

Palladium-catalyzed total synthesis of euchrestifoline using a one-pot Wacker oxidation and double aromatic C–H bond activation†

Konstanze K. Gruner and Hans-Joachim Knölker*

Received 6th August 2008, Accepted 1st September 2008

First published as an Advance Article on the web 29th September 2008

DOI: 10.1039/b813670j

We describe the total synthesis of euchrestifoline featuring an unprecedented one-pot Wacker oxidation and double aromatic C–H bond activation.

The useful biological activities of carbazole alkaloids have induced an increasing interest in their synthesis.^{1–3} We have developed a highly convergent route to carbazoles *via* palladium(0)-catalyzed Buchwald–Hartwig amination followed by palladium(II)-catalyzed oxidative cyclization.² The oxidative cyclization of the intermediate *N,N*-diarylamine is based on an earlier report by Åkermark *et al.* using stoichiometric amounts of palladium(II).⁴ By application of conditions known for the classical Wacker process (reoxidation of Pd(0) to Pd(II) with Cu(II) salts),⁵ we have shown first that the biaryl cyclization can be induced using catalytic amounts of palladium.^{6,7} Subsequently, the palladium(II)-catalyzed oxidative cyclization by double aromatic C–H bond activation has found various applications in carbazole synthesis.^{1,8,9} The present example describes for the first time a palladium(II)-catalyzed Wacker oxidation⁵ of a vinylarene to an arylketone followed by cyclization of a diarylamine to a carbazole. Execution of both transformations as a one-pot reaction leads to sequential activation of three C–H bonds in a palladium(II)-catalyzed process.

Euchrestifoline (**1**), our target molecule, was isolated in 1996 by Wu and coworkers from the leaves of the Chinese medicinal plant *Murraya euchrestifolia* (Fig. 1).¹⁰ No total synthesis has been reported so far for this natural product. However, compound **1** was used as an intermediate for a synthesis of the structurally related girinimbine (**2**) described in 1971 by Chakraborty and Islam.¹¹ Girinimbine (**2**), the first pyrano[3,2-*a*]carbazole alkaloid from natural sources, was isolated by Chakraborty and his group from the stem bark of *Murraya koenigii* and by Joshi *et al.* from the root bark of *Clausena heptaphylla*. The structural assignment of girinimbine (**2**) was based on spectroscopic studies and chemical transformations.^{12,13}

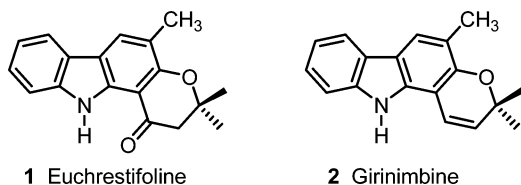
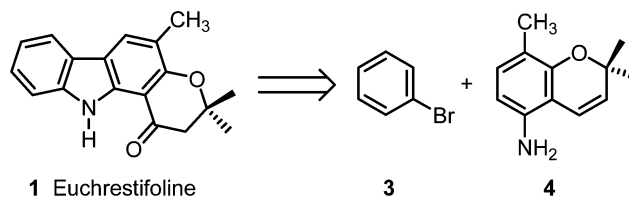


Fig. 1 Pyrano[3,2-*a*]carbazole alkaloids euchrestifoline and girinimbine.

We have developed a convergent synthesis of euchrestifoline (**1**) following our retrosynthetic analysis (Scheme 1). The tetracyclic ring system is assembled from bromobenzene (**3**) and the aminochromene **4** *via* a sequence of palladium(0)-catalyzed amination and oxidative biaryl cyclization by palladium(II)-catalyzed double C–H bond activation. Transformation of the chromene to the chroman-4-one can be achieved by a Wacker oxidation using the same reaction conditions as required for oxidative cyclization.



Scheme 1 Retrosynthetic analysis of euchrestifoline (**1**)

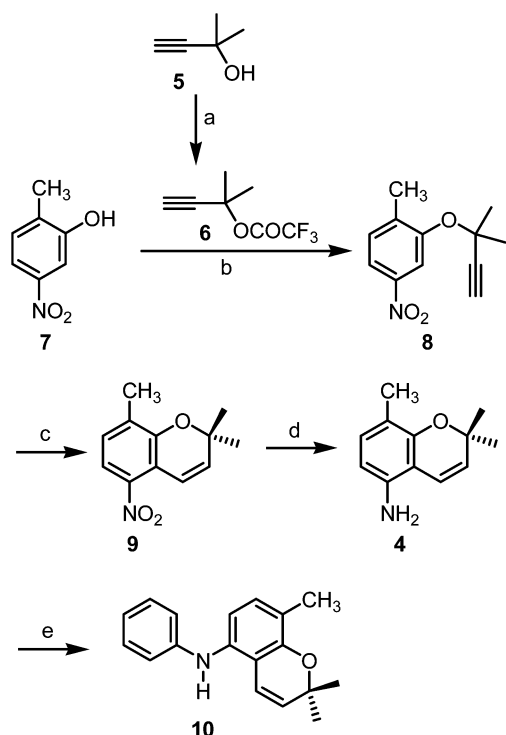
Preparation of the precursor starts with conversion of 2-methyl-3-butyn-2-ol (**5**) to the trifluoroacetate **6** (Scheme 2).¹⁴ The resulting crude product was used for alkylation of 2-methyl-5-nitrophenol (**7**) to the corresponding aryl propargyl ether **8**.^{14,15} Thermally induced [3,3]-sigmatropic rearrangement followed *in situ* by rearomatization and cyclization afforded the nitrochromene **9**. Reduction using iron in glacial acetic acid led quantitatively to the aminochromene **4**. Using this improved sequence, the aminochromene **4** is available in 3 steps and 70% overall yield based on the nitrophenol **7** (previous synthesis: 3 steps, 60% overall yield).¹⁵ Buchwald–Hartwig amination of bromobenzene (**3**) with the aminochromene **4** provided the diarylamine **10**. ‡

Heating of the diarylamine **10** with catalytic amounts of palladium(II) acetate in a mixture of acetic acid and water (10 : 1) in the presence of 2.5 equivalents cupric acetate at 90 °C for 5 h led to Wacker oxidation and afforded the chromanone **11** (Scheme 3).§ Extension of the reaction time to 24 h resulted in cyclization *via* double aromatic C–H bond activation and afforded euchrestifoline (**1**) (26% yield) along with the chromanone **11** (23% yield). Optimized conditions (heating of the diarylamine **10** for 2 days using catalytic amounts of palladium(II) acetate and cupric acetate) resulted in direct conversion to euchrestifoline (**1**).¶ The spectroscopic data of our synthetic euchrestifoline (**1**) were in good agreement with those reported for the natural product.¹⁰ Compound **1** exhibits an intense fluorescence with an emission at 501 nm and a large Stokes shift.

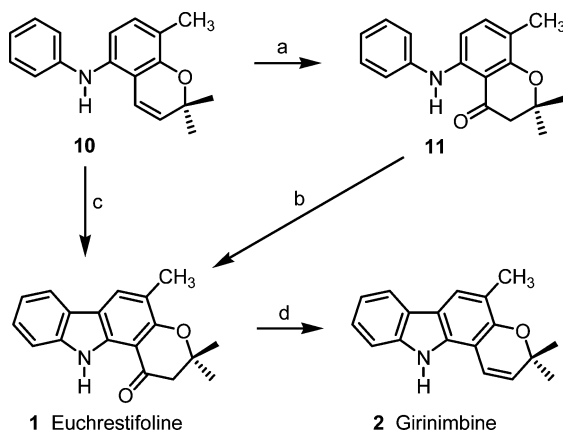
It was obvious that activation of the vinylic C–H bond, which leads to Wacker oxidation, takes place first. The subsequent activation of the aromatic C–H bonds leads to cyclization of the initially formed chromanone **11** to euchrestifoline (**1**). In order

Department Chemie, Technische Universität Dresden, Bergstrasse 66, 01069 Dresden, Germany. E-mail: hans-joachim.knoelker@tu-dresden.de; Fax: +49 351-463-37030

† Part 88 of 'Transition Metals in Organic Synthesis'; for Part 87, see: ref. 1.



Scheme 2 Synthesis of the diarylamine **10**. *Reagents and conditions:* (a) 1.0 equiv. $(\text{CF}_3\text{CO})_2\text{O}$, 1.3 equiv. DBU, MeCN, -5°C , 70 min; (b) 1.15 equiv. **6**, 1 mol% $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, 1.3 equiv. DBU, MeCN, 0°C , 7 h, 71% (over 2 steps); (c) *o*-xylene, 140°C , 18 h, 98%; (d) 10 equiv. Fe, HOAc, rt, 2 h, 100%; (e) 1.0 equiv. **3**, 1.2 equiv. **4**, 1.4 equiv. Cs_2CO_3 , 6 mol% $\text{Pd}(\text{OAc})_2$, 6 mol% BINAP, toluene, 110°C , 36 h, 93%.



Scheme 3 Pd(II)-catalyzed synthesis of euchrestifoline (**1**) and conversion into girinimbine (**2**). *Reagents and conditions:* (a) 10 mol% $\text{Pd}(\text{OAc})_2$, 2.5 equiv. $\text{Cu}(\text{OAc})_2$, HOAc– H_2O (10 : 1), 90°C , 5 h, 57%; (b) 10 mol% $\text{Pd}(\text{OAc})_2$, 10 mol% $\text{Cu}(\text{OAc})_2$, HOAc, 90°C , 24 h, 44%; (c) 10 mol% $\text{Pd}(\text{OAc})_2$, 10 mol% $\text{Cu}(\text{OAc})_2$, HOAc– H_2O (10 : 1), 90°C , 48 h, 40%; (d) 1.4 equiv. LiAlH_4 , THF, 0°C to rt, 17 h; 2. 5% HCl, 60°C , 1 h, 70%.

to confirm this assumption, it was shown that transformation of the chromanone **11** to euchrestifoline (**1**) is achieved in one day using the same reaction conditions. Previously, **1** was prepared *via* Fries rearrangement.¹¹ Finally, reduction of euchrestifoline (**1**) followed by acidic work-up led *via* elimination of water to girinimbine (**2**).|| This conversion of euchrestifoline (**1**) into girinimbine (**2**) is superior to the 3-step-sequence previously

reported by Chakraborty and Islam.¹¹ Structural assignment for girinimbine (**2**) was based on comparison of the spectroscopic data with those reported for the natural product^{12,13} and the synthetic product obtained earlier by a molybdenum-mediated approach.¹⁵

In conclusion, we have developed a highly efficient route to the aminochromene **4** (3 steps and 70% yield based on **7**), a useful building block for the synthesis of pyrano[3,2-*a*]carbazole alkaloids. Three consecutive palladium-catalyzed reactions convert compound **4** into euchrestifoline (**1**): Buchwald–Hartwig amination, Wacker oxidation, and subsequent oxidative biaryl cyclization by double aromatic C–H bond activation. As both latter transformations are palladium(II)-catalyzed, they are most efficiently accomplished as one-pot process to provide euchrestifoline (**1**) in two steps and 37% overall yield based on bromobenzene (**3**). The pyrano[3,2-*a*]carbazoles are of interest because of their potential anti-TB activity.¹⁶

Notes and references

‡ Spectroscopic data for the diarylamine (**10**): Yellow solid, mp $105\text{--}107^\circ\text{C}$; IR (ATR): $\nu = 3389, 3046, 2977, 2925, 2851, 1637, 1594, 1578, 1506, 1477, 1408, 1378, 1315, 1257, 1204, 1172, 1123, 1057, 1025, 941, 898, 875, 787, 745, 720, 689\text{ cm}^{-1}$; $^1\text{H NMR}$ (500 MHz, CDCl_3): $\delta = 1.44$ (s, 6 H), 2.17 (s, 3 H), 5.40 (br s, 1 H), 5.59 (d, $J = 9.9$ Hz, 1 H), 6.46 (d, $J = 9.9$ Hz, 1 H), 6.67 (d, $J = 8.1$ Hz, 1 H), 6.82 (m, 3 H), 6.93 (d, $J = 8.1$ Hz, 1 H), 7.20 (m, 2 H); $^{13}\text{C NMR}$ and DEPT (125 MHz, CDCl_3): $\delta = 15.29$ (CH_3), 27.62 (2 CH_3), 75.06 (C), 114.11 (CH), 115.18 (C), 115.70 (2 CH), 118.43 (CH), 119.39 (CH), 121.07 (C), 129.19 (2 CH), 129.93 (CH), 130.32 (CH), 135.82 (C), 145.54 (C), 151.62 (C); MS (EI): m/z (%) = 265 (M^+ , 39), 250 (100); HRMS: m/z calc. for $\text{C}_{18}\text{H}_{19}\text{NO}$ (M^+): 265.1467, found: 265.1450; anal. calc. for $\text{C}_{18}\text{H}_{19}\text{NO}$: C 81.47, H 7.22, N 5.28, found: C 81.22, H 7.49, N 5.06.

§ Spectroscopic data for the chromanone (**11**): Yellow oil; IR (ATR): $\nu = 3260, 3028, 2975, 2928, 1640, 1591, 1518, 1456, 1431, 1386, 1370, 1235, 1217, 1176, 1093, 1042, 912, 889, 803, 737, 692\text{ cm}^{-1}$; $^1\text{H NMR}$ (500 MHz, CDCl_3): $\delta = 1.47$ (s, 6 H), 2.08 (s, 3 H), 2.73 (s, 2 H), 6.67 (d, $J = 8.5$ Hz, 1 H), 7.08 (d, $J = 8.5$ Hz, 1 H), 7.08 (t, $J = 7.3$ Hz, 1 H), 7.25 (m, 2 H), 7.33 (m, 2 H), 10.45 (br s, 1 H); $^{13}\text{C NMR}$ and DEPT (125 MHz, CDCl_3): $\delta = 15.15$ (CH_3), 26.75 (2 CH_3), 49.39 (CH_2), 77.58 (C), 104.00 (CH), 105.98 (C), 113.99 (C), 122.89 (2 CH), 123.52 (CH), 129.20 (2 CH), 138.17 (CH), 140.56 (C), 146.44 (C), 158.43 (C), 195.41 (C=O); MS (EI): m/z (%) = 281 (M^+ , 100), 266 (68), 226 (26), 225 (17), 224 (32), 196 (12); HRMS: m/z calc. for $\text{C}_{18}\text{H}_{19}\text{NO}_2$ (M^+): 281.1416, found: 281.1403.

¶ Synthesis of euchrestifoline (**1**): A mixture of the diarylamine **10** (56.5 mg, 0.21 mmol), palladium acetate (4.8 mg, 0.02 mmol) and cupric acetate (3.8 mg, 0.02 mmol) in glacial acetic acid (5 mL) and water (0.5 mL) was heated at 90°C in air for 48 h. After cooling to rt, a small amount of silica gel was added to the reaction mixture and the solvent was removed under vacuum. Flash chromatography of the residue on Celite and silica gel (light petroleum ether–EtOAc, 9 : 1) provided euchrestifoline (**1**), yield: 23.7 mg (40%). Yellow crystals, mp 181°C (ref. 10: $187\text{--}189^\circ\text{C}$); UV (MeOH): $\lambda = 230, 256, 285, 291, 334, 386\text{ nm}$; fluorescence (MeOH): $\lambda_{\text{em}} = 501$ ($\lambda_{\text{ex}} = 386$) nm; IR (ATR): $\nu = 3381, 2969, 2919, 2849, 1710, 1649, 1608, 1590, 1492, 1450, 1384, 1369, 1311, 1213, 1193, 1171, 1136, 1039, 1003, 930, 887, 773, 744, 690, 651, 607\text{ cm}^{-1}$; $^1\text{H NMR}$ (500 MHz, CDCl_3): $\delta = 1.53$ (s, 6 H), 2.34 (s, 3 H), 2.82 (s, 2 H), 7.22 (t, $J = 7.5$ Hz, 1 H), 7.35 (t, $J = 7.5$ Hz, 1 H), 7.47 (d, $J = 7.5$ Hz, 1 H), 7.93 (d, $J = 7.5$ Hz, 1 H), 8.00 (s, 1 H), 10.14 (br s, 1 H); $^{13}\text{C NMR}$ and DEPT (125 MHz, CDCl_3): $\delta = 16.08$ (CH_3), 26.82 (2 CH_3), 48.54 (CH_2), 79.49 (C), 104.67 (C), 111.08 (CH), 116.23 (C), 117.76 (C), 119.21 (CH), 119.98 (CH), 122.27 (C), 124.62 (CH), 129.26 (CH), 137.00 (C), 139.40 (C), 157.65 (C), 194.33 (C=O); MS (EI): m/z (%) = 279 (M^+ , 100), 264 (82), 224 (35), 223 (62), 195 (15), 167 (30), 132 (15); HRMS: m/z calc. for $\text{C}_{18}\text{H}_{17}\text{NO}_2$ (M^+): 279.1259; found: 279.1261; anal. calc. for $\text{C}_{18}\text{H}_{17}\text{NO}_2$: C 77.40, H 6.13, N 5.01, found: C 77.43, H 6.28, N 4.71.

|| Spectroscopic data for girinimbine (**2**): Colorless crystals, mp 173°C (ref. 12a: 176°C); $^1\text{H NMR}$ (500 MHz, acetone- d_6): $\delta = 1.50$ (s, 6 H), 2.33 (s, 3 H), 5.81 (d, $J = 9.8$ Hz, 1 H), 6.95 (d, $J = 9.8$ Hz, 1 H), 7.14 (t, $J = 7.5$ Hz, 1 H), 7.29 (t, $J = 7.5$ Hz, 1 H), 7.43 (d, $J = 7.5$ Hz, 1 H), 7.76 (s, 1 H), 7.97 (d, $J = 7.5$ Hz, 1 H), 10.33 (br s, 1 H); $^{13}\text{C NMR}$ and DEPT (125 MHz,

acetone- d_6): δ = 16.19 (CH₃), 27.83 (2 CH₃), 76.48 (C), 105.36 (C), 111.29 (CH), 117.46 (C), 118.30 (C), 118.58 (CH), 119.64 (CH), 119.85 (CH), 121.70 (CH), 124.36 (C), 124.88 (CH), 129.80 (CH), 136.16 (C), 140.85 (C), 150.44 (C).

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