Synthesis of Indoles Isolated from *Tricholoma* Species

Björn C. Söderberg,*,[1] Angela C. Chisnell,[2] Shannon N. O'Neil,[2] and James A. Shriver

Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506-6045

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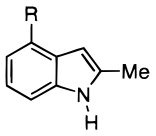
Introduction

We have recently developed a palladium−phosphine-catalyzed reductive *N*-heteroannulation of 2-nitrostyrenes forming indoles in good to excellent isolated yields.[3] For example, reaction of 6-bromo-2-nitrostyrene with carbon monoxide (60 psi), in the presence of a catalytic amount of palladium diacetate (6 mol %) and triphenylphosphine (24 mol %), in acetonitrile at 70 °C, gave 4-bromoindole in 86% yield (Scheme 1). Reaction of a number of other 2-nitrostyrenes, having either electron-withdrawing or electron-donating substituents on the aromatic ring, gave indoles in fair to excellent yield (40−100%). Several functional groups, such as esters, ethers, bromides, triflates, and additional nitro groups, have been shown to be compatible with the reaction conditions; thus, the use of protection group strategies appears not to be required.

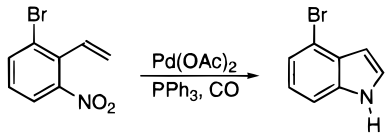
Using this methodology, we envisioned short syntheses of 2,4-dimethylindole (**1**), 4-(hydroxymethyl)-2-methylindole (**2**), and 4-(methoxymethyl)-2-methylindole (**3**), alkaloids recently isolated from two species of European Basidomycetes (*Tricholoma virgatum* and *Tricholoma sciodes*, Figure 1).[4] The synthesis of **1** also constitutes a formal synthesis of the biindolones peronatin A−B isolated from damaged fruiting bodies of *Collybia peronata* and *Tricholoma scalpturum*.[5]



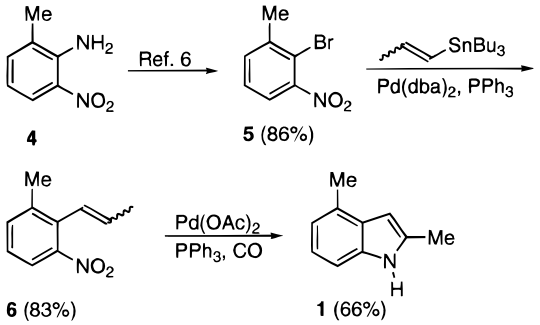
R = Me (**1**), CH_2OH (**2**), CH_2OMe (**3**)

Figure 1.

Scheme 1



Scheme 2



Results and Discussion

2,4-Dimethylindole **1** was selected as our first target molecule. Sandmeyer reaction of the commercially available 2-amino-3-methyl-1-nitrobenzene (**4**), according to literature,[6] gave 2-bromo-3-methyl-1-nitrobenzene (**5**) in very good yield (Scheme 2). The alkene moiety required for the *N*-heteroannulation was introduced by a Stille-type coupling[7] of **5** with (tri-*n*-butyl-1-propen-1-yl)stannane. The annulation precursor **6** was isolated in 83% yield as a mixture of isomers (*cis*−*trans*, 3:1). This mixture is a reflection of the isomer ratio of the commercially available 1-propen-1-ylmagnesium chloride used to prepare the tin reagent. Since we have previously shown that the yield and rate of reaction are relatively unaffected by the stereochemistry of the alkene, the isomeric mixture was used as such in the subsequent step.[3b] Thus, reaction of an acetonitrile solution of **6** (ca. 0.5 M) with carbon monoxide (60 psi) in the presence of palladium diacetate ($Pd(OAc)_2$, 6 mol %), and triphenylphosphine (PPh_3, 24 mol %) at 70 °C gave the expected indole (**1**). Spectroscopic data were in all respects identical to those previously reported.[8]

Encouraged by the results discussed above, we next turned our attention to the synthesis of the 4-hydroxymethyl-substituted methylindole (**2**). Palladium-catalyzed coupling of methyl 2-bromo-3-nitrobenzoate (**8**) with (tri-*n*-butyl-1-propen-1-yl)stannane gave styrene **9** (Scheme 3). *N*-Heteroannulation of **9**, under standard reaction conditions, produced the expected indole **10** in 90% yield. Finally, reduction of the methyl ester using DIBAL-H gave the naturally occurring indole **2** in high isolated yield.[9] In a second approach to **2**, the hydroxymethyl-substituted styrene **13** was prepared either from **5** or, more directly, by reduction of **9** with DIBAL-H. In the former sequence, benzylic bromination of **5** gave **11** which was reacted with water under acidic conditions smoothly

(1) E-mail address: bsoderbe@wvu.edu.

(2) Undergraduate research participant.

(3) (a) Söderberg, B. C.; Rector, S. R.; O'Neil, S. N. *Tetrahedron Lett.* **1999**, *40*, 3657. (b) Söderberg, B. C.; Shriver, J. A. *J. Org. Chem.* **1997**, *62*, 5838. See also (a) Akazome, M.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* **1994**, *59*, 3375. (b) Tolari, S.; Cenini, S, Crotti, C.; Gianella, E. *J. Mol. Catal.* **1994**, *87*, 2811. (c) Tolari, S.; Cenini, S, Crotti, C.; Gianella, E. *J. Mol. Catal.* **1994**, *87*, 203. (d) Crotti, C.; Cenini, R.; Todeschini, R.; Tollari, S. *J. Chem. Soc., Faraday Trans.* **1991**, 2811. (e) Crotti, C.; Cenini, S.; Rindone, B.; Tollari, S.; Demartin, F. *J. Chem. Soc., Chem. Commun.* **1986**, 784.

(4) Garlaschelli, L.; Pang, Z.; Sterner, O.; Vidari, G. *Tetrahedron* **1994**, *50*, 3541.

(5) Stachel, S. J.; Nilges, M.; Van Vranken, D. L. *J. Org. Chem.* **1997**, *62*, 4756.

(6) Krolski, M. E.; Renaldo, A. F.; Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1988**, *53*, 1170.

(7) For an excellent review, see: Farina, V.; Krishnamurthy, V.; Scott, V. J. In *Organic Reactions*; John Wiley & Sons: New York, 1997; Vol. 50, pp 1−652.

(8) (a) Reference 4. (b) Bard, R. R.; Bunnett, J. F. *J. Org. Chem.* **1980**, *45*, 1546. (c) MacDonald, G.; Proctor, G. R. *J. Chem. Soc., Chem. Commun.* **1975**, 1446. (d) Gassman, P. G.; van Bergen, T. J.; Gilbert, D. P.; Cue, B. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 6, 5495.

(9) For a related reduction, see Kozikowski, A. P.; Ishida, H.; Chen, Y.-Y. *J. Org. Chem.* **1980**, *45*, 3350.

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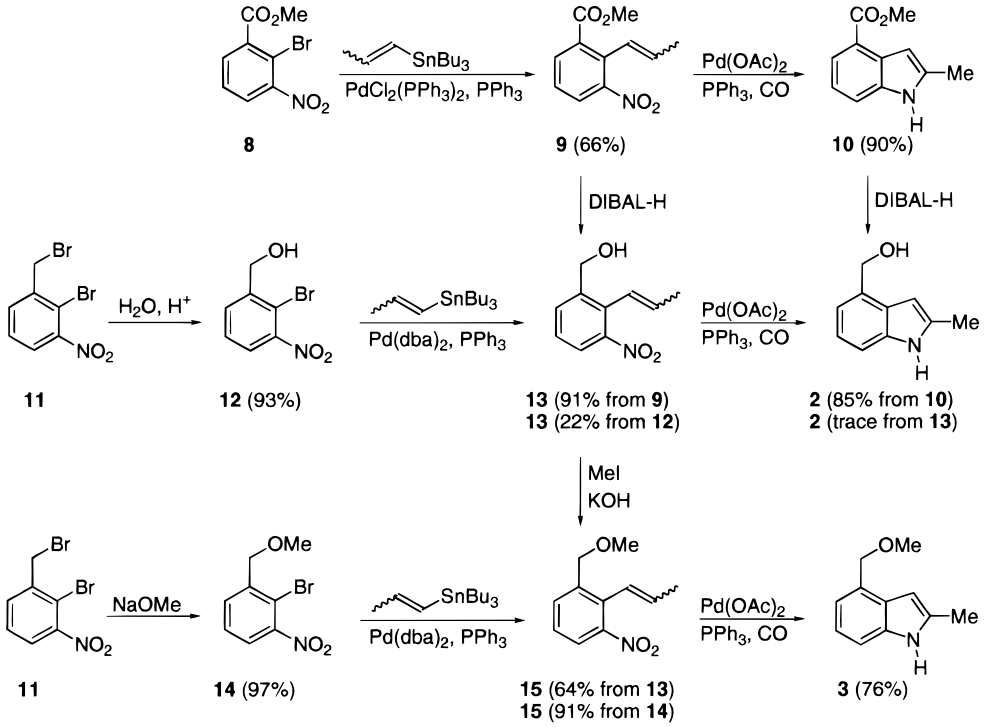
Scheme 3



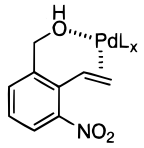


Figure 2.

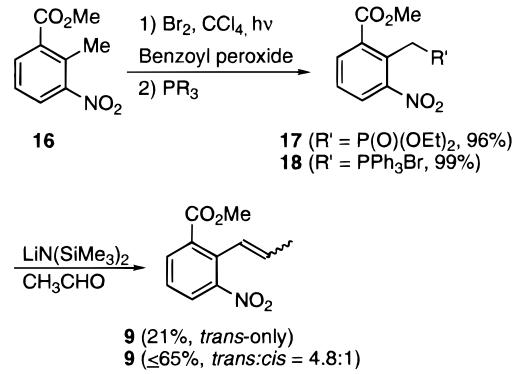
producing 2-bromo-3-(hydroxymethyl)-1-nitrobenzene (**12**). Stille-type coupling of **12**, however, gave a disappointing 22% yield of **13** using the same reaction conditions and reagents as described above for **5**. A number of different catalysts and reaction conditions were examined, all producing even lower yields of **13**.

Attempted cyclization of **13** gave only trace amounts of the expected product **2** after prolonged reaction time (7 days) and elevated temperature (120 °C). A substantial amount (66%) of starting material was recovered. The hydroxymethyl-substituted compound **13** represents only the second example of an unsuccessful *N*-heteroannulation. Coordination of palladium to both the alkene and the hydroxy group, effectively removing palladium from the proximity of the nitro group thus preventing the reduction, is a possible mechanistic explanation for the very low yield (Figure 2).

The third and final indole **3** was assembled in a related fashion (Scheme 3). The methoxymethyl-substituted annulation precursor **15** was prepared either by alkylation of **13** with iodomethane in the presence of KOH, or by treatment of **11** with sodium methoxide producing **14**, followed by coupling (tri-*n*-butyl-1-propen-1-yl)stannane. In contrast to the hydroxymethyl-substituted compound, both the Stille type coupling and the subsequent *N*-heteroannulation cleanly gave **15** and indole **3**, respectively, in good isolated yield.

Finally, a somewhat different strategy for the preparation of **9** was also pursued. Benzylic bromination of **16**,[3b] followed by reaction of the crude benzylic bromide with triethyl phosphite or triphenylphosphine, gave the phosphonate **17** and the phosphonium salt **18**,[3b] respectively (Scheme 4). Wadsworth−Emmons reaction of **17**, using lithium hexamethyldisilazide and acetaldehyde, gave pure *trans*-**9**. However, the yield of **9** was low (21%), and a substantial amount of starting material was recovered. Reaction of the corresponding triphenylphosphonium salt **18** gave an inseparable mixture of the expected compound **9** and the hydrolysis product **16**.[10] It was possible to cyclize the mixture of **9** and **16** which produced **10** in 54% yield. Indole **10** was readily separated from **16** by column chromatography on silica gel. However, we were unable to obtain a quantitative conversion of **9**; a nontrivial amount of starting material was always isolated. The presence of **16** apparently interferes with the cyclization since **10** can be obtained in 90% yield from pure **9** (Scheme 3).

Scheme 4



In conclusion, total syntheses of three naturally occurring indole alkaloids, employing a palladium−phosphine-catalyzed *N*-heteroannulation as the key step, have been

(10) For similar hydrolytic cleavages of ylides, see Maercher, A. *Org. React.* **1965**, *14*, 291. And references therein: (a) Wittig, G.; Geissler, G. *Justus Lieb. Ann. Chem.* **1953**, *580*, 44. (b) Fenton, G. W.; Ingold, C. K. *J. Chem. Soc.* **1929**, 2342.

accomplished. Further applications of this reaction in total synthesis are underway in our laboratories.

Experimental Section

General Procedures. All NMR spectra were determined in $CDCl_3$ at 270 MHz (^1H NMR) and 67.5 MHz (^{13}C NMR). The chemical shifts are expressed in δ values relative to Me_4Si (0.0, ^1H and ^{13}C) or $CDCl_3$ (77.0, ^{13}C) internal standards. $^1H-^1H$ spin−spin coupling constants are reported as calculated from spectra; thus, a slight difference between $J_{a,b}$ and $J_{b,a}$ is usually obtained. Results of APT (attached proton test) ^{13}C NMR experiments are shown in parentheses where, relative to $CDCl_3$, (−) denotes CH_3 or CH, and (+) denotes CH_2 or C. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Toluene, hexanes, dimethylformamide (DMF), triethylamine, methanol, and ethyl acetate were distilled from calcium hydride. Chemicals prepared according to literature procedures have been footnoted the first time used; all other reagents were obtained from commercial sources and used as received. All reactions were performed in oven-dried glassware under an argon atmosphere unless otherwise stated. Solvents were removed from crude reaction mixtures and products on a rotary evaporator at water aspirator pressure. Melting points were determined on a MelTemp and are uncorrected. Elemental analyses were performed by Atlantic Microlab Inc. (Norcross, GA).

2-Bromo-3-(bromomethyl)-1-nitrobenzene (11).[11] A solution of 3-methyl-2-bromo-1-nitrobenzene (**5**)[6] (5.59 g, 25.88 mmol) and freshly recrystallized *N*-bromosuccinimide (4.84 g, 27.19 mmol) in CCl_4 (52 mL) was heated at reflux. Benzoyl peroxide (314 mg, 1.30 mmol) was added in one portion, and the reaction mixture was irradiated (150 W, sun-lamp) and heated at reflux for 16 h. After being cooled to ambient temperature, the formed succinimide was removed by filtration, and the solid was washed with hexanes. The solvents were removed from the filtrate, and the solid residue was purified by chromatography using hexanes followed by hexanes−EtOAc (19:1) as eluent to give **11** (6.67 g, 19.22 mmol, 74%) as a white solid.[12] *Caution: strong lachrymator!* mp 60−64 °C; ^1H NMR δ 7.67 (dd, J = 7.5 and 1.6 Hz, 1H), 7.66 (dd, J = 8.3 and 1.5 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 4.67 (s, 3H); ^{13}C NMR δ 151.2 (+), 139.9 (+), 133.9 (−), 128.4 (−), 124.5 (−), 115.5 (+), 32.3 (+); IR (neat) 1554 cm^{-1}.

2-Bromo-3-(hydroxymethyl)-1-nitrobenzene (12). A solution of 2-bromo-3-(bromomethyl)-1-nitrobenzene (**11**) (2.50 g, 8.48 mmol) and *p*-toluenesulfonic acid (27 mg, 0.14 mmol) in a mixture of acetonitrile (45 mL) and water (5 mL) was heated at reflux (14 days). The reaction was monitored by TLC (hexanes−EtOAc, 8:2). Water (50 mL) was added, and the resulting mixture was extracted with diethyl ether. The combined organic phases were dried ($MgSO_4$), and the solvents were removed. The crude product was purified by chromatography using a sequence of eluents (hexanes−EtOAc, 19:1, 9:1, 4:1, 7:3) affording **12** (1.83 g, 7.88 mmol, 93%) as pale yellow crystals. mp 71−73 °C; ^1H NMR δ 7.77 (d with further fine splitting, J = 7.5 Hz, 1H), 7.66 (dd, J = 8.1 and 1.6 Hz, 1H), 7.50 (t, J = 7.9 Hz, 1H), 4.85 (d, J = 5.6 Hz, 2H), 2.12 (t, J = 5.7 Hz, 1H); ^{13}C NMR δ 150.7 (+), 142.9 (+), 130.9 (−), 128.1 (−), 123.7 (−), 113.0 (+), 64.5 (+); IR (neat) 3228, 1526 cm^{-1}. Anal. Calcd for $C_7H_6BrNO_3$: C, 36.24; H, 2.61. Found: C, 36.32; H, 2.59.

2-Bromo-3-(methoxymethyl)-1-nitrobenzene (14). Sodium (156 mg, 6.78 mmol) was added to a round-bottomed flask containing methanol (40 mL). After complete formation of sodium methoxide, the colorless solution was added to a cold solution of **11** (1.00 g, 3.39 mmol) in methanol (40 mL) at 0 °C. The resulting pale yellow solution was stirred at ambient temperature (45 min) followed by solvent removal to give a yellow solid residue. The crude product was purified by chromatography (hexanes−EtOAc, 19:1) to give **14** (810 mg, 3.30 mmol, 97%) as pale yellow crystals. mp 35−37 °C; ^1H NMR δ 7.71 (d, J = 7.7 Hz, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.47 (t, J = 7.9 Hz, 1H), 4.58 (s, 2H), 3.52 (s, 3H); ^{13}C NMR δ 150.6 (+), 140.8 (+), 131.1 (−), 127.8 (−), 123.5 (−), 113.0 (+), 73.4 (+), 58.7 (−); IR (CCl_4) 1538, 1358, 1121 cm^{-1}. Anal. Calcd for $C_8H_8BrNO_3$: C, 39.05; H, 3.28. Found: C, 39.08; H, 3.29.

3-Methyl-2-(1-propen-1-yl)-1-nitrobenzene (6). Bis(dibenzylideneacetone)palladium(0) (115 mg, 0.20 mmol) and triphenylphosphine (210 mg, 0.80 mmol) were added, under a positive flow of argon, to solution of 2-bromo-3-methyl-1-nitrobenzene (**5**)[6] (0.86 g, 3.98 mmol) and (tri-*n*-butyl-1-propen-1-yl)stannane[13] (1.50 g, 4.53 mmol) in toluene (25 mL). The solution was heated at reflux (45 h) whereupon a red solution containing a black precipitate was formed. The reaction mixture was cooled to ambient temperature, and the solvent was removed to give a black oil. The oil was dissolved in dichloromethane (50 mL), washed with NH_4OH (10%, aq) and water, and dried ($MgSO_4$). Filtration and removal of solvent gave a black viscous oil that was purified by chromatography (hexanes−EtOAc, 9:1) affording **6** (585 mg, 3.30 mmol, 83%) as a faint orange oil. Spectral data from a 3:1 *cis:trans* mixture.[14] IR (neat) 1529, 1354 cm^{-1}; *cis* isomer: ^1H NMR δ 7.61 (d, J = 7.9 Hz, 1H), 7.40 (d, J = 7.4 Hz, 1H), 7.25 (t, J = 7.9 Hz, 1H), 6.42 (d, J = 11.6 Hz, 1H), 5.85 (qd, J = 11.4 and 6.9 Hz, 1H), 2.26 (s, 3H), 1.38 (dd, J = 6.9 and 1.7 Hz, 3H); ^{13}C NMR δ 150.1 (+), 139.1 (+), 133.7 (−), 131.2 (+), 129.1 (−), 127.2 (−), 124.2 (−), 121.1 (−), 20.0 (−), 14.1 (−); *trans* isomer: ^1H NMR δ 7.47 (d, J = 8.2 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), ca. 6.4 overlapped by major isomer (1H), 5.67 (qd, J = 16.0 and 6.7 Hz, 1H), 2.31 (s, 3H), 1.83 (dd, J = 6.7 and 1.7 Hz, 3H); ^{13}C NMR δ 154.3 (+), 138.7 (+), 138.7 (−), 132.0 (−), 131.9 (+), 126.7 (−), 124.2 (−), 120.9 (−), 20.5 (−), 18.7 (−). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26. Found: C, 67.60; H, 6.18.

3-(Hydroxymethyl)-2-(1-propen-1-yl)-1-nitrobenzene (13). Reaction of **12** (696 mg, 3.00 mmol) with (tri-*n*-butyl-1-propen-1-yl)stannane (1.043 g, 3.30 mmol) in toluene (20 mL) in the presence of bis(dibenzylideneacetone)palladium(0) (86 mg, 0.15 mmol) and PPh_3 (157 mg, 0.60 mmol), as described above (84 h), gave, after extraction and chromatography (hexanes−EtOAc, 19:1), **13** (128 mg, 0.66 mmol, 22%) as pale yellow crystals. Spectral data from a 3:1 *cis*/*trans* mixture[14] mp 74−76.5 °C; IR (neat) 3218, 1525, 1360 cm^{-1}; *cis* isomer: ^1H NMR δ 7.76 (d, J = 7.9 Hz, 2H), 7.44 (t, J = 7.9 Hz, 1H), 6.48 (d, J = 11.1 Hz, 1H), 5.93 (qd, J = 11.3 and 6.9 Hz, 1H), 4.66 (s, 2H), 2.24 (br s, 1H), 1.42 (dd, J = 6.9 and 1.6 Hz, 3H); ^{13}C NMR δ 149.8 (+), 141.6 (+), 130.8 (−), 130.1 (−), 129.8 (+), 127.8 (−), 122.8 (−), 122.6 (−), 62.3 (+), 14.2 (−); *trans* isomer: ^1H NMR δ 7.71 (d, J = 7.9 Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.36 (t, J = 7.9 Hz, 1H), ca. 6.5 overlapped by major isomer (1H), 5.74 (qd, J = 16.0 and 6.5 Hz, 1H), 4.72 (s, 2H), 2.24 (br s, 1H), 1.88 (dd, J = 6.5 and 1.8 Hz, 3H); ^{13}C NMR δ 141.2 (+), 133.0 (−), 131.4 (+), 131.1 (−), 127.3 (−), 123.0 (−), 122.5 (−), 62.5 (+), 18.8 (−). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74. Found: C, 62.27; H, 5.81.

DIBAL-H (2.81 mL, 2.81 mmol, 1.0 M in hexanes) was added to a −78 °C cold solution of **9** (245 mg, 1.29 mmol) in Et_2O (10 mL) under an argon atmosphere. The pale yellow solution was stirred at −78 °C for 1.75 h, H_2O (ca. 5 mL) was added, and the reaction vessel was removed from the cold bath. The solution was allowed to reach ambient temperature (overnight) followed by addition of brine (10 mL). The phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine and dried ($MgSO_4$), and the solvent was removed at reduced pressure. The crude product was purified by chromatography (hexanes−EtOAc, 4:1) to give **13** (99 mg, 0.51 mmol, 91%).

3-(Methoxymethyl)-2-(1-propen-1-yl)-1-nitrobenzene (15). Reaction of **14** (492 mg, 2.00 mmol) with (tri-*n*-butyl-1-propen-1-yl)stannane (750 mg, 2.20 mmol) in toluene (20 mL) in the presence of bis(dibenzylideneacetone)palladium(0) (105 mg, 0.10 mmol) and triphenylphosphine (58 mg, 0.40 mmol) as described above (46 h), gave, after extraction and chromatography (hexanes−EtAOc, 9:1), **15** (378 mg, 1.82 mmol, 91%) as a pale yellow oil. Spectral data from a 1:3.5 *trans:cis* mixture.[14] IR (neat) 1530, 1356, 1115, 803, 745 cm^{-1}; *cis* isomer: ^1H NMR δ 7.8−7.3 (m,

(11) Plummer, E. L. U.S. Patent. US 4,329,518, 1982; *Chem. Abstr.* **1982**, *97*, 91961f.

(12) Faster moving fractions contain an inseparable mixture of starting material and 3-(dibromomethyl)-2-bromo-1-nitrobenzene (tentatively assigned). ^1H NMR δ 8.27 (dd, J = 7.9 and 1.6 Hz, 1H), 7.68 (dd, J = 7.9 and 1.6 Hz, 1H), 7.58 (t, J = 7 9 Hz, 1H), 7.15 (s, 1H).

(13) Seyferth, D.; Vaugan, L. G. *J. Organomet. Chem.* **1963**, *1*, 138.

(14) The assignments of *cis* or *trans* for ^{13}C NMR resonances are based on the intensity of the resonances and are tentative.

3H), 6.45 (d, J = 11.1 Hz, 1H), 5.91 (qd, J = 11.4 and 6.9 Hz, 1H), 4.43 (s, 2H), 3.39 (s, 3H), 1.41 (dd, J = 6.7 and 1.5 Hz, 3H); ^{13}C NMR δ 149.9 (+), 139.3 (+), 131.3 (−), 130.8 (+), 129.8 (−), 127.6 (−), 122.9 (−), 122.6 (−), 71.5 (+), 58.6 (−), 14.2 (−); *trans* isomer: ^{1}H NMR δ 7.8−7.3 (m, 3H), ca.. 6.5 (1H) overlapped by the major isomer, 5.73 (qd, J = 16.1 and 6.7 Hz, 1H), 4.43 (s, 2H), 3.39 (s, 3H), 1.88 (dd, J = 6.7 and 1.7 Hz, 3H); ^{13}C NMR δ 155.4 (+), 138.8 (+), 132.9 (−), 131.9, 131.8 (−), 127.1 (−), 123.1 (−), 71.9 (+), 58.4 (−), 18.8 (−). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32. Found: C, 63.71; H, 6.28.

Iodomethane (80 μL, 1.29 mmol) was added to a red-brown solution of **13** (125 mg, 0.65 mmol) and KOH (50 mg, 85%, 0.71 mmol) in DMSO (5 mL). The reaction mixture was stirred at ambient temperature for 69 h. A second portion of iodomethane (80 μL, 1.29 mmol) was added. After additional 51 h of stirring, water (10 mL) and diethyl ether (10 mL) were added. The phases were separated, and the aqueous phase was extracted with diethyl ether. The combined organic phases were dried ($MgSO_4$), and the solvents were removed. The resulting crude product was purified by chromatography (hexanes−EtOAc, 3:7) to give **15** (86 mg, 0.42 mmol, 65%) as a pale yellow oil followed by **13** (45 mg, 0.23 mmol).

Methyl 3-Nitro-2-(diethylphosphonomethyl)benzoate (17). A solution of methyl 2-methyl-3-nitrobenzoate (**16**) (8.75 g, 44.63 mmol) and benzoyl peroxide (540 mg, 2.23 mmol) in CCl_4 (80 mL) was heated at reflux. Bromine (2.75 mL, 53.6 mmol) dissolved in CCl_4 (20 mL) was added dropwise via an addition funnel. The reaction mixture was irradiated (150 W, sun-lamp) and heated at reflux (46 h). The reaction mixture was cooled to ambient temperature, and the solvent was removed to afford a brown solid. The residue was used as such without further purification. To the crude product was added triethyl phosphite (16.8 mL, 98.19 mmol), and the reaction mixture was heated at 160 °C (90 min). After being cooled the reaction mixture to ca. 80 °C, the excess triethyl phosphite was removed by vacuum distillation, leaving a red oil. The oil was purified by chromatography using EtOAc−MeOH (19:1) as eluent to give **17** (14.21 g, 42.89 mmol, 96%) as a pale yellow solid. Spectral data from a 2:1 ratio of rotamers: mp 30−33.5 °C; ^{1}H NMR δ 8.07 (d, J = 7.9 Hz, 1H), 7.94 (d, J = 7.9 Hz, 1H), 7.46 (dt, J = 8.1 and 2.4 Hz, 1H), 4.33 (d, J_{PH} = 23.5 Hz, 2H), 4.11 (minor, pent, J = 7.2 H, 2H), 4.00 (major, pent, J = 7.2 Hz, 2H), 3.96 (s, 3H), 1.34 (minor, t, J = 7.2 Hz, 3H), 1.22 (major, t, J = 6.9 Hz, 3H); ^{13}C NMR δ 166.8 (+), 151.5, 134.3 (d, J_{PC} = 3.1 Hz, −), 133.4 (d, J_{PC} = 5.7 Hz, +), 127.8 (d, J_{PC} = 3.1 Hz, −), 127.7, 127.3 (d, J_{PC} = 3.6 Hz, −), 63.6 (d, J_{PC} = 6.2 Hz, +), 62.2 (d, J_{PC} = 6.7 Hz, +), 52.8 (−), 24.8 (d, J_{PC} = 134.3 Hz, +), 16.1 (d, J_{PC} = 6.2 Hz, −); IR (neat) 2989, 1726, 1534, 1357, 1270, 1050, 1025 cm^{-1}. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 47.14; H, 5.48. Found: C, 47.34; H, 5.59.

Methyl 2-(1-Propen-1-yl)-3-nitrobenzoate (9). Lithium hexamethyldisilazide (338 μL, 0.338 mmol, 1.0 M in hexanes) was added, under an argon atmosphere, to a 0 °C cold solution (ice-bath) of **16** (102 mg, 0.307 mmol) in THF (10 mL). The color immediately changed to dark purple. Ethanal (172 μL, 3.07 mmol) was added via syringe, whereupon the color changed to brown. The reaction mixture was stirred at 0 °C for 10 min and at ambient temperature (overnight). Removal of the solvent at reduced pressure and purification of the crude product by chromatography (hexanes−EtOAc, 7:3) gave **9** (15 mg, 0.067 mmol, 22%).

Ethanal (large excess) was distilled into a flask containing a purple solution of the ylide formed from Wittig salt **17**[3b] (2.87 mg, 5.00 mmol) and triethylamine (2.56 mL, 20.00 mmol) in dichloromethane (100 mL) at ambient temperature. Upon addition of ethanal, the purple color of the ylide slowly changed to a pale brown-gray, which indicated the end point of the reaction. Removal of solvent at reduced pressure followed by chromatography using hexanes−EtOAc (9:1) gave a mixture of **9** and **16** (749 mg, ca. 3.4 mmol, ≤68%). The major product, **9**, was obtained as a 4.8:1 *trans-cis* mixture (^{1}H NMR).[14] Spectral data from a 4.8:1 *trans:cis* mixture. *Cis*-isomer: ^{1}H NMR δ 8.02 (dd, J = 7.7 and 1.2 Hz, 1H), 7.93 (dd, J = 7.9 and 1.2 Hz, 1H), 7.50 (t, J = 7.9 Hz, 1H), 6.71 (dd, J = 11.6 and 1.5 Hz, 1H), 5.85 (dq, J = 11.4 and 6.9 Hz, 1H), 3.94 (s, 3H), 1.41 (dd, J = 7.2 and 2.0 Hz, 3H); *trans*-isomer: ^{1}H NMR δ 7.92 (dd, J = 7.9 and 1.5 Hz, 1H), 7.82 (dd, J = 7.9 and 1.2 Hz, 1H), 7.42 (t, J = 7.9 Hz, 1H), 6.81 (qd, J = 15.8 and 1.7 Hz, 1H), 5.69 (qd, J = 16.1 and 6.4 Hz, 1H), 3.89 (s, 3H), 1.85 (dd, J = 6.7 and 1.7 Hz, 3H); IR (neat) 1734 cm^{-1}; ^{13}C NMR δ 166.6 (+), 166.2 (+), 150.6 (+), 150.1 (+), 133.4 (+), 133.0, 132.8 (−), 132.7, 132.5 (−), 131.8 (+), 131.5 (−), 128.4 (−), 127.5 (−), 127.0 (−), 126.0 (−), 125.8 (−), 124.3 (−), 123.8 (−), 52.2 (−), 18.4 (−), 13.7 (−). Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01. Found: C, 59.84; H, 4.99.

Reaction of methyl 2-bromo-3-nitrobenzoate **8**[15] (1.04 g, 4.00 mmol) with (tri-*n*-butyl-1-propen-1-yl)stannane (1.46 g, 4.40 mmol) in toluene (15 mL) in the presence of bis(dibenzylideneacetone)palladium (115 mg, 0.20 mmol) and PPh_3 (210 mg, 0.80 mmol), as described above (27 h), gave, after extraction and chromatography (hexanes−EtOAc, 19:1), **9** (732 mg, 3.31 mmol, 83%) as a pale yellow solid. A 2.1:1 *cis*−*trans* mixture was obtained.

2,4-Dimethylindole (1).[4,8] To an oven-dried, threaded ACE glass pressure tube were added **6** (177 mg, 1.00 mmol), palladium diacetate (14 mg, 0.06 mmol), triphenylphosphine (63 mg, 0.24 mmol), and MeCN (4.5 mL). The tube was fitted with a pressure head, and the solution was saturated with CO (four cycles to 60 psi of CO). The reaction mixture was heated to 70 °C (oil bath temperature) under CO (60 psi) until all starting material was consumed (17 h), as judged by TLC. The reaction mixture was diluted with HCl (aq, 10%, 10 mL) and extracted with Et_2O. The combined organic phases were washed with HCl (aq, 10%) and dried ($MgSO_4$), and the solvent was removed to give the crude product. The crude product was purified by chromatography using hexanes−EtOAc (8:2) as eluent to give **1** (95 mg, 0.66 mmol, 66%) as a pale yellow oil.

4-(Methoxymethyl)-2-methylindole (3).[4] A solution of **15** (85.9 mg, 0.415 mmol), palladium diacetate (6.0 mg, 0.025 mmol), and triphenylphosphine (26 mg, 0.099 mmol) in MeCN (2 mL) was reacted as described above (60 psi CO, 70 °C, 46 h. Extraction and purification by chromatography (hexanes−EtOAc, 9:1) gave **3** (55.1 mg, 0.314 mmol, 76%) as a pale yellow oil.

Methyl 2-Methylindole-4-carboxylate (10).[16] A solution of **9** (223 mg, 1.01 mmol), palladium diacetate (13 mg, 0.06 mmol), and triphenylphosphine (63 mg, 0.24 mmol) in MeCN (4 mL) was reacted as described above (60 psi CO, 70 °C, 24 h). Extraction and purification by chromatography (hexanes−EtOAc, 8:2) gave **10** (171 mg, 0.90 mmol, 90%) as faint yellow crystals.

4-(Hydroxymethyl)-2-methylindole (2).[4] DIBAL-H (3.50 mL, 3.50 mmol, 1.0 M in hexanes) was added, under an argon atmosphere, to a −78 °C cold solution of **10** (245 mg, 1.29 mmol) in Et_2O (30 mL). The pale yellow solution was stirred at −78 °C for 4 h; H_2O (ca.5 mL) was added, and the reaction vessel was removed from the cold bath. The solution was allowed to reach ambient temperature (over 3.5 h) followed by addition of brine (20 mL). The phases were separated, and the aqueous phases were extracted with EtOAc. The combined organic phases were washed with brine and dried ($MgSO_4$), and the solvents were removed at reduced pressure. The crude product was purified by chromatography (hexanes−EtOAc, 3:1) to give **2** (177 mg, 1.10 mmol, 85%) as pale yellow crystals. Spectral data are in all respects identical with published data. However, **2** isolated from *tricholoma* species was reported as an oil; our sample was a solid with mp 80−81 °C.

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(15) Prepared from 2-bromo-3-nitrobenzoic acid (*Organic Syntheses*; Wiley: New York, 1941; Coll. Vol. 1, p 125) according to ref 6.

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