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A novel total synthesis of the bioactive poly-substituted carbazole alkaloid carbazomadurin A

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ABSTRACT

A new total synthesis of the neuronal cell-protecting carbazole alkaloid carbazomadurin A is described. The key step was an allene-mediated electrocyclic reaction involving an indole [*b*]-bond for the construction of a highly substituted carbazole ring. The *E*-alkenyl side chain at the C1 position of carbazole was introduced between *O*-triflate and alkenyl pinacol borate using the Suzuki–Miyaura reaction. SEM groups were cleaved with TBAF and the formyl group was reduced to provide carbazomadurin A.

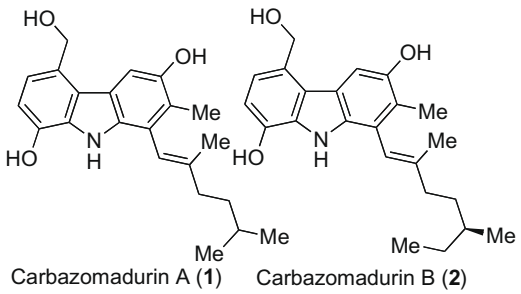
1. Introduction

Naturally occurring carbazoles are very attractive compounds because of their antioxidant activity.[1] The neuronal cell-protecting carbazole alkaloids carbazomadurins A (**1**) and B (**2**) were isolated in 1997 from the microorganism *Actinomadura madurae* 2808-SV1 by Seto and co-workers (Fig. 1).[2] The structures of both compounds except the absolute configuration for **2** were assigned based on their spectroscopic data. These compounds protect against glutamate toxicity in neuronal hybridoma N18-RE-105 cells as an in vitro ischemia model. The Knölker group achieved the first total syntheses of carbazomadurin A (**1**)[3] and B (**2**)[4] by constructing a suitable carbazole framework based on a palladium-catalyzed sequence of the Buchwald–Hartwig amination, followed by oxidative cyclization and subsequent introduction of the alkenyl group at the C1 position using the Stille coupling reaction. In their first total synthesis, the Knölker group has also assigned the absolute configuration for **2**, which was shown to have an *S*-configuration at the stereogenic center.[4]

We are interested in the synthesis of bioactive condensed heterocyclic compounds including natural products, based on a thermal electrocyclic reaction strategy with either a 6π-electron system or an aza 6π-electron system incorporating an aromatic or heteroaromatic double bond.[5–7] In the course of our studies focusing on the development of a thermal electrocyclic reaction of a 6π-electron system including an allene intermediate,[5,7] we achieved a new total synthesis of a highly functionalized carbazole alkaloid, carbazomadurin A (**1**). Our synthetic strategy of carbazomadurin A (**1**) is outlined in Scheme 1, where a 1,3,8-trioxygenated carbazole framework of **1** is obtained from 2-allenylindole intermediate **5** generated from 2-propargylindole **6**. We also hypothesized that an alkenyl side chain with an *E* configuration at the C1 position of **1** might be introduced by the Suzuki–Miyaura reaction[8] using alkenyl pinacol borate **4**.

2. Results and discussion

We initially attempted a synthesis of the required 7-oxygenated 2,3,4,7-tetrasubstituted indole **13** from the known ethyl 7-isopropoxyindole-2-carboxylate (**7**)[9] as shown in Scheme 2. Treatment of **7** with α,α-dichloromethyl methyl ether in the presence of $TiCl_4$ at −40 °C[10] for 4 h gave 4-formylindole **8**. The formyl group of **8**



Carbazomadurin A (**1**) Carbazomadurin B (**2**)

Figure 1.

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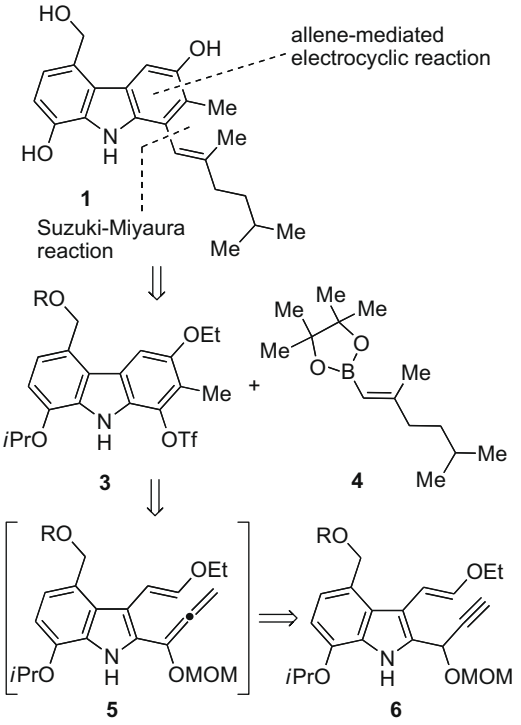
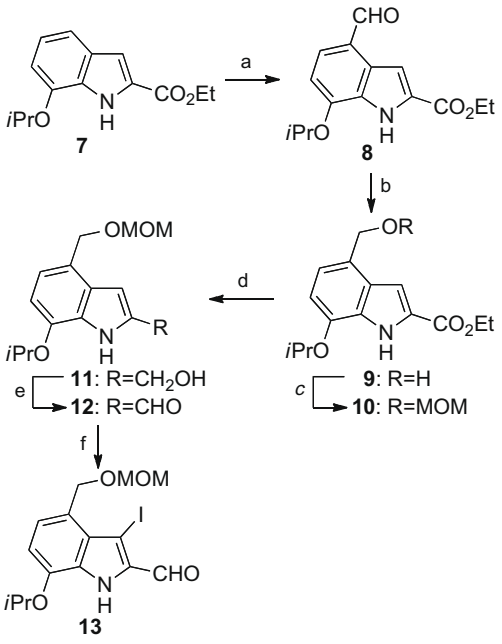
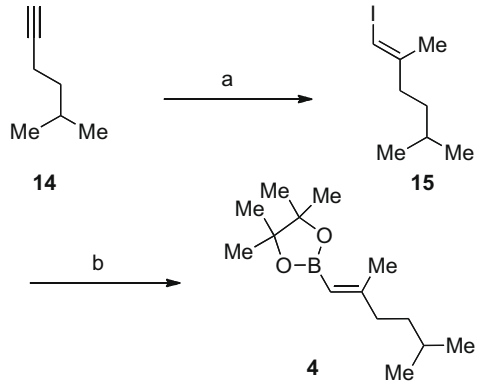


Scheme 1.



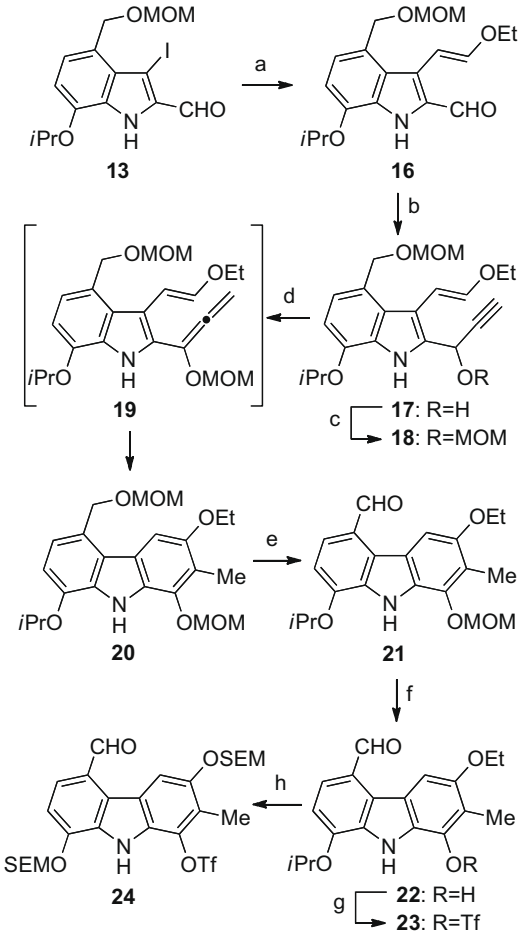
Scheme 2. Reagents and conditions: (a) CH_3OCHCl_2 1 M $TiCl_4$, CH_2Cl_2, −40 °C, 4 h, 86%; (b) $NaBH_4$, EtOH, 0 °C, 5 h, 99%; (c) MOMCl, iPr_2NEt, CH_2Cl_2, 0 °C to rt, 48 h, 86%; (d) 65% Red-Al, toluene, 0 °C, 3 h, 99%; (e) MnO_2, CH_2Cl_2, rt, 12 h, 84%; (f) KOH, I_2, DMF, 0 °C, 12 h, 94%.

was subsequently reduced to a hydroxymethyl group with $NaBH_4$, which was treated with MOMCl in the presence of *N*,*N*-diisopropylethylamine (iPr_2NEt) to yield MOM-ether **10**. Reduction of the ester moiety of **10** by Red-Al, followed by oxidation of the resulting alcohol by MnO_2 afforded the indole-2-carboxaldehyde **12**. Further treatment of **12** with I_2 in the presence of KOH gave the 7-oxygenated 2,3,4,7-tetrasubstituted indole **13** in six-steps.



Scheme 3. Reagents and conditions: (a) (1) Me_3Al, Cp_2ZrCl_2, 1,2-dichloroethane, rt, 12 h; (2) I_2, THF, 0 °C to rt, 1 h, 78%; (b) bis(pinacolato)diboron, AcOK, $PdCl_2$(dppf), DMSO, 80 °C, 1 h, 48%.

On the other hand, a pinacol borate **4** to introduce an alkenyl side chain with an *E* configuration at the C1 of carbazomadurin A (**1**) was prepared from 5-methyl-1-hexyne (**14**) in three steps as follows (Scheme 3). Zirconium-catalyzed carboalumination of 5-methyl-1-hexyne (**14**) with trimethylaluminum in the presence

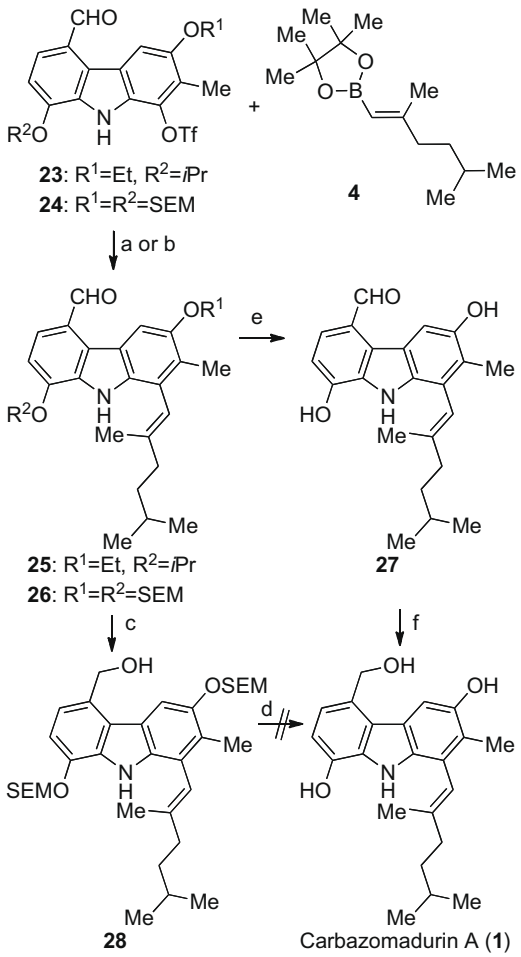


Scheme 4. Reagents and conditions: (a) ethoxyvinylstannane, $PdCl_2(PPh_3)_2$, Et_4NCl, DMF, 80 °C, 2 h, 86%; (b) ethynylmagnesium bromide, THF, 0 °C, 1 h, 81%; (c) MOMCl, iPr_2NEt, CH_2Cl_2, 50 °C, 12 h, 81%; (d) TBAF, THF, 80 °C, 6 h, 40%; (e) DDQ, CH_2Cl_2, rt, 20 min, 73%; (f) 4 M HCl, ethylene glycol, THF, 50 °C, 30 min, 91%; (g) $PhNTf_2$, NaH, THF, 0 °C, 30 min, 99%; (h) (1) BBr_3, CH_2Cl_2, −78 °C to rt, 3 h; (2) SEMCl, iPr_2NEt, CH_2Cl_2, 0 °C to rt, 12 h, 97% (two steps).

of zirconocene dichloride as reported by Negishi,[11] followed by the addition of I_2 afforded the *E*-alkenyl iodide **15**[3] in moderate yield. Subsequently, the Suzuki–Miyaura reaction[8,12] of **15** with bis(pinacolato)diboron in the presence of $PdCl_2$(dppf) afforded the pinacol borate **4** in 48% yield.

We then synthesized 1,3,8-trioxygenated 1,2,3,5,8-pentasubstituted carbazoles **23** and **24** from the 2,3,4,7-tetrasubstituted indole **13** (Scheme 4). A Stille coupling reaction of 3-iodoindole **13** with 2-ethoxyvinylstannane[13] in the presence of $PdCl_2(PPh_3)_2$ gave the 3-alkenylindole **16** in good yield. Grignard reaction of **16** with ethynylmagnesium bromide, followed by treatment of the resulting alcohol **17** with MOMCl and *i*Pr_2NEt produced the *O*-MOM-propargyl ether **18** in good yield. We subsequently attempted to construct a poly-functionalized carbazole framework **20** that was equivalent to **3**, using an allene-mediated electrocyclic reaction as a key step. When the *O*-MOM-propargyl ether **18** was heated at 90 °C in the presence of potassium *tert*-butoxide in *tert*-butyl alcohol according to the previously reported method[7] for allene generation, the expected carbazole **20** was not detected. Alternatively, treatment of **18** with TBAF in THF according to another reported method[7b] afforded the required carbazole **20** in somewhat low yield (40%). Oxidation of the *O*-MOM-methyl group[14] at the C-5 of **20** with DDQ provided the 5-formylcarbazole **21**, which was treated with 4 M HCl in the presence of ethylene glycol in THF to yield the 1-hydroxycarbazole **22**. Sequential treatment of **22** with *N*-phenylbis(trifluoromethanesulfonimide) ($PhNTf_2$) gave the corresponding triflate **23**. Cleavage of ethyl and isopropyl ethers of **23** with BBr_3 afforded the 3,8-dihydroxycarbazole, which was immediately protected with SEMCl and *i*Pr_2NEt to produce the 3,8-bis-*O*-SEM-carbazole **24**.

Carbon–carbon bond formations of two kinds of triflates **23** and **24** with the alkenyl pinacol borate **4** were then investigated (Scheme 5). The Suzuki–Miyaura cross-coupling reaction[12] of **23** with **4** in the presence of Na_2CO_3 and $Pd(PPh_3)_4$ gave the 1-alkenylcarbazole **25** in an excellent yield. In the case of cross-coupling **24** with **4**, the coupling reaction proceeded smoothly in the presence of aqueous Na_2CO_3 and $Pd(PPh_3)_4$ to give **26** in good yield. Although, removal of the ethyl and isopropyl ethers of **25** with BBr_3 was attempted, the conversion to the corresponding **27** failed. By contrast, reduction of the formyl group of **26** with DIBAL gave the 5-hydroxymethylcarbazole **28** in good yield. Cleavage of both SEM groups of **28** using TBAF in THF did not provide carbazomadurin A (**1**). As a result, removal of both SEM groups[15] of **26** with TBAF in HMPA gave the expected dihydroxycarbazole **27**. Finally, reduction of **27** with $NaBH_4$ in methanol afforded carbazomadurin A (**1**). The physical and spectroscopic data[16] of our synthetic carbazomadurin A (**1**) were identical with those of reported data.[2,3]



Scheme 5. Reagents and conditions: (a) $Pd(PPh_3)_4$, Na_2CO_3, DMF, 80 °C, 5 h, 99%; (b) $Pd(PPh_3)_4$, 3 M Na_2CO_3 aq., DMF, 70 °C, 2 h, 86%; (c) DIBAL-H, toluene, 0 °C, 1 h, 90%; (d) TBAF, THF, 80 °C, 1 h; (e) TBAF, HMPA, 100 °C, 1 h, 71%; (f) $NaBH_4$, MeOH, rt, 5 min, 70%.

3. Conclusions

The preparation of 2,3,4,7-tetrasubstituted indole **13** for the synthesis of poly-functionalized carbazoles **23** and **24** was achieved from **7** in a six-step sequence. An allene-mediated electrocyclic reaction of the propargyl ether **18** afforded the appropriate substituted carbazole **20**, which led to the desired carbazoles **23** and **24**. Introduction of the alkenyl side chain to the C1 position of carbazole *O*-triflates **23** and **24** was successfully achieved by the Suzuki–Miyaura cross-coupling reaction using alkenyl pinacol borate **4**. Carbazomadurin A (**1**) was obtained from the 3,8-*O*-bisSEM carbazole **26** in two steps. Thus a new total synthesis of carbazomadurin A (**1**) was completed in two key steps by a synthesis of the suitable substituted carbazole, based on an allene-mediated electrocyclic reaction of a 6π-electron system involving an indole [*b*]-bond and then the Suzuki–Miyaura reaction. This synthetic strategy is applicable for a series of other functionalized carbazole alkaloids.

Acknowledgment

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16. *Data of carbazomadurin A* (**1**): mp 166.5–168.5 °C; IR (ATR) ν: 3480, 3420, 1640, 1580, 1430, 1370 cm^{-1}. ^1H NMR (300 MHz, acetone-d_6) δ: 8.56 (1H, br s), 8.37 (1H, br s), 7.77 (1H, br s), 7.57 (1H, s), 6.90 (1H, d, J = 7.7 Hz), 6.71 (1H, d, J = 7.7 Hz), 6.41 (1H, s), 5.01 (2H, s), 3.90 (1H, br s), 2.33 (2H, t, J = 7.7 Hz), 2.26 (3H, s), 1.64–1.73 (1H, m), 1.50–1.57 (5H, m), 0.99 (6H, d, J = 6.6 Hz). ^{13}C NMR (75 MHz, acetone-d_6) δ: 149.9, 142.9, 142.7, 133.5, 130.3, 128.1, 123.4, 122.4, 122.3, 121.3, 120.3, 118.8, 109.6, 106.8, 64.0, 38.0, 37.7, 29.0, 22.8 (2C), 17.9, 13.5. MS m/z: 353 (M^+). HR-MS (EI) m/z: 353.1975 (M^+) (calcd for $C_{22}H_{27}NO_3$: 353.1991).