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Short Communication

A SIMPLE AND EFFICIENT METHOD FOR CONSTRUCTING AZOCINO[4,3-*b*]INDOLE

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A new synthetic procedure has been developed to prepare the biologically important azocino[4,3-*b*]indole via the tetrafluoro-1,4-benzoquinone (TFB)-mediated cyclization of a tetrahydrocarbazole derivative bearing an amide side chain at the C-2 position. For the first time, this strategy is based on a different method for the C-2 position of the tetrahydrocarbazole for the synthesis of methanoazocino[4,3-*b*]indole. The notable features of this protocol include its operational simplicity and high reaction yields. Furthermore, the structures of all the presently synthesized compounds were confirmed using spectroscopic methods (^{1}H NMR, ^{13}C NMR, FT-IR).

Keywords: dasycarpidone; indole alkaloid; strychnos alkaloids; 1,5-methanoazacino[4,3-*b*]indole

ЕДНОСТАВЕН И ЕФИКАСЕН МЕТОД ЗА ДОБИВАЊЕ АЗОЦИНО[4,3-*b*]ИНДОЛ

Развиена е нова синтетичка постапка за подготовка на биолошки важниот азоцино[4,3-*b*]индол преку со тетрафлуоро-1,4-бензохинон (TFB) - посредувана циклизација на дериват на тетрахидрокарбазол што содржи странична амидна низа во положба C-2. За прв пат, оваа стратегија за синтеза на метаноазицино[4,3-*b*]индол е заснована на посебен метод за положбата C-2 на тетрахидрокарбазол. Значаен белег на овој протокол се оперативната едноставност и високиот принос. Освен тоа, структурите на сите така синтетизирани соединенија беа потврдени со примена на спектроскопски методи (^{1}H NMR, ^{13}C NMR, FT-IR).

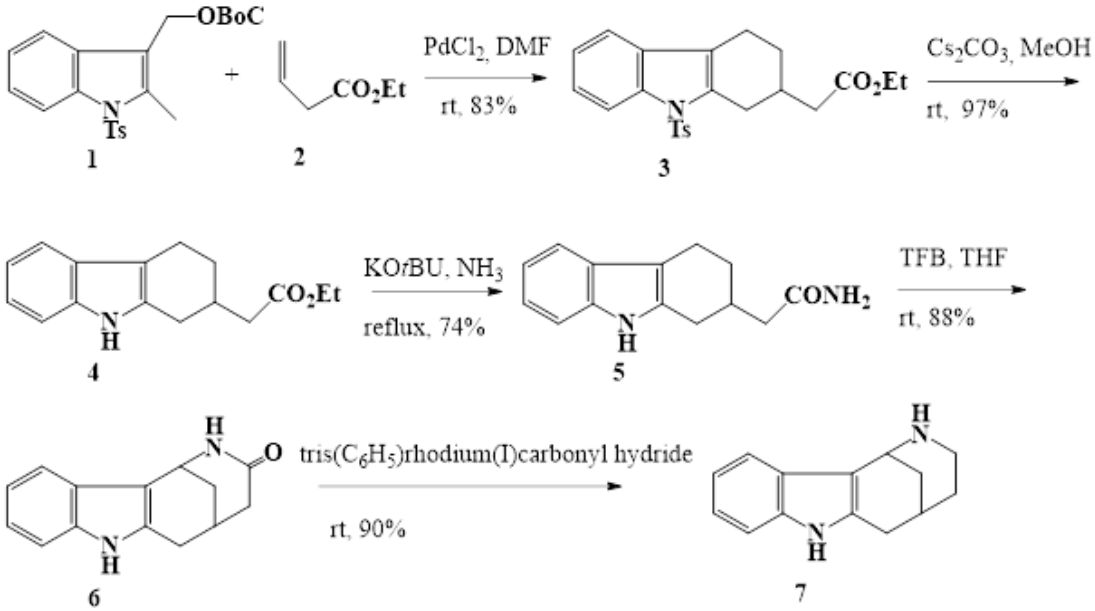
Клучни зборови: дасикарпидон; индолен алкалоид; стрихнински алкалоиди; 1,5-метаназоцино[4,3-*b*]индол

1. INTRODUCTION

Structurally azocino[4,3-*b*]indole, azocino[4,3-*b*]indoline, and its congener skeletons are of great significance in strychnos alkaloids and biologically-related areas.[1,2] In particular, the uleine-type alkaloids (Fig. 1) have attracted much interest from synthetic organic chemists.[3–8] The azocino[4,3-*b*]indole structures have received increasing attention due to their prevalence in several natural products, such as uleine, subincanadine F, dasycarpidone, and strychnine (Fig. 1).[9–12] These structures are two important classes of compounds and have been widely found in biologically active molecules and drug candidates. Moreover, diversely functionalized azocino[4,3-*b*]indoline skeletons have also been versatile synthetics in bioactive molecules.[13–16]

Syntheses of these structures are based on the construction of a methanoazocino[4,3-*b*]indole skeleton and the key element of strychnos alkaloids. A rather large number of synthetic pathways have been developed for the construction of the azocino[4,3-*b*]indole skeleton so far.[17–23] In our study, an alternative synthetic entry to the tetracyclic ring system of strychnos alkaloid is presented. We envisaged to develop an alternative strategy to reach

the tetracyclic compound **7**. The production of natural products **3–7**, involving **1** and **2** as advanced intermediates, is depicted in Scheme 1. A one-pot construction of the ABCD ring system using TFB (tetrafluoro-1,4-benzoquinone) was involved as a key step as well as the ABCD substructure of the strychnos alkaloid family. Inspired by the results of our work, we used different strategies and developed a new method that involved the required functionality at the C-2 position for the synthesis of key intermediate **7**, and the synthesis of compound **3** was applied for the first time in this study as a new method. The main goal of this work is to provide a novel route to the synthesis of carbazole-based molecules using different pathways. We previously developed a new synthetic strategy for azocino[4,3-*b*]indole through the cyclization reaction of starting tetrahydrocarbazoles bearing monoalkyl nitrile side chains at the C-2 position. Substituted nitriles are key molecular scaffolds in the synthesis of many organic compounds.[24–27] We now report an extension of this approach that leads to the synthesis of azocino[4,3-*b*]indole. Furthermore, this kind of method has never been implemented in the synthesis of strychnos alkaloids.



Scheme 1. Synthesis of tetracyclic azocino[4,3-*b*]indole

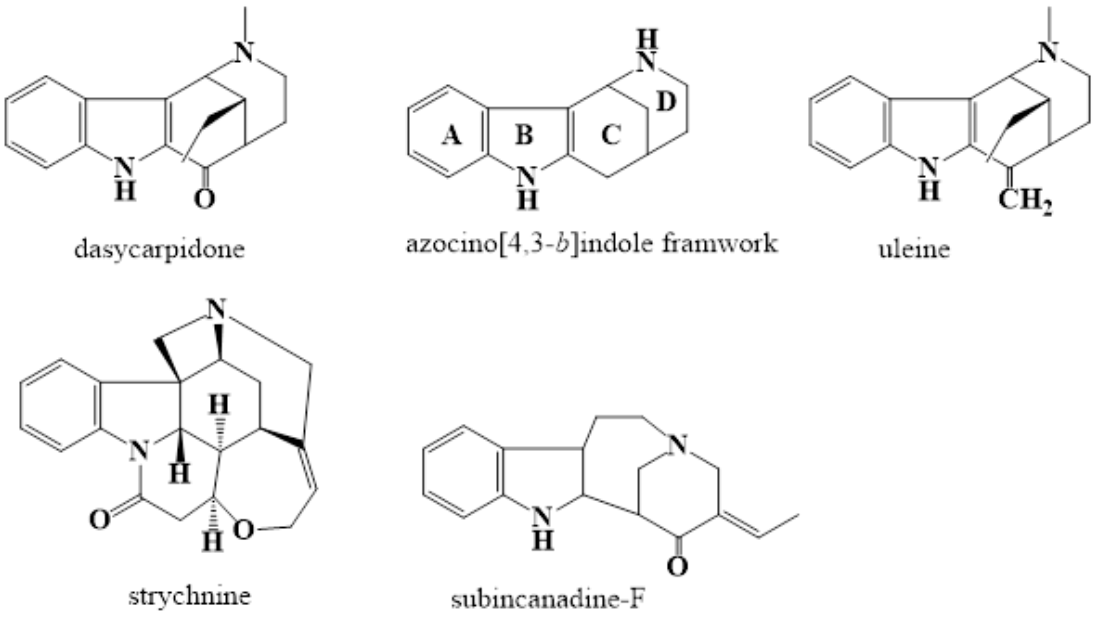


Fig. 1. Some of the bioactive tetrahydrocarbazole derivatives possessing an azocino[4,3-*b*]indole core structure

Compound **3**, synthesized from a new method, was converted to tetracyclic azocino[4,5-*b*]indole. Therefore, developing an alternative and effective way to reach the synthetic method for constructing the desired tetracyclic compound is important, and this has prompted more general development of the approach. Also, this method provides useful means for assembly of the key substructure and related strchynos alkaloids.[28–30] Further applications of this method can find significance due to the syntheses of the other members of the indole skelatal-type alkaloids.

2. EXPERIMENTAL SECTION

^{1}H NMR (Proton nuclear magnetic resonance spectroscopy) (400 MHz) and ^{13}C NMR (Carbon-13 nuclear magnetic resonance spectroscopy) (100 MHz) spectra were recorded on a Bruker DPX-400 MHz High Performance Digital FT-NMR (Fourier transform nuclear magnetic resonance) Spectrometer in $CDCl_3$ with tetramethylsilane (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. Infrared spectroscopy (IR) spectra were obtained as KBr pellets using a Mattson 1000 Fourier transform infrared spectroscopy (FT-IR) spectrometer. Melting points were determined in capillary tubes on a Gallenkamp apparatus and are uncorrected. Reactions were monitored by thin-layer chromatography (TLC) (silica gel 60 F254). Purification of solvents was performed according to standard methods.

2.1. *Ethyl 2-(9-tosyl-2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetate (**3**)*

Ethyl but-3-enoate **2** (1.6 g, 14.46 mmol) and $PdCl_2$ (2.12 g, 12.04 mmol) were added to a solution of *tert*-butyl (2-methyl-1-tosyl-1*H*-indol-3-yl)methyl carbonate **1** (3.0 g, 7.23 mmol) in 50 ml of DMF (dimethylformamide). The mixture was refluxed for 2 h under a nitrogen atmosphere. Upon completion (as monitored by TLC), the mixture was allowed to cool to room temperature and diluted with crushed ice, then the aqueous layer was extracted three times with EtOAc (Ethyl acetate) (3 × 30 ml). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (EtOAc), and the product was recrystallized from diethyl ether, producing 1.4 g (83 %) of **3** as a white solid, m.p. 196–198 ºC. TLC: R_f 0.3 (hexane); IR (KBr pellet): ν 2931, 1725, 1610, 1455, 1224, 1178, 1130, 1037, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (1H, d, J = 8.6 Hz, H_{Ar}), 7.33–7.46 (4H, m, H_{Ar}), 7.14 (2H, t, J = 6.2 Hz, H_{Ar}), 6.95 (1H, t, J = 6.1 Hz, H_{Ar}), 4.22–4.28 (2H, q, J = 7.1 Hz, CH_2), 3.21 (3H, s, CH_3), 2.91 (1H, dd, J = 16.0, 5.1 Hz, CH), 2.87–2.70 (2H, m, CH_2), 2.61 (1H, m, CH), 2.51 (2H, dd, J = 7.2, 3.2 Hz, CH_2), 2.38 (1H, CH), 2.12 (1H, m, CH), 1.78 (1H, m), 1.11 (3H, t, J = 7.44 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100MHz): δ 174.7, 144.6, 136.2, 134.4, 129.8, 126.5, 126.1, 124.3, 118.6, 118.1, 114.5, 109.2, 108.7, 60.9, 42.3, 39.8, 31.8, 30.9, 24.0, 21.7, 14.4. Calcd. mass fractions of elements for $C_{23}H_{25}NO_4S$ (411.52): C 67.13, H 6.12, N 3.40; found: C 67.22, H 6.07, N 3.41.

2.2. *Ethyl 2-(2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetate (**4**)*

Ethyl 2-(9-tosyl-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)acetate **3** (2.0 g, 4.86 mmol) was dissolved in a mixture of THF (Tetrahydrofuran) (50 ml) and MeOH (30 ml) at room temperature. Cs_2CO_3 (4.7 g, 14.58 mmol) was added to the solution. The mixture was stirred for 12 h at room temperature under a nitrogen atmosphere. Upon completion (as monitored by TLC), the mixture was evaporated under vacuum and treated with 100 ml of 10 % NaOH. After extraction with chloroform, the mixture was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give **4** as an oil. The residue was purified by column chromatography on silica gel (EtOAc-*n*-hexane, 1:1), and after the solvent was removed, the product was recrystallized from diethyl ether to form 1.21 g (97 %) of **4** as a white solid, m.p. 148–150 °C. TLC: R_f 0.6 (EtOAc); IR (KBr pellet): ν 3396, 2917, 2835, 1725 1455, 929, 867 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (1H, br s, N-H indole), 7.45 (1H, d, J = 7.8 Hz, H_{Ar}), 7.31 (1H, d, J = 7.8 Hz, H_{Ar}), 7.18 (1H, t, J = 7.8 Hz, H_{Ar}), 7.08 (1H, t, J = 7.8 Hz, H_{Ar}), 4.12–4.06 (2H, q, J = 7.3 Hz, CH_2), 2.93 (1H, dd, J = 15.8, 5.3 Hz, CH), 2.81–2.68 (2H, m, CH_2), 2.56 (1H, m, CH), 2.48 (2H, dd, J = 7.3, 3.1 Hz, CH_2), 2.29 (1H, CH), 2.16 (1H, m, CH), 1.73 (1H, m, CH), 0.93 (3H, t, J = 7.32 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz):δ 174.2, 154.3, 128.5, 124.6, 124.0, 122.7, 12 1.5, 112.8, 110.3, 66.4, 41.9, 37.2, 34.2, 31.3, 20.6, 1 4.3. Calcd. mass fractions of elements for $C_{16}H_{19}NO_2$ (257.33): C 74.68, H 7.44, N 5.44; found: C 74.76, H 7.53, N 5.36.

2.3. *(2-(2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetyl)hydroxylamine (**5**)*

A solution of the ester **4** (2.0 g, 7.72 mmol) in dry toluene (50 ml) was treated with ,3′-iminobis(*N*,*N*-dimethylpropylamine) L_n (0.3 g, 1.4 mmol), (3.2 g, 15.44 mmol), bromopentacarbonylmanganese(I) (0.2 g, 0.7 mmol), KO*t*BU (potassium *tert*-butoxide) (0.9 g, 8.2 mmol), and 15 ml of 25 % ammonium hydroxide solution (95 mmol NH_3). Then, the mixture was refluxed at 110 °C for 14 h. Upon completion (as monitored by TLC), the mixture was allowed to cool to room temperature, and the residue was purified by silica gel chromatography using MeOH. The organic layer was dried over anhydrous $MgSO_4$, then the product obtained upon removal of the solvent was recrystallized from petroleum ether to give pure compound **5** (1.76 g, 74 %) as a yellow solid, m.p. 178–180 °C. TLC: R_f 0.8 (EtOAc-acetone-Et_3N, 5:2:1); IR (KBr pellet): ν 3268, 2957, 2934, 2877, 2835, 1686, 1572, 1544, 1465, 1259, 1235, 1204, 963, 765 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.11 (1H, br s, N-H indole), 7.75 (1H, d, *J* = 8.2 Hz, H_{Ar}), 7.43 (1H, d, *J* = 8.3 Hz, H_{Ar}), 7.38 (1H, ddd, *J* = 8.3, 6.9, 1.1 Hz, H_{Ar}), 7.22 (1H, ddd, *J* = 8.0, 6.9, 1.0 Hz, H_{Ar}), 5.27 (1H, s, NH), 5.00 (1H, s, NH), 2.89–2.81 (2H, m, CH_2), 2.73–2.66 (1H, m, CH_2), 2.58 (1H, dd, *J* = 15.5, 6.8 Hz, CH), 2.49 (1H, dd, *J* = 15.5, 4.8 Hz, CH), 2.43–2.52 (2H, m, CH), 2.20–2.15 (1H, m, CH), 1.62–1.50 (1H, m, CH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.8, 138.6, 132.8, 127.1, 125.3, 123.6, 121.1, 121.8, 112.9, 44.5, 38.4, 33.6, 32.7, 25.5. Calcd. mass fraction of elements for $C_{14}H_{16}N_2O$ (228.13): C 73.66, H 7.06, N 12.27; found: C 73.57, H 7.11, N 12.34.

2.4. *1,2,4,5,6,7-hexahydro-3H-1,5-methanoazocino[4,3-b]indol-3-one (**6**)*

Tetrafluoro-1,4-benzoquinone (4.7 g, 26.52 mmol) was added to a solution of amide **5** (1.0 g, 4.42 mmol) in 50 ml of anhydrous THF. After, the reaction mixture was stirred under a nitrogen atmosphere for 1 h at room temperature. Then, the mixture was refluxed for 3 h under a nitrogen atmosphere. Afterwards, the reaction mixture was quenched with 10 % $NaHCO_3$ and diluted with EtOAc. The separated organic layer was dried over anhydrous $MgSO_4$, and the residue was purified by silica gel column chromatography, eluting with EtOAc-Et_3N (4:1). The product obtained upon removal of the solvent was recrystallized from cyclohexane to give the tetracyclic methanoazocino[4,3-*b*]indole **6**. The product was recrystallized from diethyl ether to form 880 mg (88 %) of **6** as a white solid, m.p. 248 °C. TLC: R_f 0.7 (EtOAc); IR (KBr pellet): ν 3221, 3086, 2954, 2923, 2877, 1667, 1573, 1456, 1432, 1189, 981, 779 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.48 (1H, s, N-H indole), 7.66 (1H, d, *J* = 8.2 Hz), 7.46 (1H, d, *J* = 8.2 Hz, H_{Ar}), 7.39 (1H, m, H_{Ar}), 7.38 (1H, d, *J* = 8.2 Hz, H_{Ar}), 7.16 (1H, t, *J* = 7.2 Hz, H_{Ar}), 4.73 (1H, s, CH), 2.68–2.60 (2H, m), 2.51–2.42 (2H, m), 2.22 (1H, dt, *J* = 12.3, 3.2 Hz, CH), 1.94–1.87 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 137.3, 128.6, 128.2, 127.6, 124.3, 121.2, 120.1, 113.5, 58.3, 45.1, 38.6, 37.7, 35.3.

Calcd. mass fractions of elements for $C_{14}H_{14}N_2O$ (226.28): C 74.31, H 6.24, N 12.38; found: C 74.42, H 6.18, N 12.27.

2.5. *2,3,4,5,6,7-hexahydro-1H-1,5-methanoazocino[4,3-b]indole (**7**)*

Methanoazocino[4,3-*b*]indole **6** (0.5 g, 2.21 mmol) and 0.72 g (0.8 mmol) of tris(triphenylphosphine) rhodium (I) carbonyl hydride were dissolved in 50 ml tetrahydrofuran, then 0.20 g (0.8 mmol) of diphenylsilane was added. The mixture was stirred at room temperature for 2 h. After completion of the reaction, the mixture was diluted with diethyl ether and extracted with 1 mol/l HCl (aq). The aqueous layer was basified with 15 % NaOH (aq) and extracted with ethyl acetate. The organic phase was dried over anhydrous magnesium sulfate and evaporated. The residue was purified using silica gel chromatography ($CHCl_3$–EtOAc, 4:1), and the extract was evaporated *in vacuo* to give a pale-yellow foam with a yield of 421 mg (90 %). TLC: R_f 0.5 (EtOAc); IR (KBr pellet): ν 3231, 3041, 2915, 1855, 1601, 1457, 1390, 1322, 1244, 1058, 1002, 988, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.80 (1H, s, N-H indole), 7.46 (1H, d, *J* = 7.6 Hz, H_{Ar}), 7.34 (1H, d, *J* = 7.4 Hz, H_{Ar}), 7.11–6.97 (2H, m, H_{Ar}), 4.37–4.26 (1H, m, CH), 3.21 (1H, dd, *J* = 17.1, 6.2 Hz, CH), 2.71 (1H, d, *J* = 16.9 Hz, CH), 2.54 (2H, m, CH_2), 2.39 (1H, m, CH), 2.19 (1H, dt, *J* = 11.9, 3.6 Hz, CH), 1.83 (2H, m, CH_2), 1.57 (1H, m, CH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.2, 136.9, 127.8, 122.8, 118.3, 117.8, 112.2, 107.9, 46.8, 38.7, 36.1, 34.4, 29.3, 26.5. Calcd. mass fractions of elements for $C_{14}H_{16}N_2$ (212.30): C 79.21, H 7.60, N 13.20; found: C 79.28, H 7.54, N 13.28.

3. RESULTS AND DISCUSSION

Our approach is based on the generation of the azocino[4,3-*b*]indole structure **7** through cyclization of a tetrahydrocarbazole bearing a carboxymethylene moiety at C-2 position mediated by TFB; this route has been valuable for the construction of

strychnos alkaloids.[31] The method also involved the one-step reaction of *t*ert-butyl (2-methyl-1-tosyl-1*H*-indol-3-yl)methyl carbonate **1** with ethyl 3-butenoate **2** in the presence of $PdCl_2$ in DMF to afford ethyl 2-(9-tosyl-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)acetate **3** bearing the required substituent group at C-2 position. It was hoped that the reaction of **1** and **2** would lead to the generation of the skeleton of **3** in line with previously described work.[32,33] The use of a shorter reaction time and simple operational procedures are the key advantages of this methodological procedure. Indeed, these methodologies were efficient and effective for the synthesis of carbazole derivatives. Our attention then turned to exploiting azocino[4,3-*b*]indole derivative **6**. To achieve this aim, progenitor compound **6** was prepared from ethyl 2-(9-tosyl-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)acetate **3** through a deprotection reaction, followed by TFB cyclization.[21] For most of the detosylation method, we selected indole and the related N-detosylation method. Under mild conditions, this created **4** using Cs_2CO_3 at room temperature. The reactions were carried out in a mixed solvent of THF-MeOH (5:3) in high yields (97 %).[34]

Next, we focused our attention on the synthesis of amide **5**. For this purpose, amide **5** was obtained in good yields by reacting compound **4** with 3,3′-iminobis(*N*,*N*-dimethylpropylamine) L_n, bromopentacarbonylmanganese(I), and KO*t*BU in the presence of aqueous ammonia solution. To the best of our knowledge, this is the only example of a one-pot construction of the tetracyclic compound starting with **5**.[35–37] Then, amide **5** was converted into the key azocino[4,3-*b*]indole **6** in 88 % yield by treating it with TFB.

In the final step, the treatment of **6** with tris(triphenylphosphine) rhodium(I) carbonyl hydride was utilized to complete the synthesis of azocino[4,3-b]indole **7** with an overall yield of 59 %.[38-40] By applying the designed synthesis plan, we reduced the number of steps, increased the percentage yield, and realized the synthesis of the targeted tetracyclic compound.

4. CONCLUSION

We have developed an effective TFB-mediated synthesis strategy for the key substructures and analogues of this important strychnos alkaloids system. This method thereby featured a one-pot cyclization reaction and effective construction of the ABCD tetracyclic framework of the uleine-type alkaloids. The exploration of this method for the other strychnos alkaloids will be the subject of further investigation in our research group.

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