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A NEW APPROACH TO THE TOTAL SYNTHESIS OF (±)-NORDASYCARPIDONE BY RING-CLOSURE WITH TETRACHLORO-1,4-BENZOQUINONE

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A new synthetic route for the (±)-nordasycarpidone was achieved in five steps with an overall yield of 41 %. This route involves ring closure and formation of **5** which has a methanoazocino[4,3-*b*]indole skeleton in the key step. The reaction also involved a cyclization reaction of tetrahydrocarbazole with a monoalkyl nitrile side chain at the C-2 position, and this reaction was mediated by tetrachloro-1,4-benzoquinone (TCB). The central step in the synthesis was the closure of the D-ring of the intra-molecular structure and the addition of amine, which resulted in an aza-tetracyclic substructure that contained the ABCD-ring of the *strychnos* alkaloid family.

Keywords: dasycarpidone; uleine; nordasycarpidone; 1,5-methanoazacino[4,3-*b*]indole

НОВ ПРИОД КОН ЦЕЛОСНАТА СИНТЕЗА НА (±)-НОРДАСИКАРПИДОН ПО ПАТ НА ЗАТВОРАЊЕ НА ПРСТЕН НА ТЕТРАХЛОРО-1,4-БЕНЗОХИНОН

Постигнат е нов начин за синтеза на (±)-нордасикарпидон во пет чекори со вкупен принос од 41 %. Оваа постапка во клучниот чекор вклучува затворање на прстен и образување на **5** што има метаноазоцино[4,3-*b*]индолски скелет. Реакцијата исто така вклучува реакција на циклизација на тетрахидрокарбазол со моноалкил-нитрилска споредна низа на положба C-2. Во оваа реакција како медијатор беше искористен 1,4-бензохинон (TCB). Централниот чекор на синтезата е затворање на D-прстенот во интрамолекулската структура и адицијата на амин, што резултира во аза-тетрациклична структура што го содржи ABCD-прстенот од алкалоидната фамилија *strychnos.*

Клучни зборови: дасикарпидон; улеин; нордасикарпадон; 1,5-метаноазацино[4,3-*b*]индол

1. INTRODUCTION

Nordasycarpidone represents a class of the strychos alkaloids, and these, alkaloids are characterized by a methanoazocino[4,3-*b*]indole core structure. Nordasycarpidone is a four-member, cyclic amine that is fused to an indole ring, and it has scaffolds that can be found in various synthetic and natural products that have important biological activities [1–5]. The subsequent structural modifications of nordasycarpidone led to a wide range of biological properties that established them as beneficial in analgesic, anti-inflammatory, bactericidal, anti–malarial applications [6, 7]. Most of modifications start with the A-ring and the heterocyclic skeleton, and the B- and C-rings are closed in the subsequent processing [8, 9]. This occurs in spite of the construction a significant number of D-rings from the tetrahydrocarbazole derivatives via an acid catalyst and the DDQ-mediated ring closure, as reported previously [10, 11]. Inspired by the results of our work, we used different strategies, and developed a new method, that involved an intramolecular strategy for the cyclization process as the key step. In this paper, we describe a synthetic route utilizing tetrahydrocarbazole, which has a nitrile chain that serves as a key

intermediate for the total synthesis of nordasycarpidone. However, the construction of medium-sized rings by organic synthesis is notoriously diffucult. However, these rings are valuable for the construction of tetracyclic strychnos alkaloids, and Figure 1 shows some representative examples of the synthesis of strychnos-related natural alkaloids, including nordasycarpidone and others. Numerous reports have been published concerning the development of the ingenious total synthesis of nordasycarpidone [1–5], dasycarpidone [12–14], and ulenine [15, 16].

The usefulness of the synthetic methods for constructing the desired valuable intermediates is important, as is increasing the percentage yield in these methods. It is important to note that, methanoazocino[4,3-*b*] skeletons are the framework within all of the alkaloids, and this has prompted the more general development of the approach [17]. In this paper, we describe an efficient strategy for the synthesis of nordasycarpidone (**6**, Scheme 1), and the strategy is based on the expansion of the six-atom from 3-ethyl-2,3,4,9-tetrahydro[1*H*-carbazole-1,2′(1,3)dithiolane]-2-yl)ethanamine **4** using tetra-chloro-1,4-benzoquinone (TCB) as a catalyst.

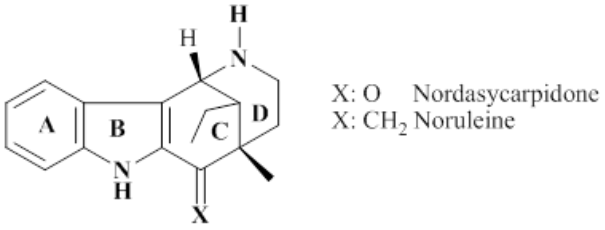
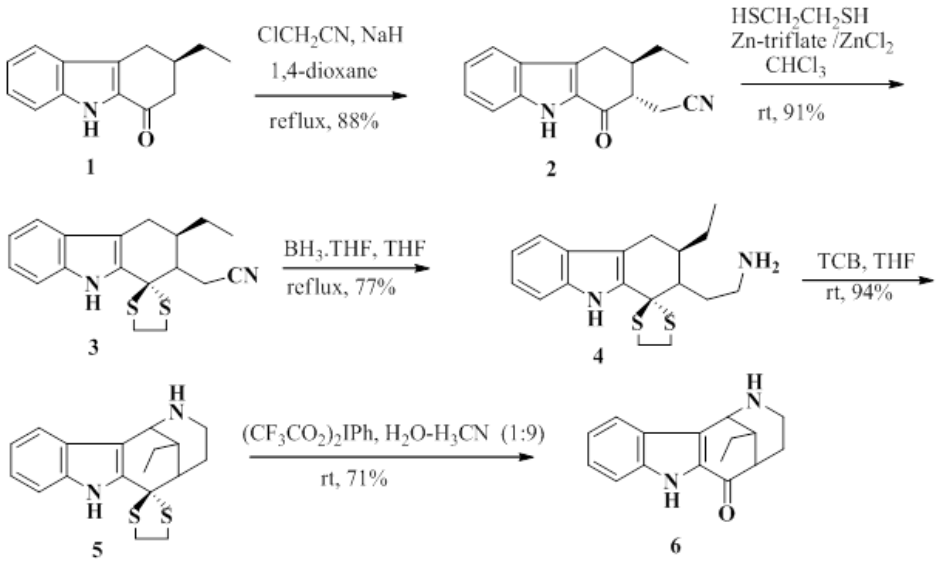


Fig. 1. Structure of nordasycarpidone-type alkaloids



Scheme 1. Synthesis of **(±)**-nordasycarpidone

2. EXPERIMENTAL SECTION

^{1}H-NMR (400 MHz) ^{13}C NMR (100 MHz) spectra were recorded on a Bruker instrument DPX-400 MHz High Performance Digital FT-NMR Spectrometer in $CDCl_3$ with tetramethyl-silane (TMS) as the internal standard at 25 °C. Chemical shifts are expressed in parts per million (δ) and the coupling constants are given in Hz. IR spectra were obtained as KBr pellets using a Mattson 1000 FT-IR spectrometer. Melting points were determined in capillary tubes on a Gal-lenkamp apparatus and are uncorrected. Reactions were monitored by thin layer chroma-tography (TLC) (silica gel 60 F254). Purification of solvents was performed according to standard methods.

2.1. *3-β-Ethyl-1-oxo-2,3,4,9-tetrahydro-1H-carbazole-2-yl)acetonitrile (**2**)*

Sodium hydride (2.3 g, 58.65 mmol, 60 % dispersion in oil) was added in several portions to a solution of carbazole **1** (5.0 g, 23.46 mmol) in 1,4-dioxane (150 ml) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 3 h, and 4.4 g (58.65 mmol) of chloroaceonitrile were added dropwise via a dropping funnel over a 30-min period. The mixture was stirred for 30 min at 0 °C, after which the mixture was heated at reflux for 27 h under a nitrogen atmosphere. Then, it was cooled in an ice bath and poured into 200 ml of 10 % HCl. After extraction with chloroform, the mixture was washed with water and brine, dried

over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude **2** as a yellow oil. The residue was purified by column chromatography on silica gel (ethyl acetate–*n*-hexane, 5:1), and, after the solvent was removed, the product was recrystallized from diethyl ether to form 5.21 g (88 %) of **2** as a white solid, m.p. 144–146 °C; TLC: R_f 0.53 (ethyl acetate); IR (KBr pellet): ν 3443, 2965, 2921, 2243, 1721, 1452, 1418, 1341 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.22 (1H, s, NH-indole), 7.93 (1H, d, *J* = 8.3 Hz, H_{Ar}), 7.41 (1H, *J* = 7.9 Hz, H_{Ar}), 7.26–7.10 (2H, m, H_{Ar}), 2.81–2.73 (2H, m, CH_2CN), 2.69 (2.61 (1H, m, 1H, CH), 2.57 (1H, dd, *J* = 11.3, *J* = 5.51 Hz, CH), 2.48 (1H, dd, *J* = 15.8, *J* = 5.51 Hz, CH), 1.93–1.80 (1H, m, CH), 1.63–1.51 (1H, m, CH), 1.33–1.26 (1H, m, CH), 1.08 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.9, 144.7, 143.1, 136.7, 127.8, 122.5, 122.0, 120.4, 119.8, 111.3, 52.8, 34.7, 31.4, 30.2, 18.7, 13.4. Anal. calcd for $C_{16}H_{16}N_2O$ (252.13): C 76.16, H 6.39, N 11.10; found: C 76.28, H 6.24, N 11.25.

2.2. *3-Ethyl-2,3,4,9-tetrahydro[1H-carbazole-1,2′(1,3)dithiolane]-2-yl)acetonitrile (**3**)*

A solution of **2** (3.0 g, 11.89 mmol) in 100 ml of chloroform, was refluxed with 1,2-ethanedithiol (2.50 ml, 29.72 mmol), zinc trifloromethanesulfonate (10.8 g, 29.72 mmol), and zinc chloride (4.05 g, mmol) for 22 h under a nitrogen atmosphere. After the mixture was allowed to cool to room atmosphere, it was treated with 100 ml of 10 % sodium hydroxide. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give **3** as a dark brown oil, which was purified by column chromatography (4:1, ethyl acatate–hexane). After the solvent was removed, and the product was recrystallized from diethyl ether-*n*-hexane (5:1), producing 3.55 g (91 %) of **3** as a yellow solid, m.p. 162–164 °C; TLC: R_f 0.68 (chloroform); IR (KBr pellet): ν 3328, 2925, 2248, 15281454 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.02 (1H, s, NH-indole), 7.33 (1H, d, *J* = 7.2 Hz, H_{Ar}), 7.22 (1H, d, *J* = 8.1 Hz, H_{Ar}), 7.14–7.01 (1H, m, H_{Ar}), 6.98 (1H, t, *J* = 7.3 Hz), 3.56–3.37 (2H, m, $-CH_2S$), 3.32-3.01 (2H, m, $-S-CH_2$), 2.94–2.81 (2H, m, CH_2CN), 2.78–2.70 (1H, m, CH), 2.63 (1H, dd, *J* = 11.4, *J* = 5.8 Hz, CH), 2.58 (1H, ddd, *J* = 15.1, *J* = 10.3, *J* = 4.7 Hz, CH), 1.98–1.85 (1H, m, CH), 1.58–1.37 (2H, m, CH_2CH_3), 1.1 (3H, t, *J* = 7.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.8, 133.7, 127.3, 120.6, 119.2, 117.3, 115.7, 112.1, 111.3, 60.7, 41.9, 39.3, 38.5, 27.1, 25.6, 21.3, 19.8, 16.3. Anal. calcd for $C_{18}H_{20}N_2S_2$ (328.11): C 65.81, H 6.14, N 8.53; found: C 65.93, H 6.27 %, N 8.48.

2.3. *3-Ethyl-2,3,4,9-tetrahydro[1H-carbazole-1,2′(1,3)dithiolane]-2-yl)ethanamine (**4**)*

BH_3.THF (1.0 M) (4.40 ml, 4.56 mmol) was added to a solution of **3** (1.5 g, 4.56 mmol) in 100 ml of tetrahydrofuran was added 4.40 ml (3.90 g, 45.6 mmol) of borane–THF by using a syringe [28]. The resulting mixture was at reflux for 6 h under a nitrogen atmosphere. After being cooled to room temperature and treated with 20 ml of methanol, the solvent was removed under reduced pressure, and the residue was heated directly at reflux with 10 % hydrochloric acid (60 ml) for 4 h and then filtred. The filtrate was made alkaline (pH = 12.0) with 10 % aqeous sodium hydroxide. The resulting solution was treated with ethyl acetate (3 × 100 ml) and concentrated under reduced pressure. The crude was dried over Na_2SO_4 and purified by column chromatography on silica gel (dichloromethane-methanol, 5:1) to give **4** (1.17 g, 77 %) as a yellow foam, TLC: R_f 0.71 (ethyl acetate); IR (KBr pellet): ν 3393, 3210, 3071, 2967, 1513, 1423, 1328, 1301 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.21 (1H, s, NH-indole), 7.56 (1H, d, *J* = 7.8 Hz, H_{Ar}), 7.35 (1H, d, *J* = 8.0 Hz, H_{Ar}), 7.20 (1H, d, *J* = 7.1 Hz, H_{Ar}), 7.12 (1H, t, *J* = 7.3 Hz, H_{Ar}), 4.32 and 4.28 (2H, brs), 3.53–3.42 (2H, m, $-CH_2-S$), 3.31–3.23 (2H, m, $S-CH_2$), 2.93–2.87 (2H, m), 2.81–2.79 (2H, m, CH_2), 2.74–2.68 (1H, m, CH_2), 2.61 (1H, dd, *J* = 12.1, *J* = 5.3 Hz, CH), 2.54 (1H, dd, *J* = 16.1, *J* = 5.3 Hz, CH), 1.93–1.86 (1H, m, CH), 1.23–114 (2H, m), 0.98 (3H, t, *J* = 7.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 133.4, 128.6, 127.5, 124.7, 119.4, 118.8, 112.3, 110.9, 65.8, 52.3, 42.7, 40.7, 39.6, 38.7, 29.4, 28.7, 22.3, 11.7. Anal. calcd for $C_{18}H_{24}N_2S_2$ (332.14): C 65.02, H 7.27, N 8.42; found: C 65.13, H 7.36, N 8.37.

2.4. *12-Ethyl-6,6-ethylenedithio-1,2,34,5,6-hexahydro-1,5-methano-2-azocino[4,3,b]indole (**5**)*

Tetrachloro-1,4-benzoquinone (2.2 g, 9.03 mmol) in one portion was added to a solution of amine **4** (1.0 g, 3.01 mmol) in 30 ml of tetrahydrofuran, and the resulting solution was stirred at room temperature for 6 h under a nitrogen atmosphere, after which it was treated with 10 % NaOH (3 × 50 ml) solution. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure, and the residue was purified

by column chromatography on silica gel (ethyl acetate–MeOH, 3:1) to produce 0.93 g (94 %) of **5** as a white solid, m.p. 224–226 °C; TLC: R_f 0.51 (hexane); IR (KBr pellet): ν 3251, 2943, 1618, 1461, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.31 (1H, s, NH-indole), 7.53 (1H, d, *J* = 7.7 Hz, H_{Ar}), 7.33 (1H, d, *J* = 8.1 Hz, H_{Ar}),7.18–7.07 (2H, m, H_{Ar}), 5.73 (1H, d, *J* = 2.7 Hz CH), 4.73–4.67 (1H, m, CH), 4.13 (1H, t, *J* = 1.4 Hz, CH), 3.62–3.37 (4H, m, CH_2), 2.61 (1H, brs), 2.43 (1H, d, *J* = 5.6 Hz, CH), 2.51–2.24 (1H, m), 1.63–1.21 (4H, m, CH_2), 1.01 (3H, t, *J* = 7.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 135.7, 134.5, 127.2, 123.2, 119.4, 119.0, 111.8, 110.6, 93.8, 73.7, 50.1, 41.8, 40.9, 40.6, 40.1, 28.9, 24.3, 11.4. Anal. calcd for $C_{18}H_{22}N_2S_2$ (330.12): C 65.41, H 6.71, N 8.48; found: C 65.49, H 6.78, N 8.37.

2.5. *12-Ethyl-6-oxo-1,2,3,4,5,6-hexahydro-1,5-methano-2-azocino[4,3-b]indole (Nordasycarpidone) (**6**)*

[*Bis*(trifluoroacetoxy)iodo]benzene (1.6 g, 3.77 mmol) was added to a solution of cyclization product **5** (0.5 g, 1.51 mmol) in aqueous acetonitrile (1:9) (40 ml), and the mixture was stirred, under a nitrogen atmosphere for 5 h at room temperature.The resulting solution was treated with saturated aqueous $NaHCO_3$ (50 ml) diluted with ethyl acetate (50 ml), washed with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was crystallized from diethyl ether to produce 0.54 g (71 %) of nordasycarpidone (**6**) as a foam. TLC: R_f 0.78 (ethyl acetate); IR (KBr pellet): ν 3253, 2963, 1651, 1537, 1468, 1329, 1196, 1128, 901, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.43 (1H, s, NH-indole), 7.53 (1H, d, *J* = 7.9 Hz, H_{Ar}), 7.33 (1H, d, *J* = 8.1 Hz, H_{Ar}), 7.19 (1H, td, *J* = 8.0 Hz, H_{Ar}), 7.11 (1H, t, *J* = 8.0 Hz, H_{Ar}), 5.23 (1H, d, *J* = 6.1 Hz, CH), 2.94 (1H, bs, NH), 2.74–2.62 (1H, m, CH), 2.41–2.29 (2H, m, CH_2), 2.18–2.05 (1H, m, CH), 2.01–1.87 (2H, m, CH_2), 1.63–1.52 (2H, m, CH_2), 0.87 (3H, t, *J* = 7.4 Hz, CH_3); ^{13}C N NMR ($CDCl_3$, 100 MHz): δ 192.8, 138.1, 133.4, 126.8, 125.1, 123.9, 122.0, 121.8, 112.6, 48.7, 48.1, 47.5, 37.3, 31.4, 24.8, 11.8. Anal. calcd for $C_{16}H_{18}N_2O$ (254.14): C 75.56, H 7.13, N 11.01; found:. C 75.48, H 7.18, N 11.12.

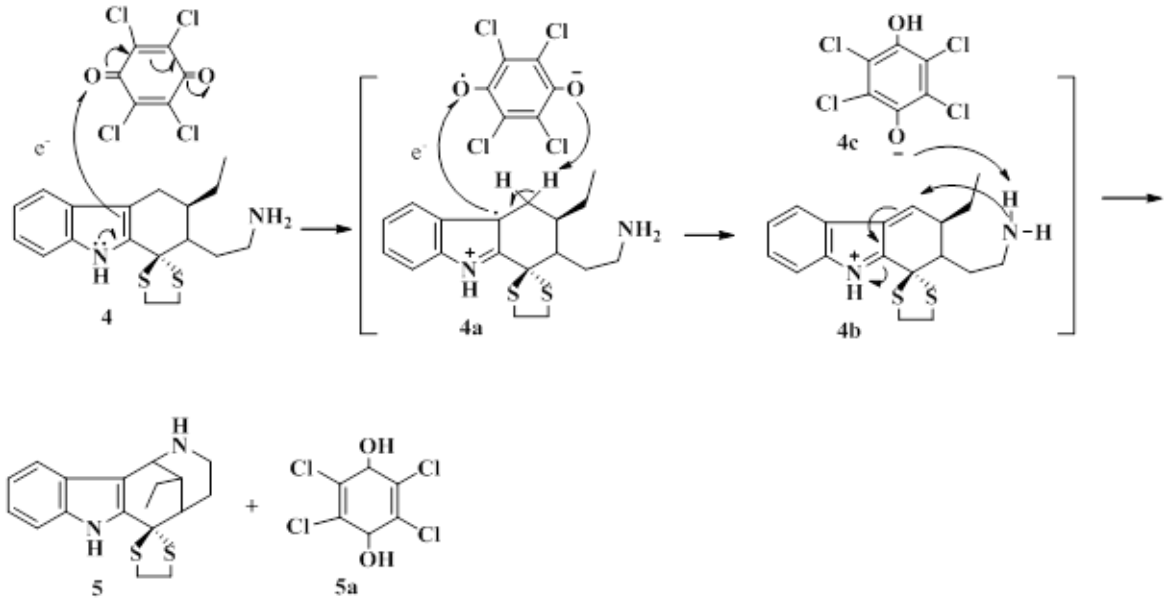
3. RESULTS AND DISCUSSION

In this work, our synthesis bagan with preparation of 3-ethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)acetonitrile (**2**) for the penultimate-intramolecular cyclization mediated by tetrachloro-1,4-benzoquinone (TCB). For this target, we selected 3-ethyl-1,2,3,4-tetrahydro-1*H*-carbazole-1-one (**1**) as the starting material. Initially, cyano-methylation of compound **1** utilizing sodium hydride and chloroacetonitrile in 1,4-dioxane gave **2** and the preparation of starting material, racemic 3-ethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-carbazole-2-yl) acetonitrile (**2**) has been previously described. [10, 15, 18]. Because of the possibility that the carbonyl group might be affected by the conditions, we used cyanomethylation of compound (**2**) followed by treatment with 1,2-ethanedithiol and zinc triflate as a catalyst, resulting in 91 % yield of compound **3** [19]. The nitrile reduction reaction of cyano-methylation **3** with amine **4** proceeded smoothly in tetrahydrofuran at reflux and provided a good yield (77 %). After intramolecular cyclization, product **5** was investigated to complete the total synthesis. Furthermore, we have also demonstrated the efficiency of this new cyclization method in this study. For the purpose, cyclization by treatment with tetrachloro-1,4-benzoquinone led to the generation of the azocino[4,3-*b*]indole skeleton. After formation of the azocino[4,3-*b*]indole, a protecting group was introduced by treatment with *bis* (trifluoroacetoxy)iodobenzene to produce (±)-nordasycarpidone in five steps [20–22].

Synthesis of nordasycarpidone-type alkaloids are based on the construction of a 1,5-methanoazocino[4,3-*b*]indole skeleton which are also found other alkaloids. In this study, we had also shown that 1,5-methanoazocino[4,3-*b*]indoles can be formed from 2-amino-1,2,3,4-tetrahydrocarbazoles. It is presented that azocino[4,3-*b*]indoles through the cyclization reaction of starting tetrahydrocarbazoles bearing a monoalkylmino moiety at C-2 position mediated by tetrachloro-1,4-benzoquinone (TCB). [18]. This reagent was used for the first time, a mechanistic proposal is given that includes formation of a vinylogous iminium cation via TCB-mediated dehydrogenation of tetrahydrocarbazole [23–25]. According to our tentatively proposed reaction mechanism as illustrated in Scheme 2, the formation of the vinylogous iminium cation **4b** in turn seems to be unequivocal. On the other hand, the phenoxide anion **4c** can act as a *Brønsted-base* to give the *syn*-selective cylization to completion of the reaction and 2,3,5,6-tetrachlorohydroquinone **5a** is formed as a side product subsequently. The most characteristic value of its ^1N NMR spectrum is a doublet of methine proton on the C-21 position at δ 5.73 ppm, which was comparable to the data observed previously for the methanoazocino structure [1, 4].

According to our proposed reaction mechanism, as illustrated in Scheme 2, spectroscopic ^{1}H NMR, ^{13}C NMR, IR, elemental analysis data of the synthetic sample were identical to those of the natural product [4, 26, 27].

In this study, we also report and efficient, practical, and high-yielding method for the synthesis of (±)-nordasycarpidone with an overall yield of 41 %. The methods and techniques we used will prove useful for future synthetic endeavors and relevant biological molecules. Application of this strategy for the synthesis of other alkaloids that have the azocino[4,3-*b*]indole moiety is underway in our laboratory.



Scheme 2. Proposed mechanism of azocino[4,3-*b*]indole with tetrachloro1,4-benzoquinone (TCB)-mediated cylization

4. CONCLUSION

We established a convenient synthetic route for producing (±)-nordasycarpidone by using tetrachloro-1,4-benzoquinone. The strategy developed here to built the azocino[4,3-*b*]indole system, combined with the efficient method for the preparation of starting 3-ethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-carbazole-2-yl)acetonitrile, provides a short, general synthetic entry to this tetracyclic system that may be applicable to the synthesis of strychnos alkaloids. This strategy will be also applicable readily to the total syntheses of related natural products, including uleine, epidasycarpidone, noruleine and synthetic analogues for structure relationship studies.

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