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First total synthesis of the neuronal cell protecting carbazole alkaloid carbazomadurin A by sequential transition metal-catalyzed reactions

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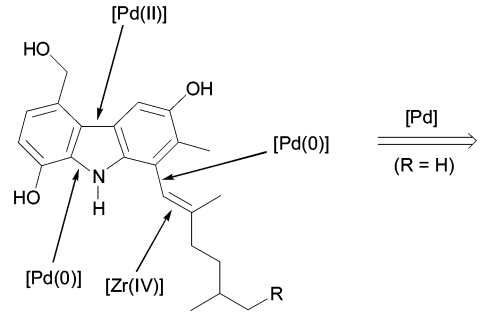
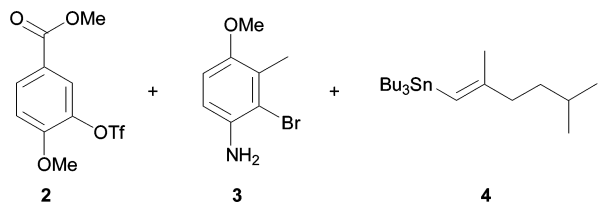
The highly oxygenated neuronal cell protecting carbazole alkaloid carbazomadurin A was synthesized in nine steps and 11% overall yield from isovanillic acid.

Carbazole alkaloids have attracted high interest because of their broad range of useful biological activities.[1–3] In 1997 Seto isolated the structurally unique alkaloids carbazomadurin A (**1a**) and B (**1b**) from the microorganism *Actinomadura madurae* 2808-SV1.[4] A biological screening of the carbazomadurins (**1**) showed a protecting activity for neuronal hybridoma N18-RE-105 cells against L-glutamate induced cell death. It is known that the high extracellular concentration of the excitatory amino acid L-glutamate occurring after brain ischemic attack leads to the destruction of cerebral tissue and therefore, radical scavengers represent potential candidates for the treatment of brain ischemia injury. The biological data suggested that the protection from glutamate toxicity by the carbazomadurins is based on their anti-oxidative activity.[4] In the course of our project focusing on the development of novel methodologies for the synthesis of biologically active carbazole alkaloids,[1] we became interested in these compounds. Herein, we describe the first total synthesis of carbazomadurin A (**1a**) by the palladium-catalyzed fusion of the three building blocks **2–4** and a zirconium-catalyzed generation of the *E*-configurated double bond (Scheme 1).

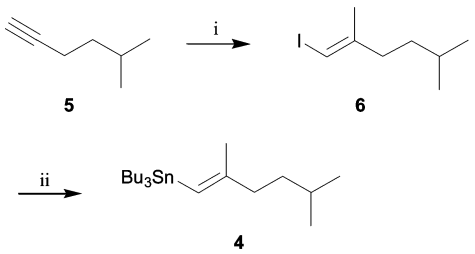
The stereospecific construction of the trisubstituted double bond of the side chain at C-1 of carbazomadurin A (**1a**) was achieved by using the zirconium-catalyzed carboalumination of alkynes developed by Negishi.[5] Treatment of 5-methyl-1-hexyne (**5**) with trimethylalane in the presence of zirconocene dichloride followed by addition of iodine afforded the vinyl iodide **6** with the desired *E* configuration of the double bond (Scheme 2). Halogen–metal exchange with *tert*-butyllithium



1a Carbazomadurin A (R = H)
1b Carbazomadurin B (R = Me)



Scheme 1 Retrosynthetic analysis of carbazomadurin A (**1a**).

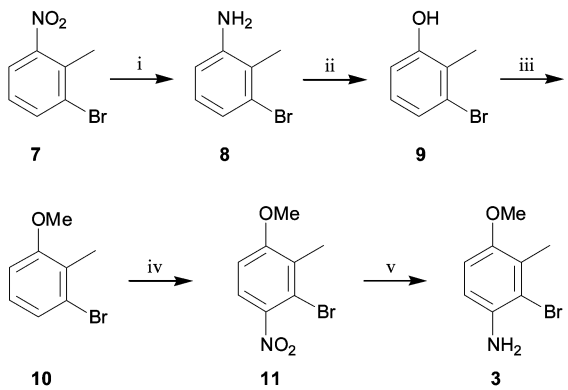


Scheme 2 Preparation of the vinylstannane **4**. *Reagents and conditions*: (i) 1. Me_3Al, Cp_2ZrCl_2, CH_2Cl_2, rt; 2. I_2, THF, 0 °C, 70%; (ii) 1. *t*BuLi, Et_2O, −78 °C; 2. Bu_3SnCl, −78 °C to rt, 74%.

and reaction of the intermediate vinyllithium compound with tributyltin chloride provided the vinylstannane **4** in good yields on a 10 g scale.

Transfer hydrogenation of 2-bromo-6-nitrotoluene (**7**) using hydrazine hydrate afforded 3-bromo-2-methylaniline (**8**), which was converted to the corresponding phenol **9** *via* diazotization (Scheme 3). The transformation to the anisole **10** and subsequent nitration using claycop[6] provided the 4-nitroanisole **11** in 67% yield along with 26% of the 2-nitro derivative. Reduction of **11** led to the arylamine **3**, which was obtained in 44% overall yield.

The aryl triflate **2** was easily prepared starting from isovanillic acid (**12**) (Scheme 4). After formation of the methyl ester **13**, the phenolic hydroxy group was converted to the triflate **2** by reaction with triflic anhydride using 2,6-lutidine as base. For the crucial C–N bond formation we envisaged the Buchwald–Hartwig coupling, a versatile method providing *N*,*N*-diarylamines in a palladium(0)-catalyzed process from arylamines and aryl halides or triflates.[7,8] We decided to use the procedure of Buchwald.[7] Reaction of the aryl triflate **2** with one equivalent of the arylamine **3** in the presence of catalytic amounts of palladium(II) acetate and (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) and an excess of caesium



Scheme 3 Preparation of the arylamine **3**. *Reagents and conditions*: (i) $N_2H_4{\cdot}H_2O$, $FeCl_3$, activated carbon, MeOH, 65 °C, 12 h, 96%; (ii) 1. $NaNO_2$, H_2SO_4, 0 °C; 2. H_2SO_4, H_2O, Δ, 83%; (iii) MeI, KOH, DMSO, rt, 1 h, 91%; (iv) claycop, Ac_2O, CCl_4, rt, 2.5 h, 67%; (v) $N_2H_4{\cdot}H_2O$, $FeCl_3$, activated carbon, MeOH, 65 °C, 13 h, 91%.

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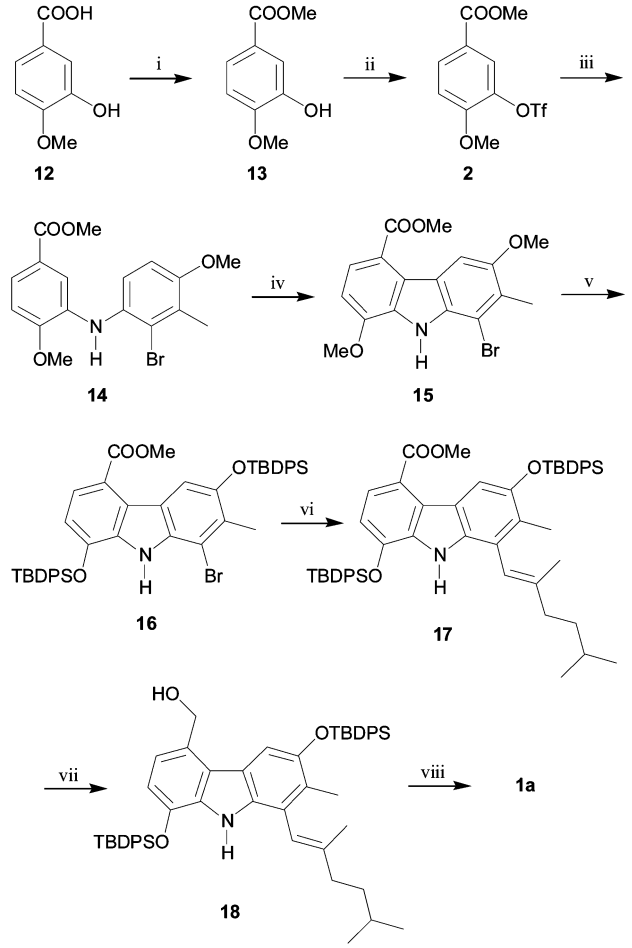

Scheme 4 Synthesis of carbazomadurin A (**1a**). *Reagents and conditions*: (i) MeOH, H_2SO_4, 65 °C, 16 h, 91%; (ii) 2,6-lutidine, Tf_2O, CH_2Cl_2, −10 °C to rt, 16 h, 100%; (iii) **3**, 5 mol % $Pd(OAc)_2$, 7.5 mol % BINAP, Cs_2CO_3, toluene, 100 °C, 10 h, 62%; (iv) $Pd(OAc)_2$, dioxane/HOAc (3:1), 100 °C, 40 h, 43%; (v) 1. BBr_3, CH_2Cl_2, −78 °C to rt, 5 d, 77%; 2. *t*$BuPh_2SiCl$, ImH, DMF, 70 °C, 19 h, 91%; (vi) **4**, 10 mol% $Pd(PPh_3)_4$, toluene, 110 °C, 67 h, 95%; (vii) DIBAL, toluene, 0 °C, 2 h, 100%; (viii) TBAF, THF, rt, 2 h, 70%.

carbonate as base afforded the diarylamine **14**. The application of alternative phosphane ligands, reported to be useful for the catalytic amination of aryl triflates even at room temperature,[9] surprisingly led only to the complete recovery of starting material. The palladium(II)-mediated oxidative cyclization[10] of the diarylamine **14** provided the carbazole **15**. By reoxidation of palladium(0) to palladium(II) with appropriate oxidizing agents the oxidative cyclization to carbazole derivatives becomes catalytic in palladium.[11–13] Preliminary studies have shown that this could also be achieved for the cyclization of **14**, however no further optimization was carried out at this stage. The conditions required for the cleavage of the two methyl ethers were not compatible with the trisubstituted double bond in the side chain of the carbazole. Therefore, we switched to the *tert*-butyldiphenylsilyl protecting group, which is stable and easily removed by fluoride ions.[14] Cleavage of both methyl ethers to the dihydroxycarbazole using an excess of boron tribromide followed by silylation gave the disilylether **16**. The palladium(0)-catalyzed Stille coupling[15] of the 1-bromocarbazole **16** with the vinylstannane **4** afforded almost quantitatively the 1-vinylcarbazole **17**. Reduction of **17** with diisobutylaluminium hydride (DIBAL) led quantitatively to the benzylic alcohol **18**. Cleavage of the silyl ethers using tetrabutylammonium fluoride (TBAF) provided carbazomadurin A (**1a**). The spectroscopic data (UV, IR, ^{1}H NMR, ^{13}C NMR and MS) of our product were in full agreement with those reported by Seto *et al.* for the natural product.[4]

In conclusion, the present synthesis provides carbazomadurin A (**1a**) in nine steps and 11% overall yield based on isovanillic acid (**12**). It demonstrates that the palladium-catalyzed sequence of Buchwald–Hartwig amination, oxidative cyclization and Stille coupling represents a very efficient and flexible approach, which can be readily utilized for the preparation of a wide range of synthetic analogues as required for a structure–activity study. This work is currently in progress in our laboratories and will be reported in due course.

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