First Total Synthesis and Assignment of the Absolute Configuration of the Neuronal Cell Protecting Alkaloid Carbazomadurin B

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Dedicated to Professor K. Peter C. Vollhardt on the occasion of his 60th birthday.

Abstract: Using a palladium-catalyzed approach, the first enantioselective synthesis of the neuronal cell protecting agent carbazomadurin B is described and its absolute configuration is assigned.

Key words: alkaloids, aminations, cross-coupling, cyclizations, palladium

Due to their useful pharmacological activities, carbazole alkaloids are continuing to attract strong interest by many research groups.[1–4] The carbazomadurins A (**1a**) and B (**1b**) have been isolated in 1997 by Seto and his group from the microorganism *Actinomadura madurae* 2808-SV1 (Figure 1).[5] These alkaloids exhibit a strong neuronal cell protecting activity against L-glutamate induced cell death. The observed biological effect is found to be dependent on their function as antioxidants.[5] The structures for both compounds have been assigned based on their spectroscopic data. However, the absolute configuration of carbazomadurin B (**1b**) has remained unknown. Herein, we describe the first enantioselective total synthesis of carbazomadurin B and the assignment of its absolute configuration.

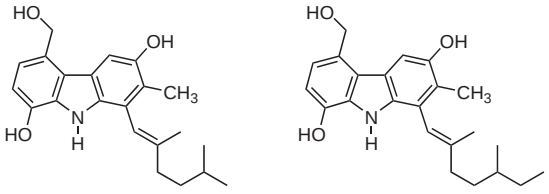
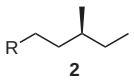


Figure 1 Carbazomadurins A and B

For a tentative assignment of the absolute configuration of carbazomadurin B (**1b**) we compared its specific rotation with values of related compounds given in the literature (Table 1). Lardicci reported the specific rotations for a series of chiral compounds **2** with a methyl, an ethyl and a 2-substituted ethyl group at the stereogenic center.[6] With an *S* configuration at the stereogenic center, they all show a positive value for the specific rotation as reported for carbazomadurin B (**1b**). The specific rotation reported by Seto for **1b** is: $[\alpha]_D^{24}$ +4 (*c* 0.05, MeOH). Compound **2c** with a double bond in the same distance to the stereogenic center as in **1b** has a specific rotation of $[\alpha]_D^{25}$ +10.30.[6] Although the absolute value of specific rotation reported for the natural product is much lower, they both have a positive value. Based on this comparison we proposed an *S* configuration for the stereogenic center of the chiral side chain of **1b**.

Table 1 Specific Rotations of (*S*)-Ethyl(methyl)(substituted-ethyl)methane Derivatives **2** and Comparison with Carbazomadurin B (**1b**)



2

Compound	R	$[\alpha]_D^{25,\ a}$
1b	$C(CH_3)$=CHAr	+4 (24 °C)[5]
2a	CH_3	+8.67
2b	CH_2CH_3	+9.34
2c	$CH=CH_2$	+10.30
2d	$CHBrCH_2Br$	+4.67
2e	C≡CH	+14.87
2f	$COCH_3$	+9.30
2g	COOH	+10.69

[a] Specific rotations of the compounds **2a**–**g** as reported in ref. 6.

We envisaged a highly convergent total synthesis of carbazomadurin B (**1b**) by sequential palladium-catalyzed cross-coupling reactions of three building blocks (Scheme 1).

The aryl triflate **3** is available from isovanillic acid (two steps, 91% yield).[4c] The arylamine **4** was prepared from 2-bromo-6-nitrotoluene (five steps, 44% yield).[4c] Assuming an *S* configuration for carbazomadurin B (**1b**), the synthesis of the chiral alkenylstannane **5** has been achieved in six steps and 11% overall yield starting from commercial (*S*)-(–)-2-methyl-1-butanol (**6**) (Scheme 2).

First, the commercial (*S*)-(–)-2-methyl-1-butanol (**6**)[7] was converted to the corresponding (*R*)-Mosher ester by reaction with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (pyridine–CCl_4, r.t., 3 h, 97% yield).[8] The

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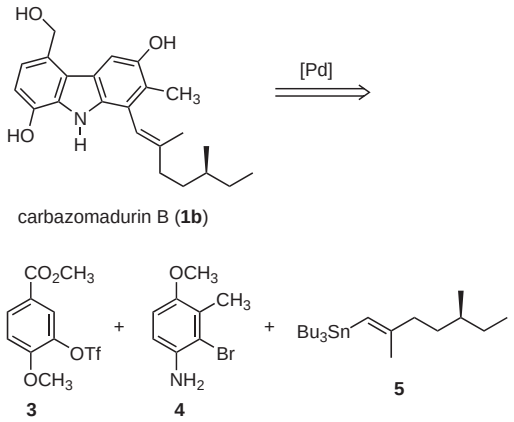
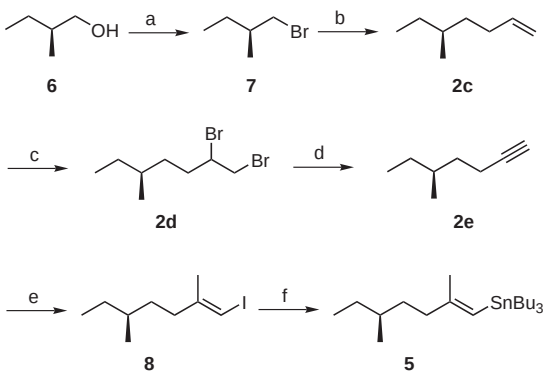
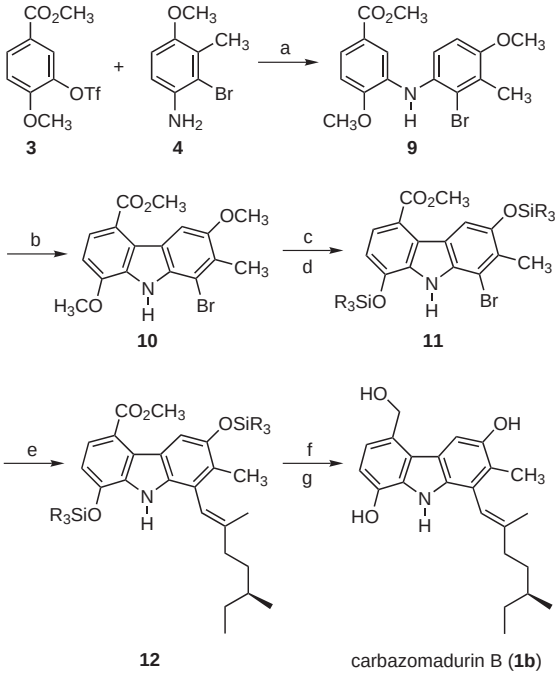


Scheme 1 Retrosynthetic analysis of carbazomadurin B (**1b**)

500 MHz ^{1}H NMR spectrum of the (*R*)-Mosher ester and doping with the corresponding diastereoisomeric Mosher esters resulting from racemic **6** confirmed an enantiomeric purity of >99% ee for our starting material. Substitution of the chiral alcohol **6** gave the bromide **7**.[9] Conversion of **7** to the Grignard reagent and Wurtz coupling with allyl bromide using a literature procedure[10] led to (*S*)-(+)-5-methyl-1-heptene (**2c**, $[\alpha]_D^{23}$ +10.1, neat). Subsequent bromination in chloroform at 0 °C afforded the dibromide **2d** as a 1:1 mixture of diastereoisomers $[\alpha]_D^{23}$ +5.9 (*c* 4.9, $CHCl_3$).[6] Double elimination of HBr from **2d** with potassium *tert*-butoxide in the presence of catalytic amounts of [18]-crown-6 provided (*S*)-(+)-5-methyl-1-heptyne (**2e**, $[\alpha]_D^{23}$ +15.3, *c* 5.1, $CHCl_3$). Using this method, no isomerization to allenes or internal alkynes occurs.[11] Moreover, it is known that the double dehydrobromination takes place without racemization,[6] which is confirmed by the specific rotation of **2e**. Transformation of the alkyne **2e** to the required alkenylstannane **5** was achieved by a two-step process using Negishi's zirconium-catalyzed carboalumination as the key step.[12] Reaction of **2e** with trimethylalane in the presence of zirconocene dichloride and subsequent treatment of the resulting alkenylaluminum with iodine led to the alkenyl iodide **8**. A halogen–metal exchange reaction using *tert*-butyllithium, followed by addition of tributyltin chloride to the alkenyllithium intermediate, afforded the alkenylstannane **5**.



Scheme 2 Synthesis of the alkenylstannane **5**. *Reagents and conditions*: a) PBr_3, pyridine, 0 °C to r.t., 2 h (63%); b) 1. Mg, Et_2O; 2. allyl bromide, r.t., 16 h (58%); c) Br_2, $CHCl_3$, 0 °C (93%); d) KO*t*-Bu, cat. [18]-crown-6, hexane, Δ, 3 h (69%); e) 1. Me_3Al, Cp_2ZrCl_2, CH_2Cl_2, r.t.; 2. I_2, THF, 0 °C (60%); f) 1. *t*-BuLi, Et_2O, –78 °C; 2. Bu_3SnCl, –78 °C to r.t. (78%).



Scheme 3 Synthesis of carbazomadurin B (**1b**). *Reagents and conditions*: a) 5 mol% $Pd(OAc)_2$, 7.5 mol% BINAP, Cs_2CO_3, toluene, 100 °C, 10 h (62%); b) $Pd(OAc)_2$, dioxane–HOAc (3:1), 100 °C, 40 h (43%); c) 5 equiv BBr_3, CH_2Cl_2, –78 °C to r.t., 5 d (77%); d) 5 equiv *t*-$BuPh_2SiCl$ (= R^3SiCl), 9 equiv imidazole, DMF, 70 °C, 19 h (91%); e) **5**, 10 mol% $Pd(PPh_3)_4$, toluene, 110 °C, 72 h (90%); f) DIBAL-H, toluene, 0 °C, 2 h (100%); g) TBAF, THF, r.t., 1.5 h (88%).

Coupling of the aryl triflate **3** and the arylamine **4** to the *N*,*N*-diarylamine **9** was achieved by a palladium(0)-catalyzed Buchwald–Hartwig amination (Scheme 3).[13] A subsequent palladium(II)-mediated oxidative cyclization[14] of **9** led to the carbazole **10**. Using an appropriate reoxidant, e.g. copper(II) acetate, this reaction can also be carried out using catalytic amounts of palladium(II).[15] Cleavage of both methyl ethers with boron tribromide followed by double silylation afforded the bis(*tert*-butyldiphenylsilyl) ether **11**.[16] Palladium(0)-catalyzed Stille coupling[17] of the 1-bromocarbazole **11** and the alkenylstannane **5** furnished the 1-alkenylcarbazole **12** in 90% yield. Reduction of the methyl ester using diisobutylaluminum hydride (DIBAL-H) to the corresponding benzylic alcohol and subsequent removal of the silyl protecting groups with tetrabutylammonium fluoride (TBAF) provided carbazomadurin B (**1b**). The spectroscopic data of our product (UV, IR, ^{1}H NMR, ^{13}C NMR and MS)[18] were in full agreement with those reported for the natural product by Seto and coworkers.[5] The value for the specific rotation of our synthetic carbazomadurin B is: $[\alpha]_D^{24}$ +13.0 (*c* 0.05, MeOH),[18] which confirms the absolute configuration to

be *S*, but is considerably higher than the one reported by Seto for the natural product: $[\alpha]_D^{24}$ +4 (*c* 0.05, MeOH).[5] An elemental analysis proved the high purity of our product.[18] On conversion to the chiral alkyne **2e** the enantiomeric purity of our chiral starting material **6** has been preserved (cf. above). Since racemization during the synthesis beyond compound **2e** is not feasible, an enantiomeric excess of >99% can be expected for **1b**.

In conclusion, using our palladium-catalyzed approach carbazomadurin B (**1b**) has been obtained in nine steps and 13% overall yield starting from commercial isovanillic acid. Based on the specific rotation, we assigned an *S* configuration to the stereogenic center of the natural product.

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(18) Carbazomadurin B (**1b**): light-yellow crystals, mp 165 °C (dec.). $[\alpha]_D^{24}$ +13.0 (*c* 0.05, MeOH); $[\alpha]_D^{19}$ +16.8 (*c* 0.37, MeOH). UV (MeOH): λ = 237, 249 (sh), 289 (sh), 299, 347, 356 nm. UV (MeOH, NaOH): λ = 236, 257, 303, 363 nm. IR (KBr): ν = 3477, 3431, 2959, 2929, 2873, 1618, 1584, 1524, 1426, 1377, 1269, 1168, 1075, 972, 819 cm^{-1}. ^1H NMR (500 MHz, acetone-d_6): δ = 0.94 (t, *J* = 7.3 Hz, 3 H), 0.99 (dd, *J* = 6.3, 5.4 Hz, 3 H), 1.22–1.28 (m, 1 H), 1.42–1.53 (m, 3 H), 1.57 (d, *J* = 1.1 Hz, 3 H), 1.67–1.73 (m, 1 H), 2.27 (s, 3 H), 2.30–2.42 (m, 2 H), 3.93 (br s, 1 H), 5.02 (s, 2 H), 6.44 (s, 1 H), 6.73 (d, *J* = 7.7 Hz, 1 H), 6.92 (d, *J* = 7.7 Hz, 1 H), 7.60 (s, 1 H), 7.79 (br s, 1 H), 8.40 (br s, 1 H), 8.87 (br s, 1 H). ^{13}C NMR and DEPT (125 MHz, acetone-d_6): δ = 11.36 (CH_3), 13.22 (CH_3), 17.65 (CH_3), 19.11 (CH_3), 29.70 (CH_2), 34.65 (CH), 35.30 (CH_2), 37.14 (CH_2), 63.49 (CH_2), 106.70 (CH), 109.34 (CH), 118.61 (CH), 120.12 (CH), 121.14 (C), 122.08 (C), 122.14 (C), 123.29 (C), 128.13 (C), 130.21 (C), 133.37 (C), 142.47 (C), 142.62 (C), 149.63 (C). MS (EI): *m/z* (%) = 367 (73) [M^+], 366 (10), 365 (27), 351 (100), 349 (11). HRMS: *m/z* calcd for $C_{23}H_{29}NO_3$ [M^+]: 367.2147; found: 367.2157. Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.12; H, 7.99; N, 3.57.