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Palladium-catalyzed syntheses of tetrahydrocarbazolones as advanced intermediates to carbazole alkaloids

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Abstract—Two sequential palladium-catalyzed reactions, an intermolecular Stille cross-coupling followed by a recently developed palladium-catalyzed reductive N-heteroannulation, have been employed as the key synthetic steps toward six tetrahydrocarbazolones. The products are advanced intermediates toward a number of naturally occurring carbazole alkaloids.

1. Introduction

Carbazole alkaloids are of significant synthetic interest due to their range of biological activities. For example, these natural products show antitumor, antibiotic, antimalarial, and antifungal properties.[1] Several carbazole alkaloids have been isolated from plants belonging to the Rutaceae family.[2] Many of these compounds have a one-carbon substituent in the 3-position and an oxygenated functionality in the 1- or 2-position. Dimeric- and quinoid-structures are also known in this group.[2] We have been interested in a number of these natural products, many of which are from plants of the genus *Murraya*. These plants consist of small trees and shrubs endemic to Southern Asia that have been used for years in folk medicine for analgesics and treatment of ailments such as eczema and rheumatism.[3]

Tetrahydrocarbazolones have been used extensively as advanced intermediates in synthetic efforts toward a number of naturally occurring carbazole alkaloids including, murrayaquinone A,[4–6] murrayanine,[7] koenigine-quinones A and B,[8] clausenalene,[9] glycoborine,[10] (+)-aspidospermidine,[11] clausenamine,[12] clausenol and clausenine,[13] clausenal,[14] dimeric murrayafoline A,[15] pyrrayaquinones A and B,[6] murrayafoline B and murrayaquinone B,[16] hepazolidine,[17] glycozolinol,[18] (−)-gilbertine,[19] and glycozoline.[20] The tetrahydrocarbazolones are usually prepared by a Japp–Klingemann condensation of diazonium salts with 2-(hydroxymethylene)-1-cyclohexanones followed by a Fischer indole synthesis of the formed hydrazones. The Fischer indole synthesis works reasonably well for 2- and 4-substituted arylhydrazones. However, the reaction usually affords regioisomeric cyclization products from the 3-substituted analogs,[21,22] and the reaction fails completely in some more substituted cases.[12] Herein is reported a new synthesis of tetrahydrocarbazolone compounds used as advanced intermediates in the synthesis of a significant number of functionalized oxygenated carbazoles.

2. Result and discussion

We have recently described a novel route to tetrahydrocarbazolones using two consecutive palladium-catalyzed reactions, a Stille-type cross-coupling and a reductive N-heteroannulation.[23] This sequence was used in a formal synthesis of murrayaquinone A as outlined in Scheme 1.

While working on the synthesis of murrayaquinone A, we initialized an alternative route to this compound via carbazolone **4** (Scheme 2). The conditions developed by Piers and Nagakura[24] to prepare 3-iodo-α,β-unsaturated ketones were used to synthesize 3-iodo-5-methyl-2-cyclohexen-1-one (**1**) from 5-methyl-1,3-cyclohexanedione. Stille-type cross-coupling of 3-iodocyclohexenone **1** and 2-nitrophenyl tributylstannane (**2**) using bis(benzonitrile)palladium dichloride, triphenylarsine, and copper iodide in *N*-methylpyrrolidinone, produced the expected product **3** in excellent yield. Palladium-catalyzed reductive N-heteroannulation of **3** gave uneventfully the expected carbazolone **4**. Carbazolone **4** is an advanced intermediate in reported syntheses of four different carbazole alkaloids, murrayaquinone A,[6] murrayafoline A,[6,7] murrayanine,[7,25] and dimeric *O*-demethylmurrayafoline A.[26]

Keywords: Carbazoles; Palladium-catalyzed; Alkaloids.
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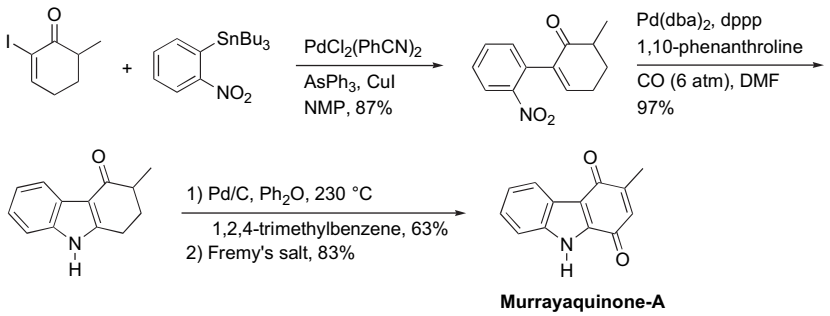
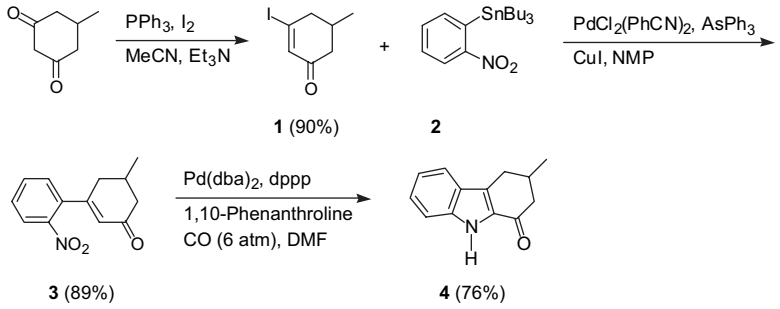


Scheme 1.

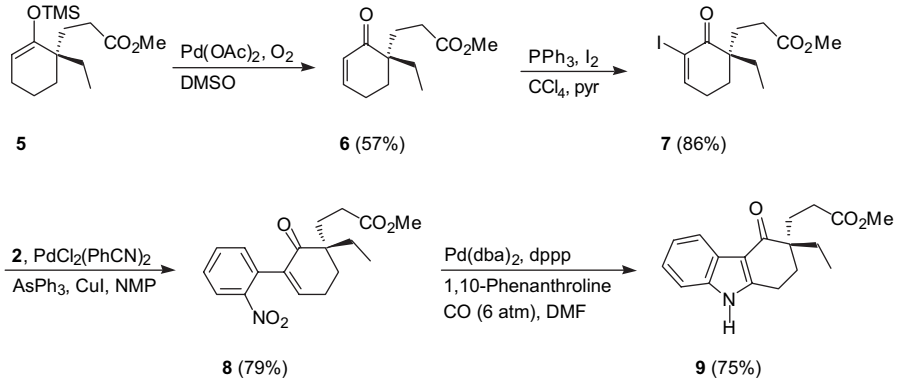


Scheme 2.

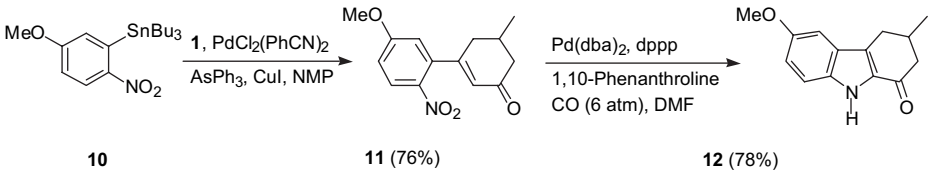
Carbazolone **9** is a key intermediate in Desmaele and d'Angelo's synthesis of (+)-aspidospermidine (Scheme 3).[11] The synthesis of this intermediate was realized in 35% overall yield starting from cyclohexenone **6**. It was anticipated that we could improve upon the synthesis of carbazolone **9** using our methodology. Cyclohexenone **6** was prepared by Desmaele and d'Angelo by a DDQ oxidation of the trimethylsilylenol ether **5**. In our hands, despite several attempts, the procedure reported in the literature completely failed to produce **6**. However, a palladium-catalyzed Saegusa oxidation[27] of **5** furnished **6** in 57% yield. Iodide **7**, prepared by treatment of **6** with iodine and pyridine in tetrachloromethane,[28] was coupled with **2** to afford **8** in good yield. The palladium-catalyzed N-heteroannulation of **8** proceeded smoothly to give carbazolone **9** in 75% yield. In comparison with the previous route to this intermediate, carbazolone **9** was obtained in a 52% overall yield starting from **6**.

The third example, 6-methoxy-3-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**12**), has been used as an advanced intermediate toward the naturally occurring alkaloids clausenol and clausenine,[13] clausenamine A,[12] and glycozoline.[29] In the event, Stille-type cross-coupling of tributyl(5-methoxy-2-nitrophenyl)stannane **10** with vinyl iodide **1** gave the expected product **11** (Scheme 4). Palladium-catalyzed annulation of **11** furnished the expected carbazolone **12**.

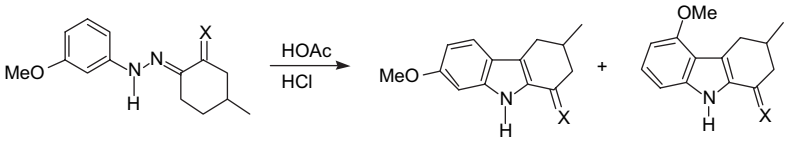
For the carbazolones **4** and **12** discussed above, the regioselectivity of the reported Fischer indole syntheses leading to the carbazolones does not pose a problem since only one isomer can be formed. In contrast, reactions of 3-substituted arylhydrazones frequently afford two regioisomeric products. For example, reaction of **13** has been described three times in the literature by the same authors. In each case, **13** was treated with a mixture of acetic and hydrochloric acid (at reflux) to afford **14** and **15** (Scheme 5). A detailed experimental procedure was not found in either of the papers. The yield of the isomers was not reported in the first paper,[30] and in the second paper the yield of **15** was reported to be 50%.[21] In the third paper, compound **14** was isolated in 65.5% yield



Scheme 3.



Scheme 4.



Scheme 5.

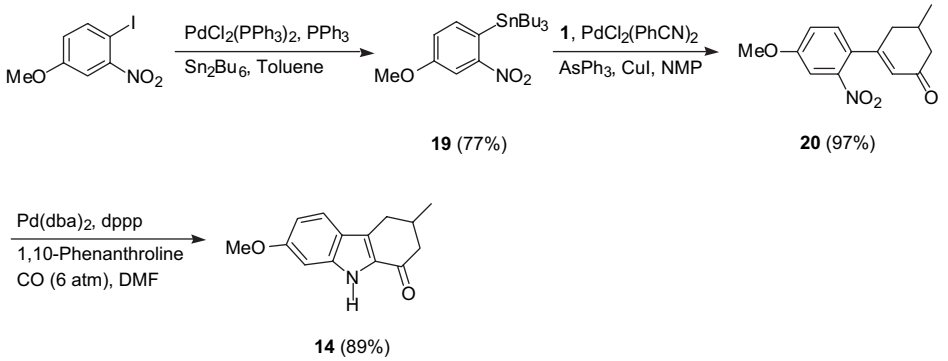
using identical reaction conditions and times with no mentioning of **15**.[8] We decided to repeat the reaction but were unable to obtain **15** as the major product using the reaction conditions described. In our hands an approximately 7:1 mixture of **14** and **15** was obtained in 57% yield. A similar result was reported by Chakravarty et al. from a Fischer indole synthesis of the corresponding 4-methylcyclohexane hydrazone derivative **16** in place of **13**.[10] In this case, a 9:1 mixture (60% yield) of the 3-methyl-7-methoxy- and 3-methyl-5-methoxy-tetrahydrocarbazoles **17** and **18** was obtained, respectively. Wolff–Kishner–Huang–Minlon reduction[21] of **14** gave the expected compound **17**, having identical ^{1}H NMR chemical shifts compared to reported data.[10]

In contrast to the Fischer indole synthesis, the palladium-catalyzed N-heteroannulation is inherently regiospecific and both **14** and **15** can be obtained in good overall yield. 7-Methoxy-3-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**14**), has been used as an advanced intermediate toward the naturally occurring alkaloids koenigenine-quinone A,[8] murrayafoline B and murrayaquinone B,[16] and pyrrayaquinones A and B.[6] The formal synthesis of these compounds using the palladium-catalyzed methodology was carried out in the same manner as described above for murrayaquinone A. Organostannane **19**[31] was first prepared starting from commercially available 1-iodo-4-methoxy-2-nitrobenzene and hexabutylditin using Kosugi's procedure (Scheme 6).[32]

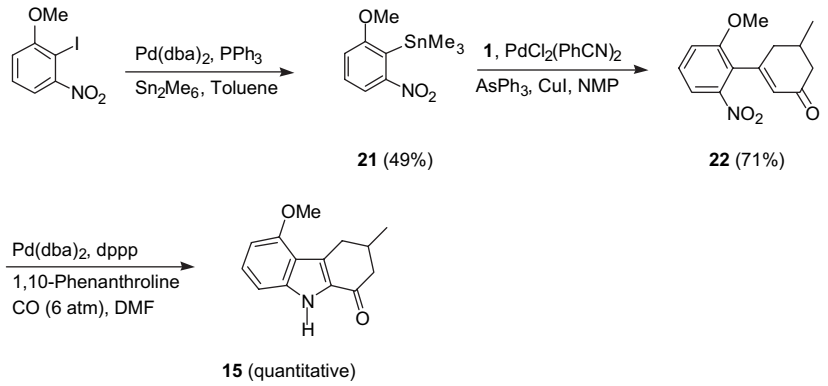
Stille-type cross-coupling of **19** with **1** under standard reaction conditions produced **20** in excellent yield. The reductive cyclization of **20** also proceeded smoothly affording the carbazolone **14**.

5-Methoxy-3-methyl-3,4-dihydrocarbazol-1(2*H*)-one (**15**) has previously been used as an intermediate in a synthesis of 5-methoxy-3-methylcarbazole; a structure initially named glycozolicine.[21] However, the structure of glycozolicine was later shown not to be 5-methoxy-3-methylcarbazole based on extensive NMR data and synthesis.[10] A second compound, glycoborine was identified as 5-methoxy-3-methylcarbazole. It should be noted that the true structure of the glycozolicine is still unknown.

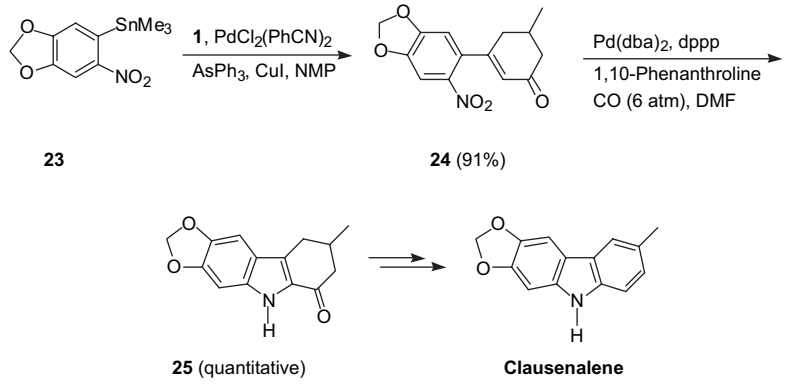
For the synthesis of **15**, a novel tin coupling partner was required. Initially, hexabutylditin was used to prepare 6-methoxy-2-nitrophenyl tributylstannane from 1-iodo-2-methoxy-6-nitrobenzene. However, the reaction was sluggish and a complex mixture of products was obtained. Turning to hexamethylditin solved this problem and **21** was obtained in 49% yield. The ensuing Stille coupling, affording **22**, and annulation proceeded uneventfully to give carbazolone **15**. The significant lower yield of products **21** and **22** compared to the previous examples is probably a reflection of the hindered nature of the substrates. The annulation, in contrast, gave a quantitative yield of product (Scheme 7).



Scheme 6.



Scheme 7.



Scheme 8.

As a final example, a synthesis of the antibacterial carbazole clausenalene, isolated from the stem bark of *Clausena heptaphylla* was pursued.[9] Clausenalene is the first reported methylenedioxy carbazole alkaloid isolated from a plant source. The known arylstannane **23** was coupled with **1** to give **24** (Scheme 8). Reductive N-heteroannulation of **24** gave tetrahydrocarbazolone **25**, which has been previously used to prepare clausenalene via a Wolff–Kishner reduction and aromatization.

3. Conclusion

In conclusion, we have successfully applied a sequential Stille-type cross-coupling reaction followed by a palladium-catalyzed reductive N-heteroannulation to the synthesis of six tetrahydrocarbazolones. The products are late intermediates in the synthesis of a number of naturally occurring carbazole alkaloids.

4. Experimental

4.1. General procedures

NMR spectra were determined in $CDCl_3$ at 270 MHz or 600 MHz (^{1}H NMR) and 67.5 MHz or 150 MHz (^{13}C NMR). The chemical shifts are expressed in δ values relative to Me_4Si (0.0 ppm, ^{1}H and ^{13}C) or $CDCl_3$ (77.0 ppm, ^{13}C) internal standards. ^{1}H–^{1}H 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.

Toluene, pyridine, hexanes, acetonitrile, and ethyl acetate were distilled from calcium hydride. Chemicals prepared according to literature procedures have been footnoted first time used; all other reagents were obtained from commercial sources and used as received. All reactions were performed under an argon or nitrogen atmosphere in oven-dried glassware unless otherwise stated. Solvents were removed from reaction mixtures and products on a rotary evaporator at water aspirator pressure or by bulb-to-bulb distillation under reduced pressure. Chromatography was performed on silica gel 60 (35–75 μm, VWR). Melting points were determined on a MelTemp and are uncorrected. High resolution mass spectra (HRMS) were performed at University of California, Riverside Mass Spectrometry Center. Elemental analyses were performed in the Department of Chemical Engineering, College of Engineering and Mineral Resources, West Virginia University.

4.1.1. 3-Iodo-5-methyl-2-cyclohexen-1-one (1). To a solution of triphenylphosphine (4.75 g, 18.1 mmol) in acetonitrile (80 mL) was added iodine (4.53 g, 17.8 mmol). The reaction mixture was stirred for 2 h. Triethylamine (2.60 mL,

18.5 mmol) was added slowly, followed by 5-methyl-1,3-cyclohexanedione (2.04 g, 16.2 mmol). The reaction mixture was stirred for 14 d at ambient temperature. The solvent was evaporated and the crude product was purified by chromatography (hexanes/EtOAc, 95:5) to give **1** (3.44 g, 14.6 mmol, 90%) as a faint yellow oil. IR (neat): 2956, 1676, 1592 cm^{-1}; ^1H NMR (270 MHz): δ 1.07 (dd, J=6.5, 1.8 Hz, 3H), 2.10 (ddd, J=12.1, 11.7, 3.6 Hz, 1H), 2.24–2.40 (m, 1H), 2.46–2.65 (m, 2H), 2.95–3.06 (m, 1H), 6.77–6.82 (m, 1H); ^{13}C NMR (67.5 MHz): δ 19.9 (−), 30.9 (+), 44.0 (−), 47.6 (−), 125.7 (+), 139.4 (−), 194.3 (+); HRMS (EI) calcd for C_7H_9IO (M^+): 235.9698, found: 235.9696; Anal. Calcd for C_7H_9IO: C, 35.62; H, 3.84. Found: C, 35.65; H, 4.01.

4.1.2. 3-(2-Nitrophenyl)-5-methyl-2-cyclohexen-1-one (3). A solution of **1** (1.00 g, 4.24 mmol), tributyl(2-nitrophenyl)stannane (**2**)[32] (2.10 g, 5.10 mmol), $PdCl_2(PhCN)_2$ (81 mg, 0.21 mmol), $AsPh_3$ (130 mg, 0.42 mmol), and CuI (81 mg, 0.42 mmol) in *N*-methylpyrrolidinone (NMP) (8.4 mL) was heated at 80 °C for 48 h. The reaction was diluted with benzene (100 mL) and washed with NH_4OH (10%, aq, 3×30 mL) and H_2O (2×30 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvents were removed by bulb-to-bulb distillation under reduced pressure. The crude product was purified by chromatography (hexanes) to give **3** (873 mg, 3.78 mmol, 89%) as a pale yellow solid. Mp 62–64.5 °C; IR (neat): 2956, 1669, 1525, 1346 cm^{-1}; ^1H NMR (600 MHz): δ 1.13 (d, J=6.6 Hz, 3H), 2.20 (dd, J=16.2, 12.6 Hz, 1H), 2.34 (ddd, J=18.6, 11.4, 2.4 Hz, 1H), 2.44–2.54 (overlapping s and m, 2H), 2.59 (dd, J=16.8, 4.2 Hz, 1H), 5.98 (d, J=2.4 Hz, 1H), 7.30 (dd, J=7.8, 1.2 Hz, 1H), 7.55 (dt, J=8.4, 1.8 Hz, 1H), 7.67 (dt, J=7.2, 1.2 Hz, 1H), 8.10 (dd, J=8.1, 1.2 Hz, 1H); ^{13}C NMR (150 MHz): δ 21.0 (+), 30.8 (+), 38.8 (−), 45.5 (−), 124.9 (+), 127.2 (+), 129.5 (+), 129.7 (+), 133.8 (+), 136.5 (−), 146.6 (-), 159.8 (−), 199.1 (−); HRMS (DEI) calcd for $C_{13}H_{13}NO_3$ (MH^+): 232.0974, found: 232.0974; Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 68.13; H, 6.01; N, 5.79.

4.1.3. 2,3,4,9-Tetrahydro-3-methyl-1*H*-carbazol-1-one (4).[15] 5-Methyl-3-(2-nitrophenyl)-2-cyclohexenone (**3**) (133 mg, 0.575 mmol), $Pd(dba)_2$ (19.9 mg, 0.0346 mmol), dppp (14.3 mg, 0.0347 mmol), 1,10-phenanthroline monohydrate (13.7 mg, 0.0691 mmol), and DMF (6 mL) were placed into a pressure tube fitted with a pressure head. The tube was flushed three times with CO and the reaction was heated and stirred at 80 °C under CO (6 atm, 72 h). The reaction mixture was filtered through Celite and the solvent was removed by bulb-to-bulb distillation under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 7:3) to give **4** (88 mg, 0.44 mmol, 77%) as a white powder. Mp 193–195 °C (lit.[32] 197 °C).

4.1.4. Methyl (*S*)-1-ethyl-2-oxo-3-cyclohexene-1-propanoate (6).[11] To a solution of methyl (*S*)-1-ethyl-2-oxo-cyclohexane-1-propanoate (**5**) (3.25 g, 15.3 mmol) in DMF (23 mL) was added triethylamine (11.3 mL, 80.4 mmol). Chlorotrimethylsilane (5.93 mL, 46.4 mmol) was added dropwise and the reaction mixture was heated (100 °C, 3 d). The reaction was allowed to cool to ambient temperature, diluted with hexanes (50 mL), and poured into cold water (50 mL). The layers were separated and the aqueous portion was extracted with hexanes (3×50 mL). The organic phases were combined, dried ($MgSO_4$), filtered, and the solvents were removed by bulb-to-bulb distillation under reduced pressure. To a portion of the crude silylenol ether **5** (1.94 g, 6.82 mmol) in DMSO (50 mL) was added $Pd(OAc)_2$ (159 mg, 0.708 mmol). The flask containing the reaction mixture was flushed with oxygen and was kept under oxygen (1 atm, balloon) while being heated at 40 °C (72 h). Additional $Pd(OAc)_2$ (95.6 mg, 0.426 mmol) was added to the reaction mixture and the reaction was heated at 60 °C (24 h). The reaction mixture was cooled and diluted with ethyl acetate (200 mL). The mixture was washed with water (3×50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 7:3) to give **6** (820 mg, 3.90 mmol, 57%) as a colorless oil. Spectral data (^1H NMR) are in complete accordance with the literature values.[11]

4.1.5. Methyl (*S*)-1-ethyl-2-oxo-3-iodo-3-cyclohexenone-1-propanoate (7). To a solution of **6** (508 mg, 2.42 mmol) in 10 mL of 1:1 CCl_4/pyridine cooled to 0 °C was added drop wise a solution of iodine (1.26 g, 4.96 mmol) dissolved in 10 mL of 1:1 CCl_4/pyridine with stirring. The reaction mixture was allowed to warm to ambient temperature overnight. The reaction mixture was diluted with ether (100 mL) and washed successively with water (40 mL), HCl (5%, aq, 2×40 mL), water (40 mL), and $Na_2S_2O_3$ (20%, aq, 40 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 8:2) to give **7** (698 mg, 2.08 mmol, 86%) as a pale yellow oil. IR (neat): 3450, 2944, 1732, 1679 cm^{-1}; ^1H NMR (270 MHz): δ 0.83 (t, J=7.5 Hz, 3H), 1.49–1.71 (m, 2H), 1.80–2.01 (m, 4H), 2.11–2.36 (m, 2H), 2.43–2.50 (m, 2H), 7.64 (t, J=4.1 Hz, 1H); ^{13}C NMR (67.5 MHz): δ 7.9 (−), 26.8 (+), 28.5 (+), 28.5 (+), 30.0 (+), 47.7 (+), 51.4 (−), 103.4 (+), 157.3 (−), 173.5 (+), 195.3 (+); HRMS (DEI) calcd for $C_{12}H_{17}IO_3$ (MH^+): 336.0222, found: 336.0210; Anal. Calcd for $C_{13}H_{13}NO_3$: C, 42.87; H, 5.10. Found: C, 42.87; H, 5.38.

4.1.6. Methyl (*S*)-1-ethyl-2-oxo-3-(2-nitrophenyl)-3-cyclohexenone-1-propanoate (8). Reaction of **7** (250 mg, 0.744 mmol), tributyl(2-nitrophenyl)stannane (**2**) (369 mg, 0.895 mmol), $PdCl_2(PhCN)_2$ (14.9 mg, 0.0388 mmol), $AsPh_3$ (23.1 mg, 0.0754 mmol), CuI (14.5 mg, 0.0761 mmol), and NMP (1.4 mL), as described for **3** (80 °C, 40 h), gave after workup and chromatography (hexanes/EtOAc, in sequence 9:1 and 8:2) **8** (196 mg, 0.591 mmol, 79%) as a yellow oil. IR (neat): 3446, 2939, 1736, 1669, 1526, 1353 cm^{-1}; ^1H NMR (600 MHz): δ 0.87 (t, J=7.2 Hz, 3H), 1.54–1.66 (m, 1H), 1.68–1.80 (m, 1H), 1.86–2.08 (m, 4H), 2.29 (t, J=8.4 Hz, 2H), 2.59 (q, J=4.2 Hz, 2H), 3.64 (s, 3H), 6.93 (t, J=4.2 Hz, 1H), 7.23 (dd, J=7.8, 1.2 Hz, 1H), 7.46 (dt, J=7.8, 1.2 Hz, 1H), 7.58 (dt, J=7.2, 1.2 Hz, 1H), 7.98 (dd, J=7.8, 1.2 Hz, 1H); ^{13}C NMR (150 MHz): δ 7.9 (+), 22.8 (−), 26.3 (−), 28.5 (−), 28.6 (−), 30.2 (−), 46.9 (−), 51.5 (+), 123.9 (+), 128.6 (+), 131.9 (+), 132.3 (+), 133.0 (−), 138.2 (−), 145.3 (+), 148.8 (−), 174.2 (−), 199.5 (−); HRMS (DEI) calcd for $C_{18}H_{21}NO_5$ (MH^+): 332.1498, found: 332.1512; Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.32; H, 7.05; N, 3.86.

4.1.7. Methyl (*S*)-[3-ethyl-4-oxo-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl]propanoate (9).[11] Reaction of **8** (184 mg, 0.555 mmol), $Pd(dba)_2$ (19.5 mg, 0.0339 mmol), dppp (14.0 mg, 0.0339 mmol), and 1,10-phenanthroline monohydrate (13.5 mg, 0.0681 mmol) in DMF (5 mL), as described for **4** (80 °C, 6 atm CO, 20 h), gave after workup and chromatography (hexanes/EtOAc, in sequence 8:2 and 1:1) and recrystallization (hexanes/EtOAc, 2:1) **9** (126 mg, 0.421 mmol, 75%) as a white solid. Mp 126–126.5 °C (lit.[11] 125–126 °C).

4.1.8. 3-(5-Methoxy-2-nitrophenyl)-5-methyl-2-cyclohexen-1-one (11). Reaction of **1** (619 mg, 2.62 mmol), tributyl(5-methoxy-2-nitrophenyl)stannane (**10**)[33] (1.29 g, 2.92 mmol), $PdCl_2(PhCN)_2$ (50.2 mg, 0.131 mmol), $AsPh_3$ (80.2 mg, 0.262 mmol), and CuI (50.0 mg, 0.262 mmol) in NMP (2 mL), as described for **3** (80 °C, 6 atm CO, 20 h), gave after workup and chromatography (hexanes/EtOAc, 8:2) **11** (577 mg, 2.21 mmol, 76%) as a yellow solid. Mp 124–126 °C; IR (neat): 3462, 2959, 2252, 1663, 912 cm^{-1}; ^1H NMR (600 MHz): δ 1.13 (d, J=6.6 Hz, 3H), 2.20 (dd, J=16.2, 12.0 Hz, 1H), 2.31 (ddd, J=18.0, 10.8, 3.0 Hz, 1H), 2.44–2.55 (overlapping dd and m, 2H), 2.58 (ddd, J=16.2, 4.2, 1.8 Hz, 1H), 3.92 (s, 3H), 5.96 (d, J=2.4 Hz, 1H), 6.71 (d, J=2.4 Hz, 1H), 6.97 (dd, J=9.0, 3.0 Hz, 1H), 8.18 (dd, J=9.0, 1.2 Hz, 1H); ^{13}C NMR (150 MHz): δ 21.1 (+), 30.8 (+), 38.9 (−), 45.5 (−), 56.1 (+), 114.0 (+), 114.6 (+), 126.6 (+), 127.7 (+), 139.2 (+), 139.3 (+), 160.8 (−), 163.7 (−), 199.3 (−); Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79. Found: C, 64.56; H, 6.27.

4.1.9. 6-Methoxy-3-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (12).[12] Reaction of **11** (220 mg, 0.842 mmol), $Pd(dba)_2$ (29 mg, 0.055 mmol), dppp (21 mg, 0.051 mmol), and 1,10-phenanthroline monohydrate (18 mg, 0.091 mmol) in DMF (5 mL), as described for **4** (80–90 °C, 6 atm, 36 h), gave after workup and chromatography (hexanes/EtOAc, 8:2) **12** (151 mg, 0.659 mmol, 78%) as a faint yellow solid. Mp 206–209 °C (lit.[12] mp 200–203 °C).

4.1.10. Tributyl(4-methoxy-2-nitrophenyl)stannane (19). To a solution of 1-iodo-4-methoxy-2-nitrobenzene (923 mg, 3.31 mmol) in toluene (6 mL) were added hexabutylditin (2.50 mL, 4.95 mmol), $PdCl_2(PPh_3)_2$ (23.6 mg, 0.0336 mmol), and PPh_3 (17.6 mg, 0.0671 mmol). The reaction was heated at 80 °C for 4 d. The reaction was diluted with benzene (100 mL) and washed with NH_4OH (10%, aq, 3×30 mL) and H_2O (2×30 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (hexanes) to give **19** (1.13 g, 2.56 mmol, 77%) as a yellow oil. IR (neat): 2956, 1528, 1344 cm^{-1}; ^1H NMR (270 MHz): δ 0.87 (t, J=7.3 Hz, 3H), 1.10 (t, J=7.7 Hz, 2H), 1.30 (sextet, J=4.0 Hz, 2H), 1.42–1.54 (m, 2H), 3.89 (s, 3H), 7.19 (dd, J=8.1, 2.6 Hz, 1H), 7.54 (d, J=8.1 Hz, 1H), 7.85 (d, J=4.3 Hz, 1H); ^{13}C NMR (67.5 MHz): δ 10.8 (+), 13.6 (−), 27.3 (+), 29.0 (+), 55.5 (−), 108.8 (−), 120.6 (−), 130.0 (+), 138.0 (−), 154.5 (+), 160.5 (+); HRMS (FAB) calcd for $C_{19}H_{33}NO_3Sn$ (M^-): 443.1482, found: 443.1491; Anal. Calcd for $C_{19}H_{33}NO_3Sn$: C, 51.71; H, 7.52; N, 3.17. Found: C, 50.31; H, 7.67; N, 3.02.

4.1.11. 3-(4-Methoxy-2-nitrophenyl)-5-methyl-2-cyclohexen-1-one (20). Reaction of **1** (208 mg, 0.881 mmol), **19** (445 mg, 1.01 mmol), $PdCl_2(PhCN)_2$ (17.2 mg, 0.0448 mmol), $AsPh_3$ (27.1 mg, 0.0885 mmol), CuI (17.8 mg, 0.0935 mmol), and NMP (2 mL), as described for **3** (80 °C, 2 d), gave after workup and chromatography (hexanes/EtOAc, in sequence 9:1 and 8:2) **20** (222 mg, 0.850 mmol, 97%) as a yellow solid. Mp 45–47 °C; IR (neat): 2953, 1666, 1531, 1350 cm^{-1}; ^1H NMR (600 MHz): δ 1.12 (d, J=6.6 Hz, 3H), 2.18 (dd, J=16.2, 12.0 Hz, 1H), 2.30 (ddd, J=18.0, 10.8, 2.4 Hz, 1H), 2.38–2.50 (m, 2H), 2.56 (dd, J=17.4, 4.8 Hz, 1H), 3.91 (s, 3H), 5.95 (d, J=2.4 Hz, 1H), 7.19 (dd, J=8.4, 2.4 Hz, 1H), 7.22 (d, J=9.0 Hz, 1H), 7.58 (d, J=3.0 Hz, 1H); ^{13}C NMR (150 MHz): δ 20.9 (+), 30.6 (+), 38.8 (−), 45.4 (−), 55.9 (+), 109.7 (+), 119.8 (+), 127.2 (+), 128.5 (+), 130.6 (−), 147.3 (−), 159.8 (−), 160.0 (−), 199.2 (−); HRMS (DEI) calcd for $C_{14}H_{15}NO_4$ (MH^+): 262.1080, found: 262.1078; Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79. Found: C, 64.08; H, 6.04.

4.1.12. 2,3,4,9-Tetrahydro-7-methoxy-3-methyl-1*H*-carbazol-1-one (14).[8] Reaction of **20** (73.6 mg, 0.282 mmol), $Pd(dba)_2$ (9.7 mg, 0.017 mmol), dppp (6.9 mg, 0.017 mmol), 1,10-phenanthroline monohydrate (6.7 mg, 0.034 mmol), and DMF (5 mL), as described for **4** (80–90 °C, 6 atm CO, 3 d), gave after workup and chromatography (hexanes/EtOAc, 7:3) **14** (57.7 mg, 0.252 mmol, 89%) as a white solid. Mp 206–209 °C (lit.[12] 200–203 °C).

4.1.13. Trimethyl(2-methoxy-6-nitrophenyl)stannane (21). To a solution of 1-iodo-2-methoxy-6-nitrobenzene[34,35] (1.83 g, 6.56 mmol) in toluene (25 mL) was added hexamethylditin (2.36 g, 7.20 mmol), $PdCl_2(PPh_3)_2$ (25 mg, 0.036 mmol), and PPh_3 (34 mg, 0.13 mmol). The reaction was heated at 80 °C (2 d). The reaction mixture was diluted with EtOAc (100 mL) and washed with NH_4OH (10%, aq, 3×30 mL) and H_2O (2×30 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated at reduced pressure. The crude product was purified by chromatography (hexanes) to give **21** (1.02 g, 3.23 mmol, 49%) as a yellow solid. Mp 49–52 °C; IR (neat): 2956, 1528, 1344 cm^{-1}; ^1H NMR (270 MHz): δ 0.87 (t, J=7.3 Hz, 3H), 1.10 (t, J=7.7 Hz, 2H), 1.30 (sextet, J=4.0 Hz, 2H), 1.42–1.54 (m, 2H), 3.89 (s, 3H), 7.19 (dd, J=8.1, 2.6 Hz, 1H), 7.54 (d, J=8.1 Hz, 1H), 7.85 (d, J=4.3 Hz, 1H); ^{13}C NMR (67.5 MHz): δ −5.7 (+), −4.33 (d, $J_{C,Sn}$=189.4 Hz), 55.8 (+), 114.1 (+), 116.2 (+), 127.6 (−), 130.5 (+), 155.6 (−), 164.9 (−); Anal. Calcd for $C_{10}H_{15}NO_3Sn$: C, 38.02; H, 4.79. Found: C, 38.37; H, 5.14.

4.1.14. 3-(2-Methoxy-6-nitrophenyl)-5-methyl-2-cyclohexen-1-one (22). Reaction of **1** (557 mg, 2.36 mmol), **21** (820 mg, 2.60 mmol), $PdCl_2(PhCN)_2$ (45 mg, 0.12 mmol), $AsPh_3$ (72.3 mg, 0.236 mmol), and CuI (50 mg, 0.26 mmol) in NMP (2 mL), as described for **3** (80 °C, 48 h), gave after workup and chromatography (hexanes/EtOAc, 8:2) **22** (437 mg, 1.67 mmol, 71%) as a yellow oil. IR (neat): 3456, 2957, 2250, 1668, 911, 726 cm^{-1}; ^1H NMR (600 MHz): δ 1.15 (d, J=3.6 Hz, 3H), 2.15–2.30 (m, 1H), 2.40–2.65 (m, 4H), 3.89 (d, J=3.0 Hz, 3H), 5.78 (s, 1H), 7.55 (d, J=7.8 Hz, 1H), 7.21 (dd, J=8.4, 1.2 Hz, 1H), 7.46 (dt, J=8.4, 2.4 Hz, 1H); ^{13}C NMR (150 MHz): δ 20.8 (+), 30.1 (+), 37.9 (−), 45.4 (−), 56.3 (+), 115.3 (+), 124.7 (−), 127.2 (+), 129.4 (+), 147.9 (−), 156.4 (−), 156.8 (−),

198.9 (−); Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79. Found: C, 64.44; H, 5.27.

4.1.15. 5-Methoxy-3-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (15).[21] Reaction of **22** (57 mg, 0.22 mmol), $Pd(dba)_2$ (7.5 mg, 0.014 mmol), dppp (5.4 mg, 0.013 mmol), and 1,10-phenanthroline monohydrate (4.7 mg, 0.024 mmol) in DMF (4 mL), as described for **4** (80–90 °C, 6 atm CO, 2 d), gave after workup and chromatography (hexanes/EtOAc, 19:1), **15** (50 mg, 0.22 mmol, 100%) as a white solid. Mp 240–242 °C (lit.[21] mp 201 °C); IR (neat): 3460, 2253, 1646, 1471, 1381, 1264, 1108 cm^{-1}; ^1H NMR (270 MHz): δ 1.14 (d, J=6.2 Hz, 3H), 2.29 (ddd, J=15.3, 11.4, 0.98 Hz, 1H), 2.45 (m, 1H), 2.56 (ddd, J=15.6, 3.2, 1.2 Hz, 1H), 2.75 (dd, J=17.1, 10.9 Hz, 1H), 3.38 (dd, J=17.1, 3.8 Hz, 1H), 3.86 (s, 3H), 6.38 (d, J=7.7 Hz, 1H), 6.91 (d, J=8.2 Hz, 1H), 7.17 (t, J=8.2 Hz, 1H), 8.98 (br s, 1H); ^{13}C NMR (67.5 MHz): δ 21.4 (−), 31.7 (+), 33.1 (−), 46.1 (+), 55.2 (−), 99.5 (−), 105.2 (−), 116.8 (+), 128.0 (−), 129.6 (+), 130.0 (+), 139.4 (+), 156.5 (+), 190.7 (+).

4.1.16. 5-Methyl-3-(6-nitro-1,3-benzodioxol-5-yl)-2-cyclohexen-1-one (24). Reaction of **1** (104 mg, 0.441 mmol), trimethyl(6-nitro-1,3-benzodioxol-5-yl)stannane (**23**)[31] (160 mg, 0.485 mmol), $PdCl_2(PhCN)_2$ (8.5 mg, 0.022 mmol), $AsPh_3$ (13.5 mg, 0.0441 mmol), and CuI (8.4 mg, 0.044 mmol) in NMP (2 mL), as described for **3** (80 °C, 48 h), gave after workup and chromatography (hexanes then hexanes/EtOAc, in sequence 19:1, 9:1, and 8:2), **24** (110 mg, 0.400 mmol, 91%) as a yellow solid. Mp 124–126 °C; IR (neat): 3619, 2254, 1711, 911, 735 cm^{-1}; ^1H NMR (600 MHz): δ 1.12 (d, J=6.0 Hz, 3H), 2.18 (dd, J=16.8, 12.6 Hz, 1H), 2.28 (ddd, J=17.4, 9.6, 2.4 Hz, 1H), 2.40–2.54 (overlapping dd and m, 2H), 2.57 (dd, J=16.2, 3.0 Hz, 1H), 5.92 (d, J=1.8 Hz, 1H), 6.17 (s, 2H), 6.65 (s, 1H), 7.61 (s 1H); ^{13}C NMR (150 MHz): δ 21.0 (+), 30.8 (+), 39.0 (−), 45.5 (−), 103.4 (−), 105.7 (+), 108.6 (+), 126.9 (+), 133.4 (−), 140.5 (−), 148.1 (−), 152.2 (−), 160.6 (−), 199.2 (−). For unknown reasons, the compound did not give satisfactory combustion analysis even after extensive purification.

4.1.17. 8-Methyl-5,7,8,9-tetrahydro-6*H*-1,3-dioxolo[4,5-*b*]carbazol-6-one (25).[9] Reaction of **24** (50 mg, 0.18 mmol), $Pd(dba)_2$ (6.5 mg, 0.012 mmol), dppp (3.9 mg, 0.095 mmol), and 1,10-phenanthroline monohydrate (4.5 mg, 0.011 mmol) in DMF (2 mL), as described for **4** (80–90 °C, 6 atm CO, 24 h), gave after workup and chromatography (hexanes then hexanes/EtOAc, in sequence 9:1 and 8:2) **25** (44 mg, 0.18 mmol, 100%) as a white solid. Mp 271–273 °C (lit.[9] mp 270 °C (dec)).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.100.

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