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An Entry to the Azocino[4,3-*b*]indole Framework through a Dehydrogenative Activation of 1,2,3,4-Tetrahydrocarbazoles Mediated by DDQ: Formal Synthesis of (±)-Uleine

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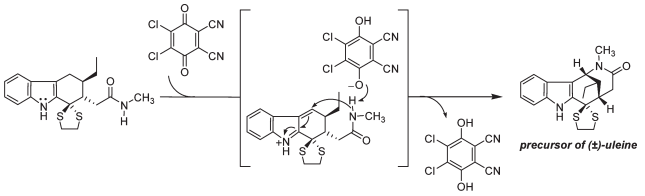

It is presented that hexahydro-1,5-methano[4,3-*b*]indoles were efficiently synthesized in high yields (up to 89% yield) through the cyclization reaction of starting tetrahydrocarbazoles bearing a monoalkylaminocarbonylmethyl moiety at the C-2 position mediated by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). A mechanistic proposal is also given that mainly includes two cascade reactions: (i) formation of a vinylogous iminium cation via DDQ-mediated dehydrogenation of tetrahydrocarbazole functionality and (ii) *intra*-molecular and *syn*-selective addition of the amide functionality as the nucleophile to the vinylogous iminium cation. Furthermore, this cyclization reaction was successfully utilized in the formal total synthesis of (±)-uleine, an Aspidospermatan skeletal type alkaloid.

Efficient and atom-economic total synthesis of complex molecules is a great endeavor in organic synthesis.[1] Consequently, applications of new (catalytic) reactions in total synthesis are of particular interest for demonstrating their efficiency and generality. Uleine-type indole alkaloids (e.g., **1**−**4**) constitute an important subgroup of the *Strychnos* alkaloids. The 1,5-methanoazocino[4,3-*b*]indole moiety bearing an ethyl chain at the bridge carbon atom is the common key structure of the uleine alkaloids (Figure 1). On the other hand, azocino[4,3-*b*]indole and azocino[4,3-*b*]indoline skeletons are also found as the key elements in other

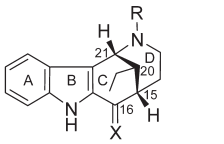

FIGURE 1. Structure of uleine-type alkaloids.

Strychnos alkaloids, such as strychnine, akuammicine, tubifolidine, etc.[2] A rather large number of synthetic pathways have been developed for the construction of the azocino[4,3-*b*]-indole skeleton so far. The majority of the reported methods for the synthesis of these tetracyclic ring systems start either from 2-(4-piperidinylmethyl)indole,[3] 3-(2-piperidinylmethyl)-indole,[4] or Fisher indolization of 2-azabicyclo[3.3.1]nonane.[5] There also have been a few reports for the building of the D-ring from tetrahydrocarbazole derivatives in quite different ways.[6,7] Recently, we reported the synthesis of

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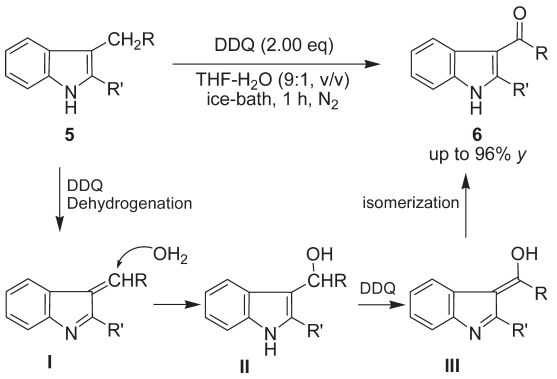
SCHEME 1. Selective Oxidation of the Side Chain at C-3 of Indoles by DDQ[10]



azocino[4,3-*b*]indole skeleton via acid-catalyzed D-ring cyclization of an appropriate 4-oxo-1,2,3,4-tetrahydrocarbazole derivative.[8] In our former studies, we had also shown that azocino[4,3-*b*]indoles can be formed from 4-amino-1-oxo-1,2,3,4-tetrahydrocarbazoles.[9] In conjunction with our ineterest in the synthesis of indole-type alkaloids, we focused our attention on the facile and efficient construction of the azocino[4,3-*b*]indole skeleton toward the synthesis of uleine (**1**). We herein present a 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)-mediated cyclization reaction of tetrahydrocarbazoles bearing monosubstituted amide side chains that makes the corresponding azocino[4,3-*b*]indole derivatives efficiently accessible. Furthermore, we have also demonstrated the efficiency of this new cyclization method in the formal synthesis of (±)-uleine (*rac*-**1**).

In 1977, Oikawa and Yonemitsu reported that 2,3-disubstituted indole derivatives such as **5** can be selectively oxidized at C-3 side chain by treatment with 2.00 equiv of DDQ in the presence of H_2O (Scheme 1).[10] A number of corresponding keto products **6** could be conveniently prepared by employing this procedure (up to 96% yield). According to the proposed mechanism as depicted in Scheme 1, four consecutive reactions take place during the DDQ-mediated oxidation of 3-alkyl-substituted indole derivatives (**5**) giving keto products (**6**): DDQ can first dehydrogenate the indole derivative **5** to form the imine intermediate **I**, which can then add one H_2O molecule to form the corresponding hydroxy intermediate **II**, then the hydroxy intermediate **II** can be dehydrogenated to form the enol intermediate **III**, which can finally isomerize to furnish the keto product **6**. The chemistry developed by Oikawa and Yonemitsu, that is the DDQ-mediated dehydrogenative imine formation from 3-alkyl-substituted indoles, was also utilized in the asymmetric synthesis of (−)-tubifolidine,[11a] (−)-19,20-dihydroakuammicine,[11b] and (+)-ajmaline,[11c] as well as gardnutine.[11d] Very recently, an enantioselective oxidative cross-coupling reaction of 3-indolylmethyl C−H bonds with 1,3-dicarbonyls mediated by DDQ was published.[12]

Inspired by the dehydrogenative imine generation from indole derivatives by DDQ that was originally developed by Oikawa and Yonemitsu,[10] we discussed that imine intermediate could also be able to add amide nucleophiles. Thus, azocino[4,3-*b*]indoles such as **10a**−**d** could be easily synthesized by treating the tetrahydrocarbazole-amide derivatives **9a**−**d** with DDQ (Scheme 2). For this purpose, the tetrahydrocarbazole-amide derivatives **9a**−**d** were first prepared in high yields from the carboxylic acid **8** by reacting it with an appropriate amine in the presence of ethyl chloroformate as the coupling reagent. Next, our attention was focused on the construction of azocino[4,3-*b*]indole skeletons **10a**−**d** from the tetrahydrocarbazole derivatives **9a**−**d** by reacting them with DDQ (Scheme 2). Fortunately, treatment of the amides **9a**−**d** with DDQ at room temperature in THF under strictly anhydrous conditions afforded the formation of the target tetracyclic compounds **10a**−**d**. In this way, the azocino[4,3-*b*]-indole skeletons **10a**−**d** could be obtained in high yields (up to 89% yield) within 3 h under mild reaction conditions. An X-ray single crystal analysis of **10c** confirmed the expected structure.[13]

Our next goal was to extend this procedure to the formal total synthesis of the natural product (±)-uleine (Scheme 3). For this purpose, the 4-oxo-tetrahydrocarbazole **11**[8a] with an amide side chain was selectively reduced to the corresponding tetrahydrocarbazole **12**. It is noteworthy that the amide side chain of the 4-oxo-tetrahydrocarbazole **11** remained intact while the 4-oxo functionality of **11** was *chemo*-selectively transformed to the dihydro-functionality.[14] Then, the tetrahydrocarbazole **12** was converted into the tetracyclic hexahydro-1,5-methanoazocino[4,3-*b*]indole system **13**, which was used as a precursor for the total synthesis of (±)-uleine (*rac*-**1**) in our previous report.[8c] The spectral data of compound **13** were found to be identical with those reported in the literature.[8c]

According to our tentatively proposed reaction mechanism as illustrated in Scheme 4, the formation of the vinylogous iminium cation **VI** in turn seems to be unequivocal. However, for the DDQ-mediated dehydrogenation pathway of the tetrahydrocarbazole **12** generating **VI** there are several possible reaction mechanisms, e.g. single electron transfer (SET) and direct hydride transfer (DHT) mechanisms.[12,15] Although further studies, such as ESR studies, are needed to elucidate the reaction mechanism more accurately we are expecting a SET governed mechanism for the formation of the iminium cation **VI** since DDQ most frequently oxidize substrates via the SET mechanism.[15,16] On the other hand, the phenoxide anion **VII** can act as a *Brønsted*-base to drive the *syn*-selective cyclization to completion of the reaction

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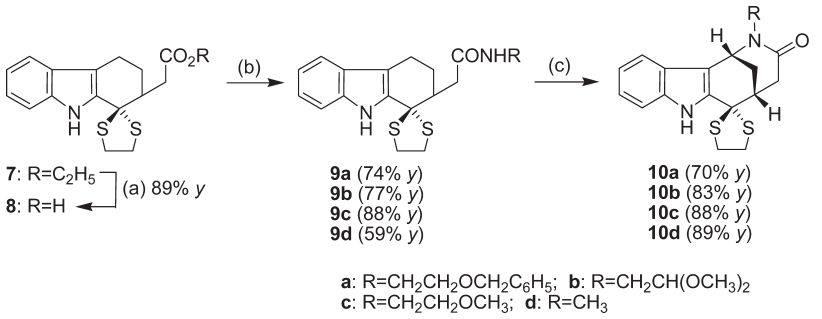
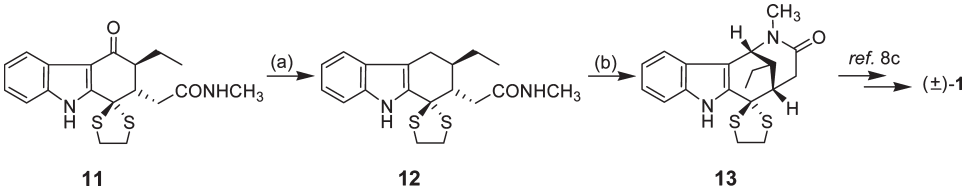
SCHEME 2. Preparation of the Tetrahydrocarbazole-Amide Derivatives 9a−d and the DDQ-Mediated Cyclization Thereof Yielding the Azocino[4,3-*b*]indole Derivatives 10a−d[a]



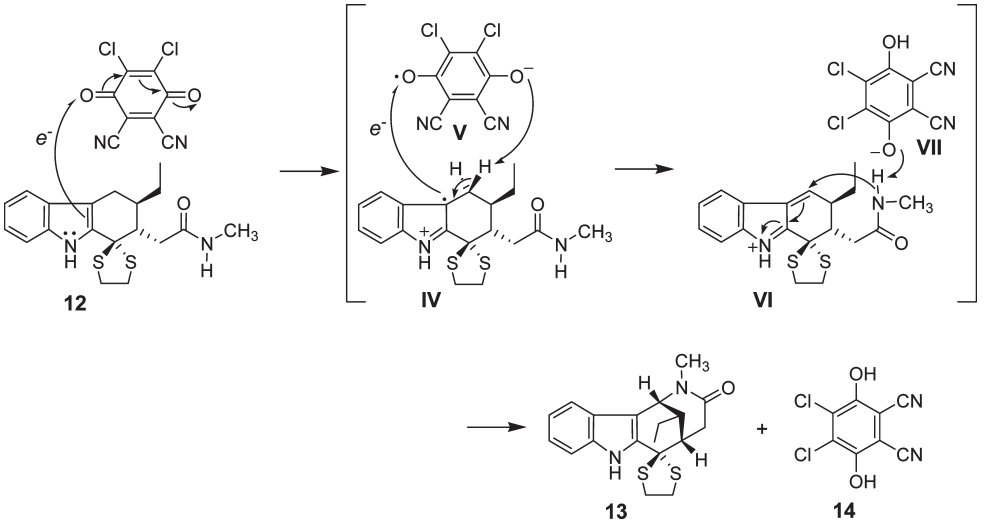
[a]Reagents and conditions: (a) (1) KOH, H_2O-MeOH-THF, rt, 5 h, (2) HCl; (b) (1) Et_3N (1.50 equiv), EtOCOCl (1.50 equiv), −5 °C, 5 h, $CHCl_3$, (2) RNH_2 (3.00 equiv), −5 °C, 3 h; (c) DDQ (1.20 equiv), THF, rt, 3 h, N_2.

SCHEME 3. Formal Synthesis of (±)-Uleine (*rac*-1)[a]



[a]Reagents and conditions: (a) BH_3·pyridine, HCl (20%), EtOH, 0 °C→rt, overnight, 75%; (b) DDQ (1.20 equiv), THF, rt, 3 h, 83%.

SCHEME 4. Tentative Mechanism for the DDQ-Mediated Cyclization of Tetrahydrocarbazoles Bearing a Monosubstituted Amide Side Chain



and 2,3-dichloro-5,6-dicyanohydroquinone (**14**) is formed as a side product subsequently.

We have shown that tetracyclic hexahydro-1,5-methano-[4,3-*b*]indole derivatives could be obtained by reacting an appropriate tetrahydrocarbazole derivative carrying a monosubstituted amide side chain with DDQ. The reaction mechanism likely proceeded through formation of a vinylogous iminium cation, which was formed from dehydrogenation of the tetrahydrocarbazole moiety by DDQ, followed by *intra*-molecular and *syn*-selective addition of the amide nucleophile to the vinylogous iminium cation. Furthermore, we have also successfully demostrated the feasibility of this cyclization reaction in the formal total synthesis of (±)-uleine,[8c] an Aspidospermatan skeletal-type alkaloid. Application of this strategy toward the synthesis of other alkaloids bearing azocino[4,3-*b*]indole moiety is underway in our laboratory.

Experimental Section

Tetrahydrofuran (THF) was freshly distilled under N_2 from sodium/benzophenone immediately prior to use. Chloroform ($CHCl_3$) and triethylamine (Et_3N) were distilled under N_2 from calcium hydride (CaH_2). All synthetic compounds are in their racemic form. 2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ),

ethyl chloroformate, and the amines, which were used for the preparation of the amides **10a**−**d**, were purchased from commercial suppliers and used as received. All melting points were determined in an open glass capillary tube and values are uncorrected. Infrared (FT-IR) spectra were recorded on a FT-IR spectrometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^1H and ^{13}C NMR spectra were recorded on a NMR spectrometer (500 MHz). Chemical shifts, δ, are reported in parts per million (ppm) relative to the residual protons in the NMR solvent ($CHCl_3$: δ 7.24; DMSO-d_6: δ 2.50) and carbon resonance of the solvent ($CDCl_3$: δ 77.00; DMSO-d_6: δ 39.43). NMR peak multiplicities were given as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Mass spectra were recorded on a gas chromatograph with mass sensitive detector (EI, 70 eV). High-resolution electrospray ionization mass spectra (HR-ESI-MS) were obtained with MeOH. Elemental analyses (EA) were performed with an elemental analyzer instrument.

12-Ethyl-2-methyl-6,6-ethylenedithio-1,2,3,4,5,6-hexahydro-1,5-methanoazacino[4,3-*b*]indole-3-one (13) (representative procedure for DDQ-mediated cyclization). Amide **12** (1.00 g, 2.77 mmol) was placed in a 50 mL oven-dried round-bottomed Schlenk flask and dissolved in 20 mL of absolute THF under an atmosphere of dry N_2. DDQ (0.75 g, 3.30 mmol) was added in one portion and the resulting reaction mixture was stirred at rt for 3 h under N_2. After the reaction mixture was quenched with 10% NaOH solution (50 mL), the mixture was extracted with EtOAc (100 mL). The separated organic layer was dried over Na_2SO_4. After all volatile components were removed by rotary evaporation in vacuo, the residue was first purified by silica gel column chromatography eluting with EtOAc/acetone/Et_3N (75:25:7). Combined fractions containing the lactam **13** were then concentrated by rotary evaporation in vacuo, crystallization of which from Et_2O/EtOAc (1:2) yielded 0.82 g (2.29 mmol, 83%) of the title compound (**13**) as a white solid. Mp 208 °C; R_f 0.76 (silica gel; EtOAc/acetone/Et_3N, 75:25:7); FT-IR (KBr) ν_{max} (cm^{-1}) 3434 (br s), 3213 (br m), 3060 (w), 2964 (m), 2925 (m), 1623 (s), 1492 (w), 1455 (s), 1394 (m), 1314 (w), 1276 (w), 1239 (m), 1196 (w), 1161 (w), 1092 (m), 1012 (w), 963 (w), 790 (m), 741 (s), 708 (m), 661 (w), 581 (w), 571 (w), 530 (w); ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (t, J = 7.3 Hz, 3H), 1.38−1.46 (m, 1H), 1.67−1.74 (m, 1H), 2.48 (t, J = 7.4 Hz, 1H), 2.71−2.80 (m, 2H), 3.00 (s, 3H), 3.25−3.37 (m, 3H), 3.42−3.53 (m, 2H), 4.32 (d, J = 1.4 Hz, 1H), 7.05 (td, J = 7.6 Hz, J = 0.9 Hz, 1H), 7.13 (td, J = 7.6 Hz, J = 0.9 Hz, 1H), 7.26 (d, J = 8.1 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 8.30 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.7 (q), 24.4 (t), 34.5 (q), 39.7 (t), 40.2 (t), 41.2 (t), 44.9 (d), 46.1 (d), 53.8 (d), 66.9 (s), 111.4 (d), 113.3 (s), 118.4 (d), 120.2 (d), 123.1 (d), 126.4 (s), 132.9 (s), 136.4 (s), 169.4 (s); HR-MS (ESI+) calcd for $C_{19}H_{23}N_2OS_2$ ($[M + H]^+$) 359.1252, found 359.1254. Elemental Anal. Calcd for $C_{19}H_{22}N_2OS_2$: C, 63.65; H, 6.19; N, 7.81. Found: C, 63.63; H, 6.17; N, 7.78.

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Supporting Information Available: Experimental procedures and characterization data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.