Total Synthesis of New Lipocarbazoles Isolated from the Actinomycete *Tsukamurella pseudospumae* Acta 1857[1]

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Abstract: New lipocarbazoles were synthesized by a sequence of three palladium-mediated coupling reactions and an improved protecting group strategy.

Key words: heterocycles, cross-coupling, total synthesis, hydroboration, natural products

Carbazole alkaloids represent an important class of N-heterocyclic natural products. They can be isolated mostly from sources like higher plants or bacteria and exhibit therefore a high structural diversity as well as a broad range of interesting biological activities.[2] Recently, we isolated a novel class of carbazoles from the fermentation foam of the actinomycete *Tsukamurella pseudospumae* Acta 1875.[3] This strain was found in activated sludge foam of sewage plants and is described as agent of foaming thus causing heavy operational problems.[4]

The lipocarbazoles A4, A3, and A2 (**1a**–**c**, Figure 1) show high structural analogy to the well-known 3-oxygenated carbazole alkaloids carazostatin (**2**)[5] and antiostatin A4 (**3**),[6] which are free-radical scavengers and can act as potent antioxidants against lipid peroxidation.[7] In contrast to these natural products the lipocarbazoles **1a**–**c** have comparatively long, saturated and unsaturated, alkyl chains. Because of the amphiphilic character of these structures they were suspected to be associated with the foaming observed during the fermentation of the strain. All lipocarbazoles characterized thus far have the same heterocyclic core structure and differ only in the type of the alkyl chain.

The construction of the carbazole framework was intensely studied over decades amongst others by the group of Knölker et al.[2] They developed efficient synthetic routes based on transition-metal-mediated coupling reactions of arylamines which found application in many total syntheses of natural occurring carbazole alkaloids.[8] Accordingly, and in order to obtain a rapid and variable synthetic access to various alkyl-chain-substituted lipocarbazoles we decided to build up the core structure first using a sequence of palladium-mediated Buchwald–Hartwig

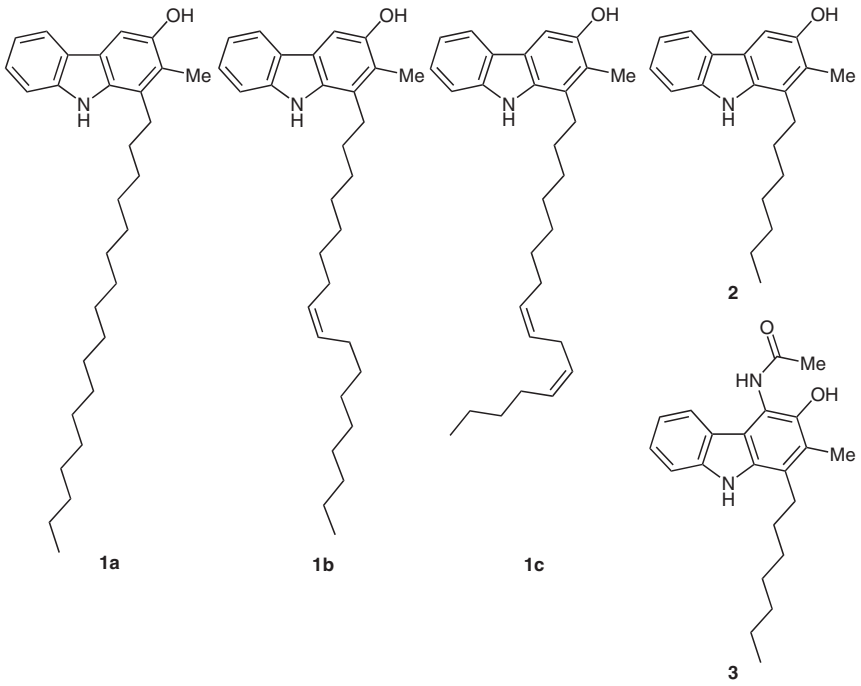

Figure 1 Lipocarbazoles A4 (**1a**), A3 (**1b**), A2 (**1c**), carazostatin (**2**), and antiostatin A4 (**3**)

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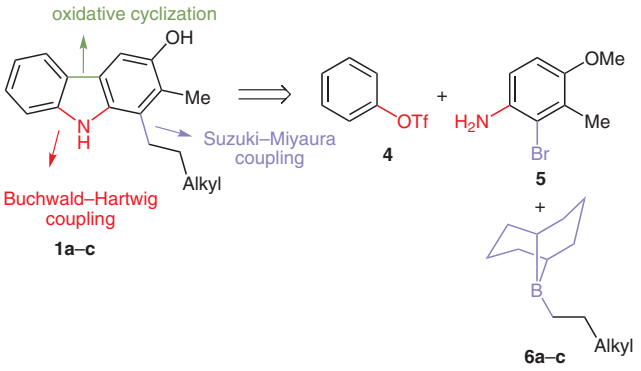
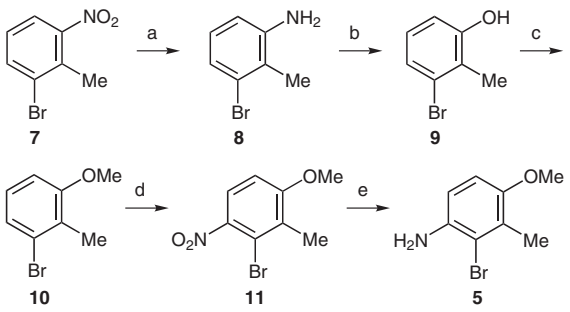
coupling and oxidative cyclization reactions (Scheme 1).[9] Introduction of the alkyl chains in a late step of the synthesis was realized by a palladium-catalyzed Suzuki–Miyaura reaction.[10]



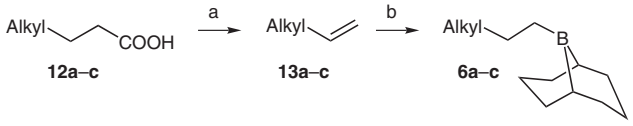
Scheme 1 Retrosynthetic strategy for lipocarbazoles[8d]

For the synthesis of arylamine **5** we conformed to the reaction sequence previously described by Knölker et al.[9a] However, for some synthetic steps alternative reagents were used. First, 2-bromo-6-nitrotoluene (**7**), as cheap starting material, was reduced to arylamine **8** using $SnCl_2$ (instead of the more toxic $N_2H_4{\cdot}H_2O$) with nearly quantitative yield within a reaction time of one hour.[11] Subsequently phenol **9** could be obtained in a two-step procedure.[12] Thus, 3-bromo-2-methylaniline (**8**) was converted into a stable aryl diazonium salt using $NOBF_4$ which could be hydrolyzed with diluted H_2SO_4 at 60 °C to yield phenol **9**. In the next step the hydroxy group was protected as methyl ether using MeI.[13] The subsequent nitration of the aromatic core with claycop[14] gave two isomeric nitro derivatives which could easily be separated by flash chromatography.[15] Similarly to the first step, reduction of **11** finally gave the desired arylamine **5** in nearly quantitative yield (Scheme 2).



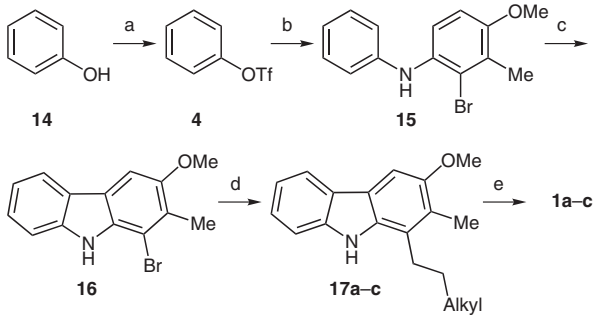
Scheme 2 Preparation of arylamine **5**. *Reagents and conditions*:[9a] (a) $SnCl_2{\cdot}H_2O$, EtOH, 70 °C, 2 h (98%); (b) (1) $NOBF_4$, CH_2Cl_2, 0 °C, 4 h; (2) 0.01 M H_2SO_4, 60 °C, 1 h (70%); (c) MeI, KOH, DMSO, r.t., 1.5 h (98%); (d) claycop, Ac_2O, hexane, r.t., 1 h (30%); (e) $SnCl_2{\cdot}H_2O$, EtOH, 70 °C, 1 h (99%).

In parallel, the precursors for the different alkyl chains with a terminal double bond **13a–c** (Scheme 3) were synthesized by oxidative decarboxylation using the corresponding fatty acids, which are stearic acid (**12a**), oelic acid (**12b**), and linolic acid (**12c**), respectively.[16] The yields for this conversion were only moderate, but particularly for the unsaturated alkyl chains a rapid access was desired as well as that the configuration of the double bonds remained intact during the reaction. The alkenes **13a–c** were further converted into the alkyl boron compounds **6a–c** using 9-borabicyclo[3.3.1]nonane (9-BBN-H).[17]



Scheme 3 Preparation of alkyl boron compounds **6a–c**. *Reagents and conditions:* (a) $Pb(OAc)_4$ (1.5 equiv), $Cu(OAc)_2$ (0.15 equiv), pyridine, benzene, 80 °C, 2 h (40% for **13a** and **13b**, 34% for **13c**); (b) 9-BBN-H, THF, 0 °C to r.t., 4 h, in situ.

Phenyltriflate (**4**) was easily obtained in one step from phenol (**14**, Scheme 4).[18] Coupling of triflate **4** with arylamine **5** was realized by a Buchwald–Hartwig reaction in the presence of 5 mol% palladium(II) acetate, (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) as ligand and cesium carbonate as a base.[9a,19] Oxidative cyclization of the diarylamine **15** turned out to be the most challenging step of the synthesis. Various reaction conditions using only catalytic amounts of palladium(II) acetate and copper(II) acetate as reoxidants were tested,[9c,d,20] but the use of stoichiometric amounts of palladium(II) acetate yielded the best results.[9a,b,21] Having the carbazole core **16** in hands, we proceeded synthesizing the different lipocarbazoles. Hence a Suzuki–Miyaura cross-coupling reaction of **16** with one of the in situ generated alkyl boron compounds **6a–c** in the presence of [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) [$PdCl_2$(dppf)] was chosen.[17] In the ultimate step of the total synthesis the methyl ether protecting group was removed under mild conditions without affecting the double bonds of the lipocarbazole precursors **17b** and **17c** using 9-iodo-borabicyclo[3.3.1]nonane (9-I-9-BBN).[22] In contrast to the



Scheme 4 Preparation of lipocarbazoles **1a–c**. *Reagents and conditions:* (a) Tf_2O, pyridine, CH_2Cl_2, 0 °C to r.t., 15 min (79%); (b) $Pd(OAc)_2$ (5 mol%), BINAP (7.5 mol%), Cs_2CO_3, toluene, 100 °C, 24 h (66%); (c) $Pd(OAc)_2$ (1 equiv), AcOH, 100 °C, 24 h (39%); (d) **6a–c**, $PdCl_2$(dppf) (5 mol%), 3 N NaOH, THF, 65 °C, 1 h (75% for **17a**, 74% for **17b**, 68% for **17c**); (e) 9-I-9-BBN, hexane, r.t., 5 min (86% for **1a**, 67% for **1b**, 60% for **1c**).

synthesis of carbazomadurin A and B reported by Knölker et al.,[9a,b] no intermediate change of the phenolic protecting group during the synthetic route is needed to prevent side reactions with the double bonds present in the alkyl chains of carbazoles **17b** and **17c** in the final deprotection step.

The analytical data (^{1}H NMR, ^{13}C NMR and MS) of the lipocarbazoles were in full agreement with those described for the isolated natural products.[3,23–25] Furthermore, the proposed configurations and positions of the double bonds in the alkyl chains of lipocarbazoles A4, A3, and A2 (**1a–c**) could be confirmed.

In surface-tension measurements for lipocarbazole **1a** using the hanging-drop technique, no surface activity could be measured for the single compound. Thus no direct connection to previously observed foaming could be verified. As described for carazostatin (**2**), lipocarbazoles **1a** and **1b** show remarkable antioxidant activity.[3] With regard to this antioxidant activity, the biological function of these compounds might be scavenging of radicals in biological membranes.

In conclusion, the lipocarbazoles **1a–c** could be synthesized using three palladium-mediated coupling reactions. The reaction sequence gives rapid access to a wide range of derivatives with different alkyl chains. Additionally, by use of total synthesis the proposed structure for the natural products isolated from *Tsukamurella pseudospumae* Acta 1875 including the correct conformation of the double bonds in the alkyl side chains was confirmed.

Acknowledgment

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(22) Fürstner, A.; Seidel, G. *J. Org. Chem.* **1997**, *62*, 2332.
(23) **Spectral Data for Lipocarbazole A4 (1a)**
IR (neat): ν = 3466, 3388, 2920, 2849, 1500, 1466, 1436, 1311, 1233, 1147, 1064, 830, 772, 738 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.65 (s, 1 H), 8.78 (s, 1 H), 7.87–7.85 (d, *J* = 8.0 Hz, 1 H), 7.41–7.39 (d, *J* = 8.0 Hz, 1 H), 7.28–7.24 (t, *J* = 8.0 Hz, 1 H), 7.26 (s, 1 H), 7.04–7.00 (t, *J* = 8.0 Hz, 1 H), 2.88–2.84 (t, *J* = 8.0 Hz, 2 H), 2.22 (s, 3 H), 1.57–

1.50 (m, 2 H), 1.45–1.38 (m, 2 H), 1.23 (br s, 13 × 2 H), 0.86–0.82 (t, *J* = 8.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 148.93, 139.97, 133.24, 124.36, 123.95, 122.73, 121.30, 119.64, 119.48, 117.48, 110.75, 101.87, 31.32, 29.36, 29.33, 29.14, 29.12, 29.05, 28.73, 28.12, 22.13, 13.97, 12.17 ppm. MS (EI): *m/z* (%) = 435 (100), 267 (10), 210 (38), 167 (4), 97 (3), 83 (4), 69 (5), 57 (7). HRMS (EI): *m/z* calcd for $C_{30}H_{45}NO$ $[M]^+$: 435.3501; found: 435.3500.

(24) **Spectral Data for Lipocarbazole A3 (1b)**
IR (neat): ν = 3471, 3382, 2923, 2853, 1593, 1500, 1461, 1436, 1311, 1231, 1146, 1062, 831, 772, 739 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.65 (s, 1 H), 8.79 (s, 1 H), 7.87–7.85 (d, *J* = 8.0 Hz, 1 H), 7.41–7.39 (d, *J* = 8.0 Hz, 1 H), 7.28–7.24 (t, *J* = 8.0 Hz, 1 H), 7.26 (s, 1 H), 7.04–7.00 (t, *J* = 8.0 Hz, 1 H), 5.35–5.27 (2 × 1 H), 2.89–2.85 (t, *J* = 8.0 Hz, 2 H), 2.22 (s, 3 H), 1.98–1.94 (m, 2 × 2 H), 1.57–1.50 (m, 2 H), 1.46–1.39 (m, 2 H), 1.29–1.21 (m, 9 × 2 H), 0.85–0.81 (t, *J* = 8.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 149.00, 140.04, 133.31, 129.74, 129.71, 124.46, 124.02, 122.80, 121.37, 119.71, 119.57, 117.58, 110.83, 101.96, 31.36, 29.37, 29.22, 29.17, 29.01, 28.90, 28.77, 28.67, 28.19, 26.67, 26.65, 22.17, 14.02, 12.07 ppm. MS (EI): *m/z* (%) = 433 (94), 210 (100), 196 (6), 180 (12), 167 (11), 97 (3), 83 (4), 69 (5), 57 (8), 55 (9). HRMS (EI): *m/z* calcd for $C_{30}H_{43}NO$ $[M]^+$: 433.3345; found: 433.3342.

(25) **Spectral Data for Lipocarbazole A2 (1c)**
IR (neat): ν = 3471, 3381, 3009, 2924, 2853, 1593, 1499, 1461, 1436, 1311, 1230, 1146, 1062, 831, 772, 739 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.65 (s, 1 H), 8.79 (s, 1 H), 7.87–7.85 (d, *J* = 8.0 Hz, 1 H), 7.41–7.39 (d, *J* = 8.0 Hz, 1 H), 7.28–7.24 (t, *J* = 8.0 Hz, 1 H), 7.26 (s, 1 H), 7.04–7.00 (t, *J* = 8.0 Hz, 1 H), 5.37–5.25 (4 × 1H), 2.89–2.85 (t, *J* = 8.0 Hz, 2 H), 2.74–2.70 (t, *J* = 8.0 Hz, 2 H), 2.22 (s, 3 H), 2.00–1.97 (m, 2 × 2 H), 1.57–1.50 (m, 2 H), 1.46–1.39 (m, 2 H), 1.30–1.21 (m, 6 × 2 H), 0.85–0.81 (t, *J* = 8.0 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 148.93, 139.96, 133.24, 129.72, 127.77, 127.73, 124.37, 123.94, 122.72, 121.30, 119.63, 119.49, 117.50, 110.75, 101.88, 30.89, 29.33, 29.30, 29.07, 28.95, 28.73, 28.10, 26.63, 26.61, 25.23, 21.97, 13.91, 11.99. MS (EI): *m/z* (%) = 431 (58), 210 (100), 196 (9), 180 (15), 167 (17), 91 (5). HRMS (EI): *m/z* calcd for $C_{30}H_{45}NO$ $[M]^+$: 431.3188; found: 431.3191.