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Efficient Synthesis of 5,6-Dihydroxyindole Dimers, Key Eumelanin Building Blocks, by a Unified *o*-Ethynylaniline-Based Strategy for the Construction of 2-Linked Biindolyl Scaffolds

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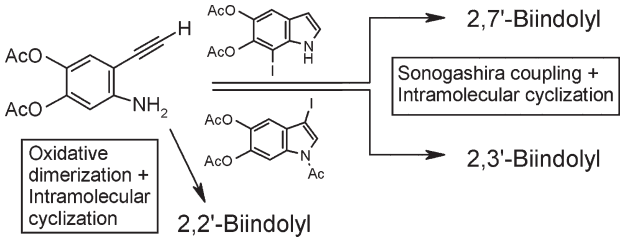
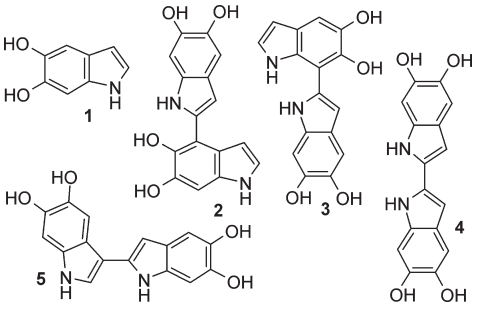


A unified convenient strategy for the synthesis of 5,6-dihydroxyindole-derived 2,7′-, 2,2′-, and 2,3′-biindolyls is reported, which is based on proper manipulation of key *o*-ethynylaniline precursors. By the same methodology 5,6-diacetoxy-7-iodoindole can also be obtained in good yield.

5,6-Dihydroxyindoles are naturally occurring, catechol-containing heterocyclic compounds[1] which provide the fundamental monomer precursors of eumelanins, the characteristic black insoluble biopolymers found in human skin, hair, and eyes.[2] Chemical or enzymatic oxidation converts the parent 5,6-dihydroxyindole (**1**) into black insoluble materials virtually indistiguishable from natural pigments. This polymerization reaction proceeds through oligomer intermediates that can be populated at the dimer level by up to four main biindolyls, **2**−**5**, sharing 2-linked indole units as a common feature.[1,3] This peculiar signature of the oxidation behavior of **1** is lost in part when the dimers are oxidatively converted to tetramers.[4] Hence, the availability of dimers from **1** is of paramount importance to enquire into the broad diversity of oligomeric architectures expected to concur with eumelanin buildup.[5] Additional motivations for pursuing **1**-derived dimers as synthetic targets derived from recognition of eumelanin-like polymers as new prototypes of bioinspired functional materials.[6−8] Moreover, 2,2′-biindolyls are of current interest as structural motifs for the preparation of anion sensing architectures,[9] and **1**-based oligomers have recently been shown to exhibit fluoride-sensing properties.[10]

Whereas numerous synthetic efforts have been directed to **1**,[11,12] the current synthetic repertoire for the preparation of related dimers is scanty, the only exception being the synthesis of the 3,3′-biindolyl.[13] Considerable constraints to the possible synthetic plans are posed by the highly oxidizable *o*-dihydroxy functionality, which requires careful selection of protecting groups, reagents, and reaction conditions. Accordingly experimental control over oxidation pathways of **1** represented so far the only means of gaining access to small amounts of dimers for structural investigations. While **2** can be practically obtained in sufficient amounts by oxidative coupling of **1**, the other dimers, especially **4**, remain difficult to prepare and are usually obtained in poor yields with significant impurities, requiring cumbersome chromatographic purification steps.



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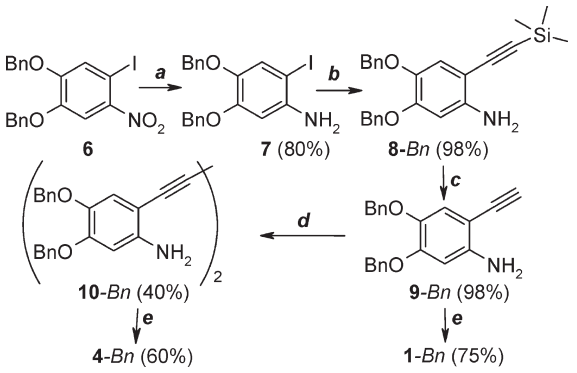
SCHEME 1. Synthesis of 5,5′,6,6′-Tetrabenzyloxy-2,2′-biindolyl (4-*Bn*)[15]



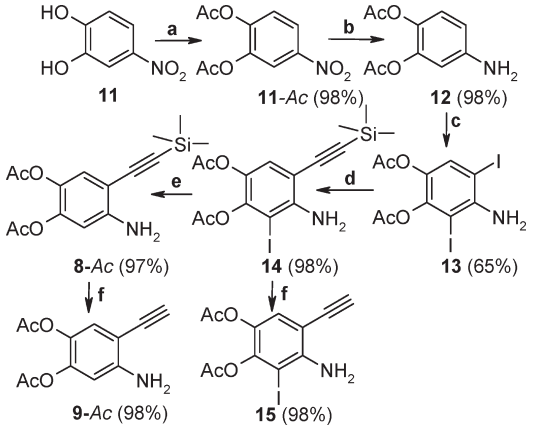
Herein we report the first successful approach to the less accessible dimers of **1**, namely the 2,7′-, 2,2′-, and 2,3′-biindolyls **3**−**5**, which relies on sequential coupling and cyclization steps involving suitably protected *o*-ethynylaniline intermediates.

The possible strategy to the 2,2′-biindolyl **4** was delineated in recent papers[9a,c,14] and was initially pursued by using 1,2-dibenzyloxy-4-iodo-5-nitrobenzene (**6**) as the starting compound (Scheme 1).

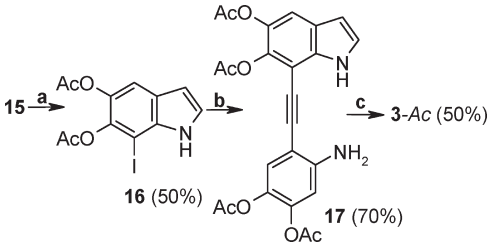
Compound **6** was readily obtained as described in the previous synthesis of the 3,3′-biindolyl.[13] Easy removal of benzyl groups by catalytic hydrogenation supported the validity of the strategy for the purposes of this study. Reduction of **6** to the iodoaniline **7** was successfully achieved with sodium dithionite in 1:1 acetone−0.1 M phosphate buffer (pH 7.4). Sonogashira coupling[16] with trimethylsilylacetylene followed by deprotection with potassium fluoride led to the *o*-ethynylaniline **9**-*Bn*. Oxidative dimerization with $Cu(OAc)_2$[17] followed by intramolecular cyclization with CuI[18] gave 5,5′,6,6′-tetrabenzyloxy-2,2′-biindolyl (**4**-*Bn*) in satisfactory overall yield. Notably, direct cyclization of **9**-*Bn* yielded **1**-*Bn* in good yield. This procedure is probably one of the best so far developed for the preparation of **1**-*Bn*.[19]

Efforts to extend the above chemistry to the preparation of dimer **3**, featuring the challenging 2,7′-biindolyl skeleton, were unsuccessful, due to difficulties with the preparation of a crucial intermediate, 3,4-dibenzyloxy-6-ethynyl-2-iodoaniline, by iodination of **9**-*Bn*. These difficulties were attributed to the electron-donating benzyloxy groups increasing the reactivity of the aromatic ring and preventing control over iodination. In seeking an alternative strategy for protection of the catechol function, we opted for acetyl groups, since these latter were expected to blunt the electron-donating effect of the hydroxyl groups thus allowing for controlled

SCHEME 2. Synthesis of *o*-Ethynylaniline Building Blocks[20]



SCHEME 3. Synthesis of 2,7′-Biindolyl 3-*Ac*[23]



ring iodination. Moreover, the acetyl groups can be conveniently removed in situ by a very mild hydrolytic step just prior to oxidative polymerization experiments.[4] Central to this strategy was reduction of the nitro group prior to iodination, which was envisioned to lead to a diacetoxyaniline more amenable to iodination. In line with this expectation, 4-nitrocatechol (**11**), was acetylated and then subjected to catalytic hydrogenation to give the corresponding diacetoxyaniline **12** (Scheme 2).

Iodination of **12** with $NaI/NaClO_2$[21a] gave an *o*,*o*-diiodoaniline (**13**), which eventually led to the desired 3,4-diacetoxy-6-ethynyl-2-iodoaniline (**15**) in good overall yield following a regioselective Sonogashira coupling. An efficient deiodination step then afforded the key intermediate 4,5-diacetoxy-2-ethynylaniline (**9**-*Ac*). This latter compound could not be obtained via controlled iodination of **12**, since attempts to insert only one iodo substituent failed under a variety of conditions.

With the same synthetic approach it was possible to obtain 5,5′,6,6′-tetraacetoxy-2,7′-biindolyl (**3**-*Ac*) in satisfactory yields via cyclization of **15** to give a 7-iodoindole derivative (**16**), followed by coupling with **9**-*Ac* and final cyclization to give the 2-substituted indole moiety (Scheme 3). In this sequence, the yield of the CuI-promoted intramolecular cyclization of **15** could not be increased above 50% due to

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(15) Reagents and conditions: (a) $Na_2S_2O_4$, acetone/0.1 M phosphate buffer (pH 7.4), 60 °C, 2h ; (b) PPh_3, CuI, $(PPh_3)_2PdCl_2$, trimethylsilylacetylene, TEA/toluene, Ar atm, 60 °C, 30 min ; (c) KF, DMF, 2 h ; (d) $Cu(OAc)_2$, dry pyr, Ar atm, 16 h ; (e) CuI, dry DMF, Ar atm, 110 °C, 3 h. Yields refer to the isolated compound.

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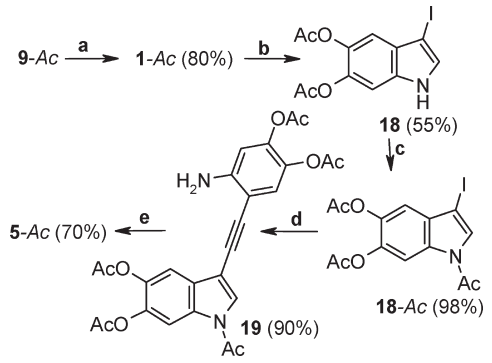
(20) Reagents and conditions: (a) Ac_2O, pyr, 320 W, 6 min ; (b) 10% Pd/C, 20 atm H_2, $CHCl_3$, 6 h ; (c) $NaClO_2$, NaI, HCl, H_2O/methanol, 1 h ; (d) PPh_3, CuI, $(PPh_3)_2PdCl_2$, trimethylsilylacetylene, TEA/toluene, Ar atm, 60 °C, 30 min ; (e) Zn, AcOH, 30 min ; (f) KF H_2O/DMF, 30 min. Yields refer to the isolated compounds.

(21) (a) Lista, L.; Pezzella, A.; Napolitano, A; d'Ischia, M. *Tetrahedron* **2008**, *64*, 234–239. (b) Pezzella, A.; Crescenzi, O.; Natangelo, A.; Panzella, L.; Napolitano, A.; Navaratman, S.; Edge, R.; Land, E. J.; Barone, V.; d'Ischia, M. *J. Org. Chem*. **2007**, *72*, 1595–1603.

SCHEME 4. Synthesis of 2,3′-Biindolyl 5-*Ac*[24]



partial decomposition of the unstable iodoindole product. In the same scheme, change to aluminum chloride as the catalyst for cyclization of **17** was prompted by the low efficiency of CuI due probably to unfavorable steric interactions of this bulky cation with the hindered substrate. To the best of our knowledge, this is the first total synthesis of a 2,7′-biindolyl system that does not rely on heavily substituted preformed indole precursors.[23]

The successful strategy to **3**-*Ac* was next applied to the synthesis of the 2,3′-biindolyl as the acetyl derivative (**5**-*Ac*) (Scheme 4).

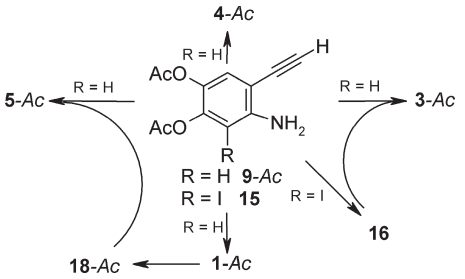
Thus, **9**-*Ac* was converted to 5,6-diacetoxyindole (**1**-*Ac*) via CuI-promoted intramolecular cyclization, and then regioselectively iodinated at the 3-position by a recently developed preocedure[21b] to give 5,6-diacetoxy-3-iodoindole (**18**). Reaction of **18** with **9**-*Ac* under Sonogashira conditions was unsuccessful. However, the problem was circumvented by *N*-acetylating the indole substrate just prior to the Sonogashira coupling. The *N*-acetylation of **18** with acetic anhydride and dimethylaminopyridine makes the iodoindole derivative more prone to the coupling with **9**-*Ac*, giving the 3-alkynyl-substituted 5,6-diacetoxy-1-acetylindole **19** in good yields; this latter was subjected to the final cyclization step to afford **5**-*Ac*.

A straightforward extension of this chemistry to the 2,2′-biindolyl system eventually led to the acetyl derivative **4**-*Ac* via oxidative dimerization of **9**-*Ac* to **10**-*Ac* (86%) followed by double concerted intramolecular cyclization (70%), using the same reaction conditions detailed in Scheme 1 for **4**-*Bn* synthesis.

In a final set of experiments a representative dimer, **3**-*Ac*, was efficiently deacetylated by treatment with *t*-BuO^- in MeOH under an Ar atmosphere, and pure **3** was completely characterized for the first time by NMR (see the SI).

In conclusion, we have reported the first total synthesis of 2,2′-, 2,3′-, and 2,7′-biindolyls based on the unified strategy summarized in Scheme 5. This allows access to diverse biindolyl scaffolds and monomer derivatives by manipulation of only two key *o*-ethynylaniline derivatives, **9**-*Ac* and

SCHEME 5. Summarizing Scheme of the Unified Strategy to 3-*Ac*−5-*Ac*



15, which, in turn, can be obtained from a common precursor, **14**.

Attempts at synthesizing dimer **2**-*Ac* by a proper variant of the unified strategy were thwarted by difficulties encountered with the preparation of 4,5-diacetoxy-2-ethynyl-3-iodoaniline as the necessary intermediate. Since this dimer is easily available by oxidation of **1**, the search for alternate approaches was postponed to studies currently under development.

Experimental Section

Synthesis of 4,5-Dibenzyloxy-2-(trimethylsilylethynyl)aniline (8-*Bn*). A solution of **7** (500 mg, 1.2 mmol) in triethylamine (9.5 mL) and toluene (9.5 mL) was treated with PPh_3 (30 mg, 0.12 mmol), CuI (22 mg, 0.12 mmol), $(PPh_3)_2PdCl_2$ (40 mg, 0.06 mmol), and trimethylsilylacetylene (900 μL, 6.3 mmol) under an argon atmosphere at 60 °C. After 30 min the reaction mixture was extracted with a 10% water solution of NH_4Cl and toluene. The organic layers were dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford pure **8**-*Bn* (456 mg, 98%, R_f 0.53, eluant: petroleum ether/EtOAc 8:2 (v/v)).

8-*Bn*: ^{1}H NMR (300 MHz, CDCl3) δ (ppm) 0.27 (9H, s, $Si(CH_3)_3$), 3.80 (2H, br s, NH_2), 5.02 (2H, s, OCH_2Ph), 5.08 (2H, s, OCH_2Ph), 6.31 (1H, s, H-6), 6.96 (1H, s, H-3), 7.0−7.2 (10H, m, H-2, H-3, H-4, H-5, H-6/OBn); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 0.47 ($Si(CH_3)_3$), 71.1 (OCH_2Ph), 73.1 (OCH_2Ph), 98.8 (—C≡C—Si), 100.1 (—C≡C—Si), 101.8 (C-6), 102.2 (C-2), 120.2 (C-3), 127−129 (10 × CH, C-2, C-3, C-4, C-5, C-6/OBn), 137.1 (C-1/OBn), 137.8 (C-1/OBn), 141.2 (C-1), 144.9 (C-4), 151.9 (C-5); HRMS (ESI) m/z $C_{25}H_{28}NO_2Si$ $[M + H]^+$ calcd 402.1889, found 402.1893.

Synthesis of 4,5-Dibenzyloxy-2-ethynylaniline (9-*Bn*). A solution of **8**-*Bn* (320 mg, 0.8 mmol) in DMF (7.2 mL) was treated with KF (70 mg, 1.2 mmol) at room temperature. After 2 h the reaction mixture was extracted with chloroform and a 10% water solution of NH_4Cl, and the organic layers were dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford pure **9**-*Bn* (257 mg, 98%, R_f 0.35, eluant: petroleum ether/EtOAc 7:3 (v/v)).

9-*Bn*: FT-IR ($CHCl_3$) ν 2096 (—C≡C—), 3400−3500 (NH_2) cm^{-1}; ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ (ppm) 3.84 (1H, s, —C≡CH), 4.81 (2H, br s, NH_2), 5.02 (2H, s, OCH_2Ph), 5.08 (2H, s, OCH_2Ph), 6.60 (1H, s, H-6), 6.97 (1H, s, H-3), 7.3−7.5 (10H, m, H-2, H-3, H-4, H-5, H-6/OBn); ^{13}C NMR (50 MHz, $(CD_3)_2CO$) δ (ppm) 70.8 (OCH_2Ph), 73.1 (OCH_2Ph), 81.7 (—C≡CH), 82.7 (—C≡CH), 98.0 (C-2), 101.5 (C-6), 120.9 (C-3), 128−129 (10 × CH, C-2, C-3, C-4, C-5, C-6/OBn), 137.9 (C-1/OBn), 138.7 (C-1/OBn), 140.6 (C-1), 147.1 (C-4), 152.6 (C-5); HRMS (ESI) m/z $C_{22}H_{20}NO_2$ $[M + H]^+$ calcd 330.1494, found 330.1489.

Synthesis of 2-[4′-(2″-Amino-4″,5″-dibenzyloxyphenyl)-1′,3′-butadiinyl]-4,5-dibenzyloxyaniline (10-*Bn*). A solution of **9**-*Bn*

(22) (a) Black, D. St. C.; Ivory, A. J.; Kumar, N. *Tetrahedron* **1996**, *52*, 7003–7012. (b) Black, D. St. C.; Ivory, A. J.; Kumar, N. *Tetrahedron* **1996**, *52*, 4697–708.

(23) Reagents and conditions: (a) CuI, TEA/toluene, Ar atm, 130 °C, 1.5 h ; (b) PPh_3, CuI, $(PPh_3)_2PdCl_2$, 9-Ac, TEA/toluene, Ar atm, 60 °C, 1 h ; (c) $AlCl_3$, toluene, Ar atm, 110 °C, 3.5 h. Yields refer to the isolated compound.

(24) Reagents and conditions: (a) CuI, TEA/toluene, Ar atm, 130 °C, 1.5 h ; (b) oxone, NH_4I, I_2, acetonitrile, 2 h ; (c) DMAP, Ac_2O, toluene, 30 min ; (d) PPh_3, CuI, $(PPh_3)_2PdCl_2$, 9-Ac, TEA/toluene, Ar atm, 60 °C, 1 h ; (e) CuI, dry DMF, Ar atm, 110 °C, 1.5 h. Yields refer to the isolated compound.

(682 mg, 2.1 mmol) in dry pyridine (7 mL) was treated with $Cu(OAc)_2$ (455 mg, 2.3 mmol) at room temperature under an argon atmosphere. After 16 h the reaction mixture was filtered on Celite, evaporated under reduced pressure, and extracted with chloroform and a saturated solution of $NaHCO_3$. The organic layers were washed with brine, dried over anhydrous sodium sulfate, and evaporated under reduced pressure and the residue was fractionated on silica gel (cyclohexane/EtOAc, gradient from 7:3 to 6:4) to afford pure **10**-*Bn* (272 mg, 40%, R_f 0.44, eluant: cyclohexane/EtOAc 6:4 (v/v)).

10-*Bn*: FT-IR ($CHCl_3$) ν 2200 (—C≡C—), 3400−3500 (NH_2) cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ (ppm) 4.95 (2H × 2, br s, NH2), 5.03 (2H × 2, s, OCH2Ph), 5.12 (2H × 2, s, OCH_2Ph), 6.57 (1H × 2, s, H-6, H-3″), 6.93 (1H × 2, s, H-3, H-6″), 7.2−7.6 (10H × 2, m, H-2, H-3, H-4, H-5, H-6/OBn); ^{13}C NMR (50 MHz, $(CD_3)_2CO$) δ (ppm) 71.0 (2 × OCH_2Ph), 73.1 (2 × OCH_2Ph), 78.9 (—C≡C—C≡C—), 80.9 (—C≡C—C≡C—), 97.4 (C-2, C-1″), 101.5 (C-6, C-3″), 120.8 (C-3, C-6″), 128−129 (10 CH × 2, C-2, C-3, C-4, C-5, C-6/OBn), 138.1 (2 × C-1/OBn), 138.9 (2 × C-1/OBn), 141.0 (C-5, C-4″), 148.7 (C-1, C-2″), 153.5 (C-4, C-5″); MS (MALDI) m/z 657 ($[M + H]^+$); HRMS (ESI) m/z $C_{44}H_{37}N_2O_4$ $[M + H]^+$ calcd 657.2753, found 657.2758.

Synthesis of 5,5′,6,6′-Tetrabenzyloxy-2,2′-biindolyl (4-*Bn*). A solution of **10**-*Bn* (170 mg, 0.25 mmol) in dry DMF (2.6 mL) was treated with CuI (99 mg, 0.50 mmol) at 110 °C under an argon atmosphere. After 3 h the reaction mixture was filtered on Celite and extracted with chloroform and a 10% solution water of NH_4Cl. The organic layers were dried over anhydrous sodium sulfate and evaporated under reduced pressure and the residue was fractionated on preparative TLC (eluant: benzene/acetone 9:1 (v/v) plus 1% acetic acid) to afford pure **4**-*Bn* (102 mg, 60%, R_f 0. 62, eluant: benzene/acetone 9:1 (v/v) plus 1% acetic acid).

4-*Bn*: UV−vis (DMSO) λ 357, 376 nm; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ (ppm) 5.15 (2H × 2, s, OCH_2Ph), 5.17 (2H × 2, s, OCH_2Ph), 6.71 (1H × 2, s, H-3, H-3′), 7.06 (1H × 2, s, H-7, H-7′), 7.20 (1H × 2, s, H-4, H-4′), 7.3−7.6 (10H × 2, m, H-2, H-3, H-4, H-5, H-6/OBn), 10.40 (1H × 2, br s, NH); ^{13}C NMR (50 MHz, $(CD_3)_2CO$) δ (ppm) 71.8 (2 × OCH_2Ph), 72.2 (2 × OCH_2Ph), 98.0 (C-3, C-3′), 98.5 (C-7, C-7′), 106.8 (C-4, C-4′), 123.3 (C-4a, C-4a′), 127−129 (10 CH × 2, C-2, C-3, C-4, C-5, C-6/OBn), 131.3 (C-2, C-2′), 132.6 (C-7a, C-7a′), 138.3 (4 × C-1/OBn), 145.4 (C-5, C-5′), 147.3 (C-6, C-6′); MS (ESI+) m/z 657 ($[M+H]^+$), 679 ($[M + Na]^+$); HRMS (ESI) m/z $C_{44}H_{37}N_2O_4$ $[M + H]^+$ calcd 657.2753, found 657.2762.

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Supporting Information Available: Material and methods and experimental procedures, and NMR spectra for compounds **1**-*Ac*, **1**-*Bn*, **3**, **3**-*Ac*, **4**-*Ac*, **4**-*Bn*, **5**-*Ac*, **7**, **8**-*Ac*, **8**-*Bn*, **9**-*Ac*, **9**-*Bn*, **10**-*Ac*, **10**-*Bn*, **11**-*Ac*, **12**, **13**, **14**, **15**, **16**, **17**, **18**-*Ac*, **19**. This material is available free of charge via the Internet at http://pubs.acs.org.