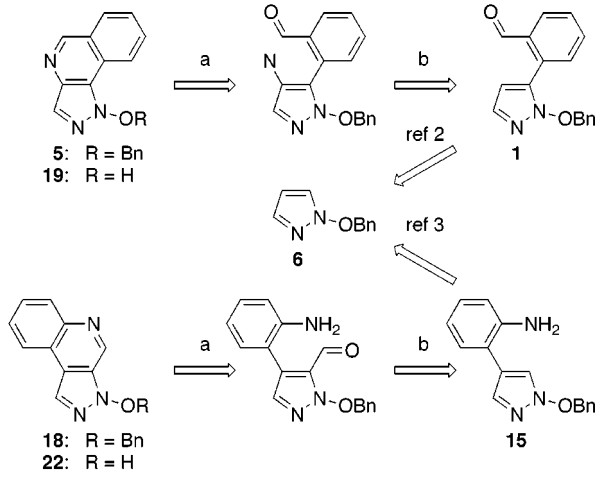
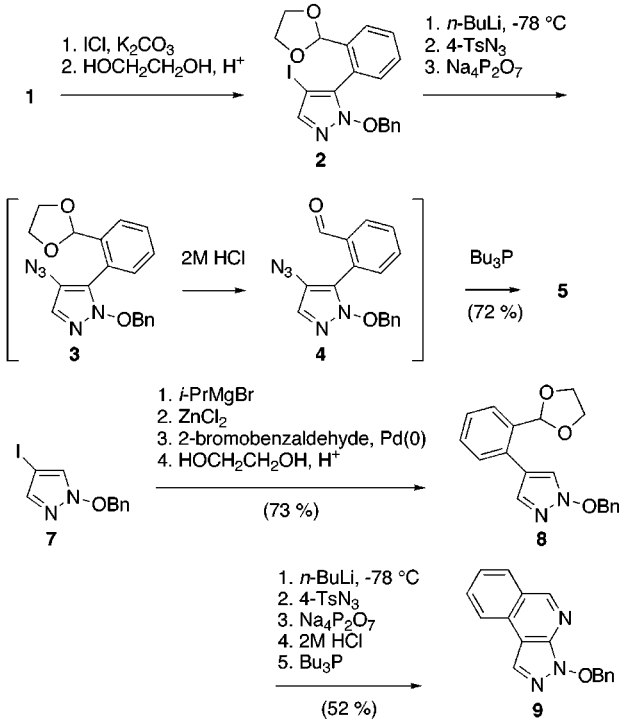
Scheme 1



first step of this synthesis involves regioselective C-5 or C-4 arylation of the pyrazole nucleus using previously described palladium-catalyzed Negishi type[5] cross-coupling methodologies,[2,3] followed by protection of the *o*-phenyl group introduced in the cross-coupling step. The salient step involves the introduction of a nitrogen-containing functionality or a formyl group at the 4- or 5-position of the pyrazole ring (step b). This was envisaged via an organometallic intermediate, which could be quenched with an appropriate electrophile. Subsequent deprotection followed by an intramolecular cyclization form the pyridine ring (step a). Finally, the 1-benzyl group used for protection of the N−OH group in the synthetic sequences could be removed via hydrogenolysis or acid-catalyzed debenzylation to give the targets **19** and **22**. Analogous approach as for **19** could be used to build **20**, and similarly **21** could be made, employing the same strategy as for the synthesis of **22**.

Preparation of Pyrazoloisoquinolines 5 and 9. Pyrazole **2** was prepared in overall 77% yield by regioselective C-4 iodination of **1**[3], using 3 equiv of iodine monochloride, followed by acetalization of the formyl group. No competitive iodination in the C-5 phenyl ring was observed, most likely due to its deactivation by the electron-withdrawing formyl group. The presence of bulky substituents in **2** (iodine and 1,3-dioxolane) caused restricted rotation around the pyrazole−phenyl C−C bond, giving rise to atropoisomerism, as observed in ^{1}H NMR of **2**, where the CH_2 protons of the benzyloxy group resonate as a characteristic AB system (J_{gem} = 10.4 Hz) at 5.21 and 5.07 ppm. Iodine−lithium exchange with **2** proved to be a suitable method to introduce a nitrogen-containing electrophile at the C-4 position. In a test experiment, **2** was treated with *n*-BuLi at −78 °C for 5 min. Subsequent reaction with MeOD resulted in complete conversion and nearly quantitative (98%) deuterium incorporation at C-4 (collapse of the benzylic AB system to a singlet in ^{1}H NMR). Introduction of the azido functionality was achieved by employing the procedure described for preparation of azidothiophenes.[6,7] Interception of the putative pyrazol-4-yllithium intermediate with 4-toluenesulfonyl azide in THF solution at −70 °C for 5 h followed by treatment of the resulting triazene salt with an aqueous solution of tetrasodium pyrophosphate at room temperature furnished azide **3**.[8] 4-Azido-1-(benzyloxy)-5-(2-formylphenyl)pyrazole (**4**) was then obtained by hydrolysis of ethylene acetal group in **3** by treatment with 2 M HCl at room temperature. Finally, **4** was subjected to a Staudinger/intramolecular aza-Wittig reaction[9] using tributylphosphine in a 15:1 toluene:THF mixture[10] at room temperature to furnish the cyclized pyrazoloisoquinoline **5** in 72% yield (from **2**).

Scheme 2

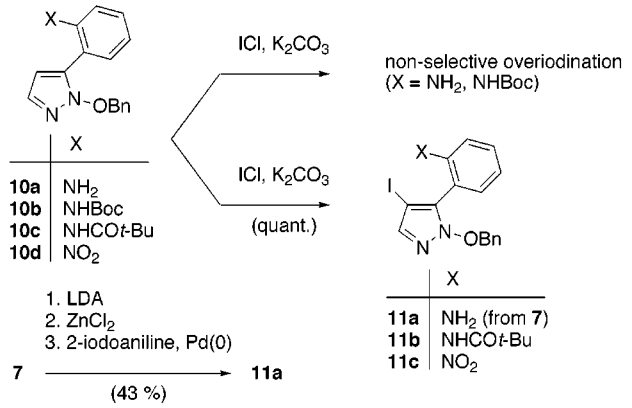


The pyrazoloisoquinoline **9** was synthesized using a similar approach as for the synthesis of **5**. Employing our recently reported[3] methodology for regiospecific arylation in the 4-position of 1-(benzyloxy)pyrazole via iodine magnesium exchange of 1-(benzyloxy)-4-iodopyrazole (**7**) followed by transmetalation with $ZnCl_2$ and then by Pd-catalyzed Negishi cross-coupling using 2-bromobenzaldehyde furnished 1-(benzyloxy)-4-(2-formylphenyl)pyrazole. Immediate protection of the formyl group via acetalization produced the ethylene acetal **8** in 73% yield (two steps). Pyrazole **8** was selectively lithiated at C-5 when treated with 1.2 equiv of *n*-BuLi in THF at −78 °C for 5 min (Scheme 2). Quenching the pyrazol-5-yllithium intermediate with 4-toluenesulfonyl azide and subsequent workup with tetrasodium pyrophosphate as described above produced the C-5 azido intermediate along with unchanged starting material **8** in a 55:45 ratio as determined from relative intensities of ethylene acetal CH signals at 5.65 and 5.50 ppm, respectively, in the ^{1}H NMR spectrum of the crude product. This ratio appeared quite constant, even when we attempted to increase the

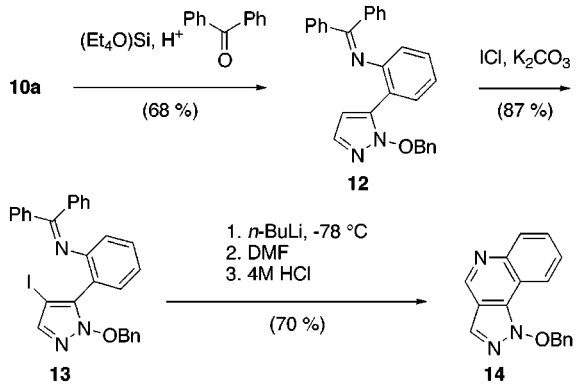
(5) Negishi, E. I.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821.
(6) Spagnolo, P.; Zanirato, P. *J. Org. Chem.* **1978**, *43*, 3539.
(7) Spagnolo, P.; Zanirato, P.; Gronowitz, S. *J. Org. Chem.* **1982**, *47*, 3177.

(8) Almost no (less than 5%) competitive C-4 protonation was seen in the ^{1}H NMR spectrum of crude **3**.
(9) For recent reviews related to the application of the Staudinger/aza-Wittig protocol in heterocyclic synthesis, see: (a) Gusar, N. I. *Russ. Chem. Rev.* **1991**, *60*, 146. (b) Eguchi, S.; Matsushita, Y.; Yamashita, K. *Org. Prep. Proced. Int.* **1992**, *24*, 209.
(10) As **4** was not well soluble in toluene, used as a common solvent for this reaction, THF was added to allow a homogeneous mixture.

Scheme 3



Scheme 4



conversion by extending the reaction time (30 h at −78 °C) or raising the reaction temperature (up to 0 °C for 1 h). The noticeably lower (ca 55%) incorporation of the azido group into **8** than in the case of **2** (>95%) may be explained by a less-favored conversion of **8** to its triazene salt due to steric hindrance at the pyrazole C-5 position caused by the presence of two bulky neighboring groups (benzyloxy and 2-[1,3]dioxolan-2-yl-phenyl).[11] In contrast, the conversion of **2** to its triazene analogue is only hampered by the presence of one bulky neighboring group (2-[1,3]dioxolan-2-yl-phenyl) allowing 4-toluenesulfonyl azide better access to the reaction center and subsequently affording a sterically less-hindered triazene salt. Subsequent hydrolysis of **8** by 2 M HCl followed by the Staudinger/intramolecular aza-Wittig reaction afforded the cyclized pyrazoloisoquinoline **9**. The two final steps were effected in almost quantitative yield, leaving the triazene salt formation as the only yield limiting reaction of the **8** to **9** sequence, thereby producing **9** in 52% yield (from **8**). The major side product 1-(benzyloxy)-4-(2-formyl-phenyl)pyrazole (ca 35%) was easily separated by chromatography after the final workup and could be recycled.

Preparation of Pyrazoloquinolines 14 and 18. As suggested in the retrosynthetic analysis (Scheme 1), construction of **14** was intended starting from **10a**−**d** (Scheme 3).[2] Halogenation followed by halogen−metal exchange would give a C-4 metalated pyrazole. Reacting such species with a suitable electrophile (e.g., DMF) followed by acidic workup would then produce a C-4 formylated intermediate and lead to a facile cyclization to **14** (Scheme 4). In search for useful precursors for a convenient C-4 metalated pyrazole, we initially synthesized **11c**, in a quantitative yield via regioselective C-4 iodination of **10d**,[2] using ICl. Introduction of formyl group via iodine−metal exchange would allow examination of a ring-closing methodology involving nitro and formyl groups used successfully for synthesis of furo[2,3-*c*]-quinolines[12] and phenanthridines.[13] However, all our attempts to introduce even a fast electrophile such as deuterium (MeOD) into **11c** via iodine−magnesium exchange using *i*-PrMgBr (used smoothly for functionalization of **7**[3]) or iodine−lithium exchange using *t*-BuLi failed.[14] Instead, we decided to investigate compounds containing a properly protected amino group. However, attempted C-4 iodination of **10a** or **10b** using ICl (Scheme 3) caused cleavage of the Boc-group in **10b** and nonselective iodination in the phenyl ring, giving rise to a mixture of three products identified as tri-, di-, and monoiodinated aniline derivatives according to LC/MS. Moreover, iodine in the monoiodinated compound was situated in the phenyl ring, reflecting its activation by the amino group.

Although pyrazole **11a** could be made from **7** by LDA-promoted C-5 lithiation followed by $ZnCl_2$ transmetalation and Negishi type[5] cross-coupling with 2-iodoaniline under Pd(0) catalysis (Scheme 3), the yield of this reaction was only 43%.[15] Moreover, Boc protection of **11a** appeared cumbersome since starting material was recovered even after 24 h of reflux with 4 equiv of Boc_2O. We then examined iodination of the more stable pivaloyl-protected derivative **10c**, obtained in 100% yield from **10a**. Pyrazole **10c** was quantitatively converted into **11b**,[16] using ICl. To investigate the iodine−metal exchange, **11b** was reacted with different bases followed by quenching with MeOD. *i*-PrMgBr gave ca. 45% (50 min at 0 °C), ca. 50% (30 min at room temperature), and 100% (90 min at room temperature) iodine−magnesium exchange, *n*-BuLi afforded ca. 50% iodine−lithium exchange (5 min at −78 °C), and MeLi furnished 100% iodine−lithium exchange (5 min at −78 °C) as determined from relative intensities of the benzylic CH_2 group signals of **10c** and **11b** at 5.17 and 5.12 ppm, respectively. Despite the MeOD quenching after the base treatments, quantitative competitive protonation took place at C-4 in all the cases. This proton might be transferred from the secondary amide, indicating that iodine−metal exchange is faster than amide deprotonation. This transfer happened even when we attempted to remove the amide proton (e.g., with NaH or LDA) prior to treatment with *i*-PrMgBr, *n*-BuLi, or MeLi.

Hence we decided to di-protect the amino group in **10a** as a benzophenoneimine. Using the method described by Love and Ren[17] for preparation of sterically hindered

(11) A control experiment consisting of reacting the pyrazol-5-yllithium intermediate with the fast, less bulky electrophile methyl iodide resulted in quantitative conversion to the corresponding 5-methylated compound, clearly demonstrating complete formation of the anion within 5 min at −78 °C.

(12) Yang, Y. *Synth. Commun.* **1989**, *19*, 1001.

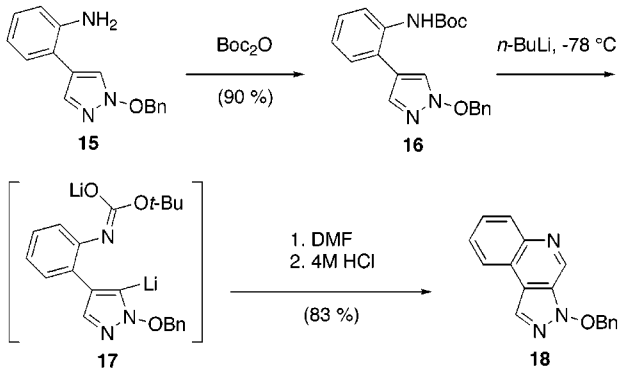
(13) Li, D.; Zhao, B.; LaVoie, E. J. *J. Org. Chem.* **2000**, *65*, 2802.

(14) There are successful examples of iodine−lithium exchange of nitro-functionalized aryl and alkenyl iodides, typically performed at −80 to −100 °C: (a) Tucker, C. E.; Majid, T. N.; Knochel, P. *J. Am. Chem. Soc.* **1989**, *114*, 3983 and the references therein. (b) Klement, I.; Rottländer, M.; Tucker, C. E.; Majid, T. N.; Knochel, P. *Tetrahedron* **1996**, *52*, 7201.

(15) Quenching of the putative 5-lithio-4-iodo-1-benzyloxypyrazole gave 83% deuteration and 17% of starting material, according to ^1H NMR.

(16) Alternatively **11b** was made by pivaloylation of **11a** in 92% yield, but this route is clearly disfavored by the low yield (43%) in the cross-coupling step from **7** to **11a**.

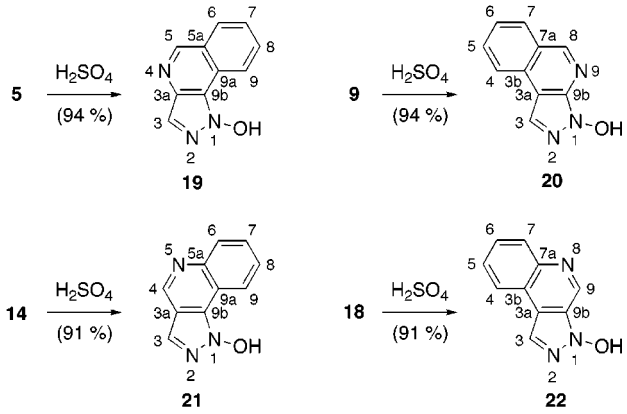
Scheme 5



imines, **12** was prepared in 68% yield by heating a mixture of amine **10a**, benzophenone, tetraethyl orthosilicate, and catalytic amounts of concentrated sulfuric acid with continuous removal of ethanol using a Dean−Stark trap. Subsequent iodination produced **13** in 87% yield. Careful reaction time control (2 h at room temperature) was required to obtain good results, as prolonged reaction time caused substantial cleavage of the imine followed by iodination in the aminophenyl ring. To optimize formation of **14** via a C-4 formylated intermediate, iodine−magnesium and iodine−lithium exchange in **13** was investigated. Treatment of **13** with *i*-PrMgBr at 0 °C for 1 h followed by a MeOD quench gave almost complete cleavage of the imino group, resulting in formation of benzophenone and **11a**. Almost no iodine−magnesium exchange was observed. MeLi exhibited only partial (ca 25%) iodine−lithium exchange at −78 °C, whereas reaction of **13** with *n*-BuLi under similar conditions gave almost complete I−Li exchange and no significant addition to the imine.[18] However, approximately 30% competitive protonation at C-4 took place. This reaction was suppressed by adding **13** to a solution of *n*-BuLi (2.2 equiv) in THF at −78 °C, and after 15 min the putative 4-lithio intermediate was reacted with DMF for 1 h at room temperature. Quench with 4 M HCl provided the C-4 formylated intermediate, and simultaneous hydrolysis of the imine followed by spontaneous cyclization afforded the desired tricyclic pyrazoloquinoline **14** in 70% yield (Scheme 4).

Finally, **18** was made from **15**[3] in a simple two-step sequence. First the amino group in **15** was Boc protected to give **16** in 90% yield. Compound **16** was then treated with 2.2 equiv of *n*-BuLi for 5 min at −78 °C to produce a positionally stable lithiodianion **17**.[19] This dianion was then reacted with DMF. Subsequent heating to room temperature and quenching with 4 M HCl triggered three, spontaneous processes: (i) Acid-induced Boc-deprotection; (ii) hydrolysis of the aminal to give a formyl group; (iii) condensation of the amino and the formyl groups thus formed to produce **18** in 83% yield (Scheme 5). A similar ring-closing strategy involving interaction of *N*-(*tert*-butoxycarbonyl)amino- and formyl groups based on directed metalation and cross-coupling tactics has been described for the synthesis of a series of functionalized phenantridines,[20] though in this case the formyl group was preinstalled in the cross-coupling step.

Scheme 6



Debenzylation. Debenzylation of **5**, **9**, **14**, and **18** to give corresponding *N*-hydroxypyrazoloquinolines/isoquinolines **19**−**22** was examined by two different strategies. First we investigated palladium-catalyzed hydrogenolysis, as related structures previously were deprotected this way.[21] However, it appeared that this methodology is of limited applicability to our case, since attempted debenzylation of **5** using 10% Pd/C in MeOH at 1 atm H_2 resulted in unchanged starting material even at elevated temperature (68 °C) for prolonged time (36 h). When **18** was subjected to the same treatment with H_2 at 2 atm, a mixture of **22** and its dehydroxylated analogue was formed in approximately 1:1 ratio according to ^{1}H NMR. On the basis of the preliminary studies, it seems difficult to achieve a Pd-catalyzed hydrogenolysis debenzylation protocol for **5**, **9**, **14**, and **18** to give **19**−**22** with acceptable chemoselectivity, and we turned to investigate acid-induced debenzylation. In fact, selective debenzylation of **5**, **9**, **14**, and **18** to give **19**−**22** could be effected using concentrated H_2SO_4 at 70 C° for 30 min to afford **19**−**22** in 91−94% yields (Scheme 6). Alternatively, the debenzylation could be achieved with 47% HBr at 70 C° for 1 h, as shown by deprotecting **18** to **22**.

In conclusion, we furnished **19**−**22** starting from C-4 and C-5 substituted benzyloxypyrazoles **1**, **7**, **10a**, and **15** in short, relatively high yielding de novo sequences. Benzyloxypyrazoles **5**, **9**, **14**, and **18** were produced in a few steps, with focus on organometallics containing suitably protected electron-donating and electron-withdrawing groups, generated using metalation and halogen−metal exchange tactics. These key intermediates were then used as sources for ring closure precursors in a new, uncommon way. Quantitative and easily extensible methodology for deprotection of **5**, **9**, **14**, and **18** to **19**−**22** was developed. In that manner, a family of four classes of unique, novel tricyclic fused *N*-hydroxyheteroaromatics was accessed.

Experimental Section

General Methods. See ref 3. The assignment of ^{1}H and ^{13}C NMR signals of the tricyclic compounds were based on the two singlets from the α-pyridine and H-3 protons having distinct shift values at ca. 9.1 ppm and 8.1−8.6 ppm, respec-

(17) Love, B. E.; Ren, J. *J. Org. Chem.* **1993**, *58*, 5556.

(18) Buchwald and co-workers have reported that benzophenone imine protected 4-bromoaniline undergoes bromine−lithium exchange without substantial (<5%) addition to the imine when subjected to n-BuLi in THF at −78 °C: Wolfe, J. P.; Åhman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367.

(19) The positions of the charges were confirmed quenching the dianion **17** with excess of methyl iodide, producing the corresponding N,C-5 dimethylated derivative in quantitative yield.

(20) Siddiqui, M. A.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 5463.

(21) Vedsø, P.; Begtrup, M. *J. Org. Chem.* **1995**, *60*, 4995.

tively. The remaining protons could then be assigned from 2D H−H correlated (COSY and/or NOESY) spectra. The C−H carbon signals were then assigned from correlations in the HSQC spectra, and finally the quaternary carbon signals were determined from correlations in the HMBC spectra. Aromatic ^{1}H NMR and ^{13}C NMR signals from the benzyloxy group are referred to as arom H and arom C; quaternary carbon signals from the same group are referred to as C_i.

1-Benzyloxy-5-(2-[1,3]dioxolan-2-yl-phenyl)-4-iodopyrazole (2). **1**[2] (1.7 g, 6.1 mmol) was dissolved in CH_2Cl_2 (10 mL), K_2CO_3 (2.63 g, 18.3 mmol) was added, and the reaction mixture was treated with ICl (2.98 g, 18.3 mmol) dissolved in CH_2Cl_2 (10 mL). After stirring for 16 h at room temperature, the reaction was quenched with Na_2SO_3 (1 M, 20 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried over $MgSO_4$ and evaporated to dryness. A mixture of the crude product (2.45 g, 6.1 mmol), dry ethylene glycol (0.75 g, 12 mmol), benzenesulfonic acid (0.10 g), and toluene (100 mL) was refluxed for 2 h, removing the water formed in a Dean−Stark trap. Most of the solvent was removed under reduced pressure, and extraction with ether (3 × 10 mL), washing with 5% aqueous sodium hydrogen carbonate and water, drying over $MgSO_4$, and removal of the ether gave the crude product, which was subjected to flash chromatography (FC) (EtOAc−heptane, 1:2), to give 2.1 g (77%) of 1-benzyloxy-5-(2-[1,3]dioxolan-2-yl-phenyl)-4-iodopyrazole **2** as colorless crystals, mp 101−102 °C (EtOAc−heptane). R_f (EtOAc−heptane, 1:2) 0.37. δ_H ($CDCl_3$) 7.72 (dd, J = 7.9, 0.9 Hz, 1H), 7.50 (dt, J = 7.6, 1.1 Hz, 1H), 7.44 (s, 1H), 7.35−7.18 (m, 4H), 7.00−6.97 (m, 2H), 6.78 (dd, J = 7.6, 1.0 Hz, 1H), 5.71 (s, 1H), 5.21 (d, J = 10.4 Hz, 1H), 5.07 (d, J = 10.4 Hz, 1H), 4.05−3.88 (m, 4H). δ_C ($CDCl_3$): 137.75, 137.70, 136.47, 133.20, 131.27, 129.92, 129.81, 129.10, 128.97, 128.48, 126.75, 126.58, 101.49, 80.49, 65.35, 65.24, 58.36. Anal. Calcd for $C_{19}H_{17}IN_2O_3$: C, 50.91; H, 3.82; N, 6.25. Found: C, 51.02; H, 3.81; N, 6.22.

1-Benzyloxypyrazolo[4,3-*c*]isoquinoline (5). To a solution of **2** (200 mg, 0.45 mmol) in THF (2 mL) was added dropwise *n*-BuLi (0.23 mL, 0.49 mmol, 2.12 M in hexanes) with stirring at −78 °C. After 5 min, tosyl azide[22] (110 mg, 0.54 mmol) in THF (1 mL) was added dropwise. When the addition was complete, the resulting mixture was stirred for 5 h at −78 °C, and the solution was allowed to warm to room temperature. Tetrasodium pyrophosphate decahydrate (240 mg, 0.54 mmol) in water (10 mL) was added, and after stirring overnight at room temperature, the organic layer was separated and the aqueous solution was extracted twice with ether (2 × 10 mL). The combined organic extracts were stirred with 2 N HCl (50 mL) at room temperature for 3 h, to give 2-(4-azido-1-benzyloxy-pyrazol-5-yl)benzaldehyde (**4**), which was washed with 5% aqueous sodium hydrogen carbonate and water, dried over $MgSO_4$, and evaporated to dryness. The residue was dissolved in toluene (15 mL) with dry THF (1 mL) under nitrogen, and tributylphosphine (100 mg, 0.49 mmol) was added. The mixture was stirred for 2 h at room temperature, washed with saturated aqueous KOH (10 mL), and dried over $MgSO_4$, before the solvents were evaporated. FC (heptane/EtOAc, 4:1 → 1:1) gave 86 mg (72%) of **5** as slightly yellowish crystals, mp 91−92 °C (EtOAc−heptane). R_f (EtOAc−heptane, 1:2) 0.18. δ_H ($CDCl_3$) 8.98 (s, 1H, H-5), 8.47 (d, J = 8.2 Hz, 1H, H-9), 8.10 (s, 1H, H-3), 8.08 (d, J = 7.9 Hz, 1H, H-6), 7.80 (dt, J = 7.1, 1.2 Hz, 1H, H-8), 7.68 (dt, J = 7.6, 1.2 Hz, 1H, H-7), 7.48−7.31 (m, 5H, H arom), 5.50 (s, 2H, OCH_2Ph). δ_C ($CDCl_3$): 150.18 (C-5), 133.21 (C_i) 132.78 (C-3A), 130.87 (C-8), 129.93 (arom C), 129.45 (C-6), 128.73 (arom C and C-3), 127.58 (C-7), 127.26 (arom C-5A), 122.58 (C-9B), 122.10 (C-9A), 121.81 (C-9), 80.72 (CH_2 Bn). Anal. Calcd for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N 15.26. Found: C, 73.98; H, 4.78; N, 14.96.

1-Benzyloxy-4-[2-(dioxolan-2-yl)phenyl]pyrazole (8). To a stirred solution of 1-(benzyloxy)-4-iodopyrazole (**7**)[3] (900 mg, 3 mmol) in THF (3 mL) at 0 °C was added 0.85 M *i*-PrMgBr in THF (4.5 mL, 3.9 mmol) over 2 min. Stirring was continued for 1 h at 0 °C, before 1 M $ZnCl_2$ in Et_2O (4.5 mL, 4.5 mmol) was added. After stirring for 1 h at room temperature, 2-bromobenzaldehyde (830 mg, 4.5 mmol) and $Pd(PPh_3)_4$ (0.06 mmol) in DMF (7.5 mL) was added. After heating to 80 °C for 1 h, saturated aqueous NH_4Cl (20 mL) and water (20 mL) were added. Extraction with dichloromethane (3 × 20 mL), drying of the combined organic phases ($MgSO_4$), filtration, and removal of the dichloromethane gave crude 1-(benzyloxy)-4-(2-formylphenyl)pyrazole. FC (heptane/EtOAc 3:1) and acetalization as described for **2** gave 0.70 g (73%) of **8** as yellow brownish crystals, mp 112−113 °C (EtOAc−heptane). R_f (EtOAc−heptane, 1:2) 0.30. δ_H ($CDCl_3$): δ 7.70−7.66 (m, 1H), 7.49 (d, J = 1.0 Hz, 1H), 7.39−7.25 (m, 9H), 5.50 (s, 1H), 5.33 (s, 2H), 4.21−3.90 (m, 4H). δ_C ($CDCl_3$): δ 134.00, 133.86, 133.05, 131.84, 129.88, 129.35, 129.30, 129.19, 128.68, 127.14, 126.02, 122.90, 117.40, 101.06, 80.47, 65.32. Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.91; H, 5.73; N, 8.65.

1-Benzyloxypyrazolo[3,4-*c*]isoquinoline (9). **8** (320 mg, 1 mmol) was subjected to the same procedure as described for **2**. FC (heptane/EtOAc 3:1) gave 140 mg (52%) of **9** as yellow crystals, mp 91−92 °C (EtOAc−heptane). R_f (EtOAc−heptane, 1:2) 0.35. δ_H ($CDCl_3$): 9.01 (s, 1H, H-8), 8.17 (d, J = 8.2 Hz, 1H, H-4), 8.12 (s, 1H, H-3), 8.07 (d, J = 8.1 Hz, 1H, H-7), 7.83 (dt, J = 7.1, 1.2 Hz, 1H, H-5), 7.59 (dt, J = 7.0, 1.0 Hz, 1H, H-6), 7.55−7.32 (m, 5H, H arom), 5.52 (s, 2H, OCH_2Ph). δ_C ($CDCl_3$): 153.83 (C-8), 141.12 (C-9a), 133.82 (C_i), 132.00 (C-5), 130.23 (C-7a), 129.81 (arom C), 129.37 (arom C), 129.13 (arom C), 128.50 (arom C), 125.55 (C-6), 125.36 (C-3b), 124.72 (C-3), 122.24 (C-4), 107.75 (C-3a), 81.02 (CH_2 Bn). Anal. Calcd for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N 15.26. Found: C, 74.16; H, 4.83; N, 15.13.

***N*-2-(1-Benzyloxypyrazol-5-yl)phenylbenzophenoneimine (12).** A mixture of benzophenone (4.15 mmol), **10a**[2] (3.77 mmol), $Si(OEt)_4$ (4.6 mmol), and one drop of concd H_2SO_4 was placed in a flask equipped with a still head. The solution was heated at 160 °C under nitrogen overnight. The distillate (EtOH) was discarded, the residue was dissolved in Et_2O (20 mL), washed with saturated $NaHCO_3$ solution and H_2O (10 mL each), and dried ($MgSO_4$), and the solvents were removed. FC (heptane/EtOAc 5:1) gave 1.1 g (68%) of **12** as bright yellow crystals, mp 128−130 °C (EtOAc−heptane). R_f (EtOAc−heptane, 1:2) 0.46. δ_H ($CDCl_3$) 7.75−6.75 (m, 20H), 6.24 (d, J = 2.3 Hz, 1H), 4.62 (s, 2H). δ_C ($CDCl_3$): 167.85, 149.41, 139.09, 135.99, 133.44, 132.90, 132.35, 130.86, 129.93, 129.63, 129.43, 129.04, 128.91, 128.83, 128.69, 128.41, 128.25, 127.86, 123.04, 121.52, 117.96, 105.21, 80.21. Anal. Calcd for $C_{29}H_{23}N_3O$: C, 81.09; H, 5.40; N, 9.78. Found: C, 81.18; H, 5.11; N, 9.60.

***N*-2-(1-Benzyloxy-4-iodopyrazol-5-yl)phenylbenzophenoneimine (13).** **12** (0.40 g, 0.92 mmol) was iodinated the same way as **1**, quenching the reaction after 2 h. FC (heptane/EtOAc 5:1) gave 0.45 g (87%) of **13** as yellow brownish crystals, mp 144−146 °C (EtOAc−heptane). R_f (EtOAc−heptane, 1:2) 0.56. δ_H ($CDCl_3$) 7.66−6.70 (m, 19H), 7.31 (s, 1H), 5.22 (d, J = 10 Hz, 1H), 5.19 (d, J = 10 Hz, 1H). δ_C ($CDCl_3$): 168.13, 149.94, 139.45, 138.03, 136.11, 135.85, 133.51, 131.37, 130.63, 129.62, 129.55, 129.45, 128.94, 128.85, 128.42, 128.02, 127.94, 125.90, 122.94, 121.28, 118.89, 80.30, 58.09. Anal. Calcd for $C_{29}H_{22}IN_3O$: C, 62.71; H, 3.99; N, 7.57. Found: C, 62.69; H, 4.07; N, 7.48.

1-Benzyloxypyrazolo[4,3-*c*]quinoline (14). To a solution of *n*-BuLi (1.05 mL, 2.20 mmol, 2.12 M in hexanes) in THF (2 mL) was added dropwise **13** (0.55 g, 1 mmol) in THF (2 mL) with stirring at −78 °C. After 15 min, DMF (1.50 mL, 19.5 mmol) was added. Stirring was continued for 1 h, and the reaction mixture was allowed to warm to room temperature over 1 h and stirred for a further 1 h before 5 mL of 4 M HCl was added. The solution was stirred overnight and extracted with CH_2Cl_2 (3 × 10 mL), the organic layer was washed with saturated $NaHCO_3$ solution and H_2O (10 mL each) and dried ($MgSO_4$), and the solvents were removed. FC (heptane/EtOAc 2:1 → 1:2) gave 190 mg (70%) of **14** as yellow brownish crystals, mp 112−113 °C (EtOAc−heptane). R_f (EtOAc−heptane, 1:2) 0.23. δ_H ($CDCl_3$) 9.10 (s, 1H, H-4), 8.50 (dd, J = 8.3, 1.3 Hz,

(22) Regitz, M.; Hocker, J.; Liedhegener, A. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 179.

1H, H-9), 8.18 (dd, $J = 8.0$, 0.5 Hz, 1H, H-6), 8.01 (s, 1H, H-3), 7.73 (m, 1H, H-7), 7.64−7.55 (m, 1H, H-8), 7.49−7.31 (m, 5H, H arom), 5.52 (s, 2H, OCH_2Ph). δ_C ($CDCl_3$): 145.61 (C-4), 145.43 (C-5a), 132.90 (C_i), 132.63 (C-9b), 129.95 (arom C), 129.86 (C-6), 129.59 (arom C), 129.19 (C-7), 128.79 (arom C), 128.67 (C-3), 126.85 (C-8), 122.34 (C-9), 114.89 (C-9a), 114.68 (C-3a), 81.00 (CH_2 Bn). Anal. Calcd for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N 15.26. Found: C, 74.20; H, 4.78; N, 15.08.

1-Benzyloxypyrazolo[3,4-*c*]quinoline (18). A solution of **15**[3] (0.25 g, 0.95 mmol) and di-*tert*-butyl dicarbonate (0.23 g, 1.04 mmol) in THF (10 mL) was heated at reflux temperature for 16 h, THF was removed, the residue was dissolved in ethyl acetate, and this solution was washed successively with 1 M citric acid solution and brine (15 mL each). FC (heptane/EtOAc 0:1 → 1:4) gave 310 mg (90%) of **16** as a yellow oil. To a solution of **16** (100 mg, 0.27 mmol) in THF (1 mL) was added dropwise with stirring at −78 °C *n*-BuLi (0.31 mL, 0.66 mmol, 2.12 M in hexanes). After 5 min, DMF (4.0 mmol, 0.31 mL) was added, and the reaction was worked up the same way as **14**. FC (heptane/EtOAc 3:1) gave 62 mg (83%) of **18** as slightly yellow crystals, mp 105−106 °C (Et_2O−hexane). R_f (EtOAc−heptane, 3:5) 0.33. δ_H ($CDCl_3$): 8.65 (s, 1H, H-9), 8.19 (s, 1H, H-3), 8.18−8.08 (m, 2H, H-4, H-7), 7.70−7.58 (m, 2H, H-5, H-6), 7.38−7.25 (m, 5H, H-arom), 5.48 (s, 2H, OCH_2Ph). δ_C ($CDCl_3$): 142.62 (C-7A), 135.72 (C-9), 133.43 (C_i), 130.18 (C-7), 129.99 (arom C), 129.83 (arom C), 128.86 (arom C), 128.62 (C-9a), 128.01 (C-5 or C-6), 127.00 (C-5 or C-6), 125.90 (C-3), 122.60 (C-4), 121.25 (C-3b), 120.13 (C-3a), 81.23 (CH_2 Bn). Anal. Calcd for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N 15.26. Found: C, 74.44; H, 4.75; N, 15.00.

Debenzylation of 1-(Benzyloxy)pyrazoles 5, 9, 14, and 18.

1-Hydroxypyrazolo[4,3-*c*]isoquinoline (19). A mixture of **5** (50 mg, 0.18 mmol) and concentrated H_2SO_4 (10 mL) was stirred for 1 h at 80 °C. Washing with toluene (1 mL), adjustment of the pH of the aqueous solution with 4 M NaOH to pH 10, washing with dichloromethane (3 × 10 mL), addition of concentrated HCl to pH ca. 5, extraction with Et_2O (3 × 10 mL), drying of the combined organic phases, and removal of the solvent afforded 32 mg (94%) of **19** as slightly yellowish crystals, mp 202−203 °C (methanol). R_f (EtOAc−heptane−methanol, 4:1:1) 0.52. δ_H (CD_3OD): 8.98 (s, 1H, H-5), 8.77 (d, $J = 7.9$ Hz, 1H, H-9), 8.25 (d, $J = 8.1$ Hz, 1H, H-6), 8.00−7.90 (m, 1H, H-8), 7.93 (s, 1H, H-3), 7.84−7.76 (m, 1H, H-7). δ_C (CD_3OD): 151.16 (C-5), 133.35 (C-9b), 132.91 (C-8), 130.45 (C-6), 129.24 (C-7), 128.81 (C-5a), 127.41 (C-3), 124.20 (C-9a), 124.00 (C-3a), 123.24 (C-9). HRMS (ESI) calcd for $C_{10}H_8N_3O$ $(M + H)^+$ 186.0667, found 186.0665 ± 0.0005.

1-Hydroxypyrazolo[3,4-*c*]isoquinoline (20). Following the procedure described for preparation of **19** using **9**, extraction with Et_2O (3 × 10 mL) gave 32 mg (94%) of **20** as green yellowish crystals, mp 182−185 °C (methanol). R_f (EtOAc−heptane−methanol, 4:1:1) 0.48. δ_H (DMSO-d_6): 13.55 (br s, OH), 9.17 (s, 1H, H-8), 8.37 (d, $J = 7.9$ Hz, 1H, H-4), 8.21 (s, 1H, H-3), 8.25 (d, $J = 8.0$ Hz, 1H, H-7), 7.91 (dt, $J = 7.0$, 1.2 Hz, 1H, H-5)0.7.63 (dt, $J = 7.1$, 1.0 Hz, 1H, H-6). δ_C (DMSO-D_6): 153.34 (C-8), 140.42 (C-9A), 132.10 (C-5), 129.64 (C-3B), 129.44 (C-7), 125.43 (C-6), 124.72 (C-7A), 123.58 (C-3), 122.32 (C-4), 106.97 (C-3A). HRMS (ESI) calcd for $C_{10}H_8N_3O$ $(M + H)^+$ 186.0667, found 186.0669 ± 0.0005. Anal. Calcd for $C_{10}H_7N_3O{\cdot}10H_2O$: C, 64.22; H, 3.88; N 22.48. Found: C, 64.43; H, 3.86; N, 22.12.

1-Hydroxypyrazolo[4,3-*c*] quinoline (21). Following the procedure described for preparation of **19** using **14**, continuous extraction with Et_2O for 12 h gave 31 mg (91%) of **21** as yellow crystals, mp 211−212 °C (methanol). R_f (EtOAc−heptane−methanol, 4:1:1) 0.36. δ_H (DMSO-D_6): 13.50 (br s, OH), 9.16 (s, 1H, H-4), 8.68 (dd, $J = 7.9$, 1.1 Hz, 1H, H-6), 8.12 (d, $J = 6.3$ Hz, 1H, H-9), 8.11 (s, 1H, H-3), 7.82−7.65 (m, 2H, H-7, H-8). δ_C (DMSO-d_6): δ 146.04 (C-4), 144.62 (C-5A), 130.97 (C-9B), 129.28 (C-3), 128.81 (C-7), 127.42 (C-6), 126.67 (C-8), 122.32 (C-9), 115.04 (C-9A), 114.38 (C-3A). HRMS (ESI) calcd for $C_{10}H_8N_3O$ $(M + H)^+$ 186.0667, found 186.0672 ± 0.0005. Anal. Calcd for $C_{10}H_7N_3O{\cdot}24H_2O$: C, 63.78; H, 3.91; N 21.60. Found: C, 63.38; H, 3.98; N, 22.17.

1-Hydroxypyrazolo[3,4-*c*]quinoline (22). Following the procedure described for preparation of **19** using **18**, extraction with Et_2O (3 × 10 mL) gave 31 mg (91%) of **22** as orange crystals, mp 191−192 °C (methanol). R_f (EtOAc−heptane−methanol, 4:1:1) 0.28. δ_H (CD_3OD): 9.18 (s,1H, H-9), 8.37−8.31 (m, 1H, H-4), 8.27 (s, 1H, H-3), 8.18−8.12 (m, 1H, H-7), 7.77−7.65 (m, 2H, H-5, H-6). δ_C (CD_3OD): 143.18 (C-7a), 137.54 (C-9), 130.07 (C-7), 129.65 (C-5), 129.34 (C-9a), 128.44 (C-6), 125.72 (C-3), 124.30 (C-4), 123.21 (C-3a), 121.90 (C-3b). HRMS (ESI) calcd for $C_{10}H_8N_3O$ $(M + H)^+$ 186.0667, found 186.0665 ± 0.0005.

1-Hydroxypyrazolo[3,4-*c*]quinoline (22). A mixture of **18** (50 mg, 0.18 mmol) and 10 mL of aqueous hydrogen bromide (47%) was stirred for 1 h at 60 °C, before washing with toluene (1 mL). Evaporation of HBr and FC (EtOAc−heptane−methanol, 4:1:2) gave 33 mg (97%) of **22**, identical with the material described above.

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Supporting Information Available: The description of the synthesis of compounds **11a**−**c**, and ^1H and ^{13}C NMR spectra of compounds **11a**, **11c**, and **19**−**22**. This material is available free of charge via the Internet: http://pubs.acs.org.

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