Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 60 (2004) 1513–1516

Synthesis of carbazomycin B by radical arylation of benzene

David Crich* and Sochanchingwung Rumthao

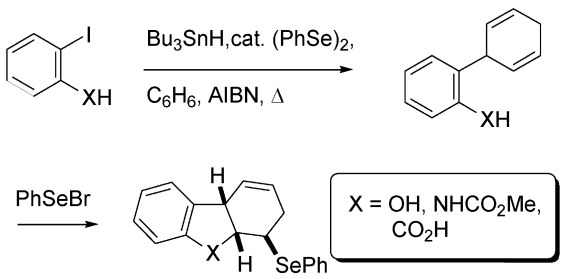
Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, IL 60607-7061, USA

Received 12 November 2003; revised 5 December 2003; accepted 5 December 2003

Abstract—Iodination of 2-methoxy-3,4-dimethyl-5-nitrophenol followed by acetylation yields (6-iodo-2-methoxy-3,4-dimethyl-5-nitrophenyl) acetate. Reduction with iron and acetic acid followed by reaction with methyl chloroformate then provides *N*-methoxycarbonyl-3-acetoxy-2-iodo-4-methoxy-5,6-dimethylaniline. Treatment of this substance in benzene at reflux with tributyltin hydride and a catalytic quantity of diphenyl diselenide leads to the formation of *N*-methoxycarbonyl-3-acetoxy-2-(2,5-cyclohexadienyl)-4-methoxy-5,6-dimethylaniline which on exposure to phenylselenenyl bromide affords a phenylselenenyl tetrahydrocarbazole. Oxidation deselenation and rearomatization are achieved by heating with *tert*-butylhydroperoxide finally affording carbazomycin B after saponification.

1. Introduction

Benzeneselenol catalyzes the stannane-mediated addition of aryl radicals to benzene with the predominant formation of 3-aryl-1,4-cyclohexadienes.[1] When the aryl radical is functionalized in the *ortho*-position, subsequent cyclization reactions lead to tetrahydrocarbazoles and/or tetrahydrodibenzofurans depending on the nature of the functionality employed (Scheme 1).[2]



Scheme 1. Formation of tetrahydrocarbazoles and dibenzofurans from benzene.

We considered that, when coupled to a suitable rearomatization step, this sequence would provide a ready and direct entry into a number of carbazole alkaloids,[3] especially those heavily functionalized in one benzenoid ring yet devoid of substitution in the other. An extreme example of the kind is carbazomycin B (**1**), an inhibitor of 5-lipoxygenase[4] and of the growth of some phytopathogenic fungi,[5] with weak antibacterial activity.[5] Accordingly, we selected this target as a test bed for the intended chemistry. Previous syntheses of carbazomycin B have involved (i) the formation of a simpler carbazole skeleton followed by introduction of the remaining functionality; (ii) Friedel–Crafts alkylation of a functionalized aniline with the η^5-cyclohexadienylirontricarbonyl cation, followed by an aromatizing cyclization with 'highly active' manganese dioxide,[6] and (iii) a radical cyclization approach employing an *N*-cyclohexadien-3-yl-*o*-bromoaniline.[7] The synthesis that we describe here differs significantly from the precedent in so far as one ring is derived directly from benzene with no prior functionalization, adjustment of oxidation state, or complexation to a metal required.

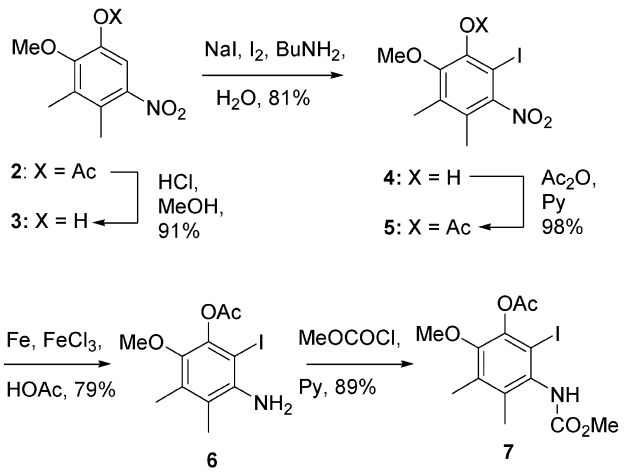
2. Results and discussion

Nitrophenol **3** was readily derived from the acetate **2**, whose synthesis was previously described by Clive and co-workers.[7] Iodination of **3** with sodium iodide, iodine, and butylamine in water afforded the iodide **4**, which was acetylated to provide **5**. This was then cleanly reduced, with iron and ferric chloride in acetic acid,[8] to the aniline **6**, derivatization of which afforded the iodocarbamate **7** (Scheme 2) ready for the key radical reaction.

In the key radical dearomatization step, an 0.05 M solution of iodide (**7**) and diphenyl diselenide (20 mol%) in benzene was treated at reflux dropwise with tributyltin hydride and AIBN.[9] After partitioning of the reaction mixture between hexanes and acetonitrile,[10] the adduct **8** was obtained by chromatography of the acetonitrile phase in 40% yield, together with 8% of the recovered substrate and 12% of the

Keywords: Radical; Arylation; Cyclohexadienyl; Dearomatization; Carbazole.
* Corresponding author. Tel.: +1-312-996-5189; fax: +1-312-996-2183; e-mail address: dcrich@uic.edu

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.015



Scheme 2. Formation of the iodocarbamate **7**.

deiodinated product **9** (Scheme 3). Treatment of **8** with phenylselenenyl bromide in dichloromethane then afforded the tetrahydrocarbazole **10** in 74% yield. Mindful of the earlier work of Barton and co-workers in which benzeneseleninic anhydride was demonstrated to be an efficient reagent for the oxidation of indolines to indoles,[11,12] **10** was heated to reflux in benzene with an excess of *tert*-butyl hydroperoxide resulting in the formation of the fully aromatic species **11** in 53% isolated yield. Finally, exposure of **11** to hot methanolic sodium hydroxide afforded carbazomycin B (**1**) in 75% yield (Scheme 3) with spectral data consistent with the literature values.[7]

3. Experimental

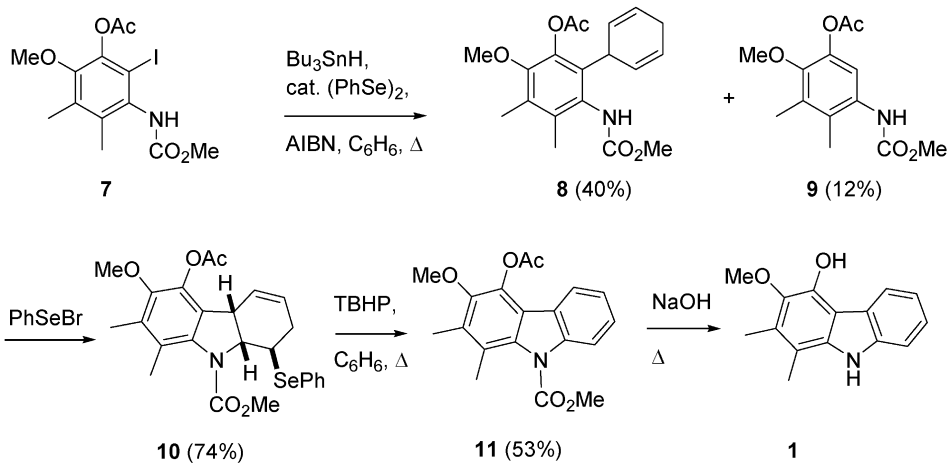
3.1. General

3.1.1. 2-Methoxy-3,4-dimethyl-5-nitrophenol (3). Anhydrous HCl in MeOH (20 mL of 7 M) was added under Ar to acetate **2**[7] (5.76 g, 24.0 mmol), after which the reaction mixture was heated to 70 °C with stirring for 4 h. The reaction mixture was cooled to room temperature, concentrated and the residue was diluted with EtOAc and washed with water. The organic layer was dried, concentrated and purified by silica gel column chromatography eluting with ethyl acetate–hexane (1:4) to afford the title phenol as viscous yellow oil (4.28 g, 91%). ^{1}H NMR ($CDCl_3$): δ 7.23 (s, 1H), 6.43 (br s, 1H), 3.76 (s, 3H), 2.48 (s, 3H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 149.1, 146.9, 146.7, 132.4, 124.4, 109.5, 61.1, 15.3, 13.1; ESIHRMS Calcd for $C_9H_{10}NO_4$ $[M-H]^-$ 196.0610, found 196.0609.

3.1.2. 2-Iodo-6-methoxy-4,5-dimethyl-3-nitrophenol (4). A solution of NaI (5.03 g, 34 mmol) and iodine (4.77 g, 19 mmol) in water (17 mL) was added dropwise to a 20% aqueous solution of $BuNH_2$ (24 mL) and **3** (2.24 g, 11 mmol) at room temperature. The resulting brown solution was stirred for 30 min at ambient temperature then diluted with dichloromethane. The organic layer was washed with water, 10% aqueous sodium thiosulphate solution, dried, and concentrated. The residue was filtered through a short silica gel pad and recrystallized from EtOAc–Hex to afford the crystalline iodophenol **4** (3.00 g, 81%). Mp 178–180 °C; ^{1}H NMR ($CDCl_3$): δ 6.26 (br s, 1H), 3.79 (s, 3H), 2.22 (s, 3H), 2.14 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 153.0, 148.4, 145.8, 132.0, 122.0, 71.3, 61.3, 15.0, 13.2; ESIHRMS Calcd for $C_9H_9NO_4I$ $[M-H]^-$ 321.9576, found 321.9576.

3.1.3. 2-Iodo-3-acetoxy-4-methoxy-5,6-dimethyl nitrobenzene (5). To a solution of iodophenol **4** (3.0 g, 10.6 mmol) in Ac_2O (3.3 g, 32 mmol) was added pyridine (0.042 g, 0.53 mmol) and DMAP (0.195 g, 1.6 mmol) at room temperature. The reaction mixture was stirred for 10 h at room temperature then quenched with ice/water. The precipitate formed was filtered off and washed with water, then was taken up in dichloromethane and filtered through a short silica gel pad to afford acetate **5** (3.34 g, 98%). Mp 150–151 °C; ^{1}H NMR ($CDCl_3$): δ 3.73 (s, 3H), 2.38 (s, 3H), 2.21 (s, 3H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 167.7, 152.5, 151.4, 144.2, 133.9, 128.6, 81.0, 61.3, 21.0, 15.6, 13.2; ESIHRMS Calcd for $C_{11}H_{12}NO_5I[M]^+$ 364.9760, found 364.9776.

3.1.4. 2-Iodo-3-acetoxy-4-methoxy-5,6-dimethylaniline (6). A solution of nitrobenzene **5** (2.58 g, 8.0 mmol) and AcOH (1.55 mL) in EtOH (13 mL) was heated to reflux with stirring for 10 min before iron powder (3.23 g,



Scheme 3. Completion of the synthesis.

58 mmol) and $FeCl_3{\cdot}6H_2O$ (0.13 g, 0.48 mmol) were added. The resulting mixture was heated to reflux with stirring for 4 h before it was cooled to room temperature and concentrated. The residue was extracted with EtOAc and the organic layer was washed with water, brine, and dried. Purification of the extracts by silica gel column chromatography eluting with EtOAc–Hex (3:7) afforded aniline **6** (1.85 g, 79%). Mp 85–87 °C; IR ($CHCl_3$): 3404, 1797 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.02 (br s, 2H), 3.65 (s, 3H), 2.38 (s, 3H), 2.19 (s, 3H), 2.09 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.5, 142.9, 142.6, 142.2, 131.5, 119.4, 79.1, 61.1, 21.2, 14.9, 13.1; ESIHRMS Calcd for $C_{11}H_{15}NO_3I$ $[M+H]^+$ 336.0097, found 336.0097.

3.1.5. *N*-Methoxycarbonyl-2-iodo-3-acetoxy-4-methoxy-5,6-dimethylaniline (7). To a solution of aniline **6** (0.78 g, 2.6 mmol) in pyridine (4.2 g, 53.2 mmol) was added dropwise methyl chloroformate (0.38 g, 4.0 mmol) at 0 °C under Ar. The reaction mixture was stirred for 4 h at room temperature then diluted with water and extracted with EtOAc. The organic layer was washed with water, 20% $CuSO_4$ solution, dilute HCl, brine, and dried. Concentration of the extracts and purification by silica gel column chromatography eluting with EtOAc–Hex (2:3) afforded carbamate **7** (0.93 g, 89%). Mp 119–121 °C; IR ($CHCl_3$): 3450, 1783 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.29 (br s, 1H), 3.77 (br s, 3H), 3.71 (s, 3H), 2.36 (s, 3H), 2.22 (s, 3H), 2.19 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.2, 154.9, 149.7, 143.3, 135.6, 133.1, 132.5, 77.4, 61.0, 53.0, 21.1, 16.6, 13.3; ESIHRMS Calcd for $C_{13}H_{15}NO_5I$ $[M-H]^-$ 391.9995, found 391.9995.

3.1.6. *N*-Methoxycarbonyl-2-(2,5-cyclohexadienyl)-3-acetoxy-4-methoxy-5,6-dimethylaniline (8) and *N*-Methoxycarbonyl-5-acetoxy-4-methoxy-2,3-dimethylaniline (9). To a stirred solution of iodide **7** (0.120 g, 0.31 mmol) and diphenyl diselenide (0.019 g, 0.06 mmol) at reflux in benzene (6.0 mL) under Ar was added a solution of Bu_3SnH (0.106 g, 0.37 mmol) and AIBN (0.005 g, 0.02 mmol) in benzene (2.5 mL) over 10 h. After the addition was complete, the reaction mixture was further stirred for an additional 1 h at 85 °C, then cooled to room temperature and concentrated. The residue was partitioned between acetonitrile and hexane and the acetonitrile layer was concentrated and purified by silica gel column chromatography eluting with EtOAc–Hex to give the adduct **8** (0.042 g, 40%), recovered **7** (0.025 g, 8%), and the desiodo compound **9** (0.012 g, 12%). **8**: IR (film): 3387, 1767, 1716, 1505, 1457, 1185 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.50 (s, 1H), 5.95–5.85 (m, 2H), 5.55 (br d, J=8.1 Hz, 2H), 4.29–4.22 (m, 1H), 3.71 (s, 3H), 3.68 (br s, 3H), 2.80 (m, 2H), 2.31 (s, 3H), 2.20 (s, 3H), 2.14 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 169.8, 155.8, 135.6, 131.3, 130.9, 129.6, 127.3, 126.5, 61.3, 61.1, 52.8, 52.6, 34.4, 25.9, 21.7, 20.9, 15.1, 13.7, 13.4; ESIHRMS Calcd for $C_{19}H_{23}NO_5Na$ $[M+Na]^+$ 368.1474, found 368.1467. **9** Mp 117–119 °C; IR (film): 3320, 1768, 1727, 1199 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.26 (s, 1H), 6.30 (br s, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 2.32 (s, 3H), 2.21 (s, 3H), 2.12 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 169.6, 147.4, 141.9, 132.0, 131.7, 61.2, 54.6, 20.9, 14.3, 13.9; ESIHRMS Calcd for $C_{13}H_{17}NO_5Na$ $[M+Na]^+$ 290.1004, found 290.0995.

3.1.7. Methyl 5-acetoxy-6-methoxy-7,8-dimethyl-1-phenylselenenyl-1,2,4a,9a-tetrahydrocarbazole-9-carboxylate (10). To a stirred solution of cyclohexadiene **8** (0.036 g, 0.10 mmol) in dichloromethane (2 mL) was added phenylselenenyl bromide (0.027 g, 0.11 mmol) at −78 °C under Ar. The reaction mixture was allowed to come to room temperature, then was stirred for 10 h, before it was diluted with dichloromethane, washed with water and dried. Concentration and purification of the crude reaction mixture by silica gel column chromatography eluting with EtOAc–Hex afforded the tetrahydrocarbazole **10** carbazole (0.038 g, 74%); IR (film): 1770, 1715, 1457, 1194 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.58 (d, J=6.8 Hz, 2H), 7.26–7.19 (m, 3H), 5.88–5.86 (m, 1H), 5.73–5.69 (m, 1H), 4.80 (dd, J=7.0, 11.6 Hz, 1H), 4.06 (br s, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 3.31 (dt, J=5.4, 11.2 Hz, 1H), 2.31 (s, 3H), 2.35–2.25 (m, 2H), 2.18 (s, 3H), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.4, 155.8, 148.0, 138.6, 136.9, 136.0, 133.8, 131.1, 129.3, 128.9, 128.6, 128.1, 127.9, 127.0, 123.5, 66.9, 61.2, 53.3, 43.9, 40.8, 32.2, 23.0, 17.3, 13.1; ESIHRMS Calcd for $C_{25}H_{27}NO_5SeNa$ $[M+Na]^+$ 524.0952, found 524.0970.

3.1.8. Methyl 4-acetoxy-3-methoxy-1,2-dimethyl-carbazole-9-carboxylate (11). To a solution of selenide **10** (0.047 g, 0.093 mmol) in benzene (2 mL) was added 70% aqueous ^{t}BuOOH (0.047 mL, 0.5 mmol) at room temperature. The reaction mixture was heated to reflux with stirring for 2.5 h, then was cooled and concentrated. The crude reaction mixture was purified by silica gel column chromatography eluting with EtOAc–Hex (3:7) to afford carbazole **11** (0.017 g, 53%); IR (film): 1770, 1738, 1194 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.08 (d, J=7.2 Hz, 1H), 7.83 (d, J=7.6 Hz, 1H), 7.43 (t, J=7.6 Hz, 1H), 7.32 (t, J=7.6 Hz, 1H), 4.03 (s, 3H), 3.81 (s, 3H), 2.52 (s, 3H), 2.37 (s, 3H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.6, 153.1, 146.9, 140.4, 135.9, 135.7, 130.9, 126.9, 124.6, 124.1, 123.6, 121.2, 118.8, 115.4, 61.1, 53.8, 20.8, 18.0, 13.2; ESIHRMS Calcd for $C_{19}H_{19}NO_5Na$ $[M+Na]^+$ 364.1161, found 364.1165.

3.1.9. Carbazomycin B (1). A solution of carbamate (**11**) (2 mg, 0.006 mmol) and NaOH (0.006 g, 0.15 mmol) in MeOH–H_2O (1:1, 1 mL) was heated with stirring in an oil bath at 92 °C for 3 h. The methanol was then removed under vacuum and the remaining solution was neutralized (~pH 7) with dil. HCl (1 mL) and extracted with EtOAc. Concentration of the extracts and purification by silica gel column chromatography eluting with EtOAc–Hex (3:7) afforded carbazomycin B (**1**) (1 mg, 75%) with spectra data comparable to the literature values;[7] ^1H NMR ($CDCl_3$): δ 8.23 (d, J=7.5 Hz, 1H), 7.77 (br s, 1H), 7.38–7.35 (m, 2H), 7.25–7.18 (t, J=7.5 Hz, 1H), 6.01 (s, 1H), 3.82 (s, 3H), 2.39 (s, 3H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 142.4, 139.6, 138.8, 137.1, 127.3, 125.1, 123.6, 123.0, 119.8, 110.3, 109.6, 63.4, 13.6, 13.2; ESIMS Calcd for $C_{15}H_{15}NO_2Na$ $[M+Na]^+$ 241.29, found 241.29.

Acknowledgements

We thank the NSF (CHE 9986200) for partial support of this work, Dr. Mousumi Sannigrahi for the initial preparation of **2**, and Professor Derrick Clive (Edmonton) for provision of experimental details for the preparation of **2**.

References and notes

1. Crich, D.; Hwang, J.-T. *J. Org. Chem.* **1998**, *63*, 2765–2770.
2. Crich, D.; Sannigrahi, M. *Tetrahedron* **2002**, *58*, 3319–3322.
3. Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303–4427.
4. Hook, D. J.; Yacobucci, J. J.; O'Connor, S.; Lee, M.; Kerns, E.; Krishnan, B.; Matson, J.; Hesler, G. *J. Antibiot.* **1990**, *53*, 1347–1348.
5. Sakano, K.-I.; Ishimaru, K.; Nakamura, S. *J. Antibiot.* **1980**, *33*, 683–689.
6. Knölker, H.-J.; Bauermeister, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1468–1470.
7. Clive, D. L. J.; Etkin, N.; Joseph, T.; Lown, J. W. *J. Org. Chem.* **1993**, *58*, 2442–2445.
8. Gabrielle, B.; Salerno, G.; Veltri, L.; Costa, M.; Massera, C. *Eur. J. Org. Chem.* **2001**, 4607–4613.
9. In this chemistry benzeneselenol, the active catalyst, is conveniently introduced as the diselenide, which is reduced in situ by the stannane: Crich, D.; Jiao, X.-Y.; Yao, Q.; Harwood, J. S. *J. Org. Chem.* **1996**, *61*, 2368–2373.
10. Berge, J. M.; Roberts, S. M. *Synthesis* **1979**, 471–473.
11. Barton, D. H. R.; Lusinchi, X.; Milliet, P. *Tetrahedron* **1985**, *41*, 4727–4738.
12. Ninomia, I.; Hashimoto, C.; Kiguchi, T.; Naito, T.; Barton, D. H. R.; Lusinchi, X.; Milliet, P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 529–532.