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Formal Syntheses of (±)-Stemonamine and (±)-Cephalotaxine

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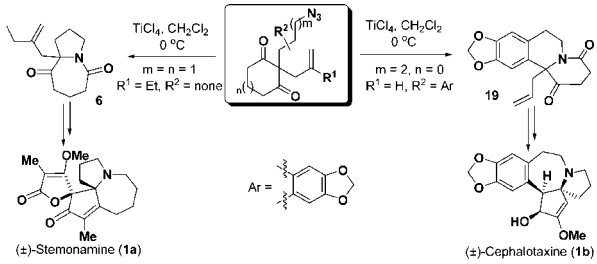
Received January 23, 2009



A short and efficient approach to aza-quaternary pyrrolo[1,2-*a*]azepine **8** and aza-quaternary indolizine **23**, as the crucial intermediates for syntheses of stemonamine (**1a**) and cephalotaxine (**1b**), has been developed on the basis of the key intramolecular Schmidt reaction of symmetric azidodiones **5** and **18**, respectively.

The alkaloids stemonamine (**1a**)[1] and cephalotaxine (**1b**)[2] (Figure 1) represent a number of natural polycyclic aza-quaternary alkaloids, respectively. As a potential drug, **1a** and its analogues were used in China and Japan for centuries for the treatment of respiratory diseases and as insecticides. A number of derivatives of **1b** (i.e., harringtonine and homoharringtonine) have been found to be highly effective for the treatment of acute human leukemia and are currently undergoing clinical trials.[3] Owing to their unique structures and important biological activities, **1a** and **1b** have always attracted considerable interest from synthetic organic and medicinal chemists. Over the past years, a number of great efforts have been made toward the syntheses of these alkaloids for the purpose of fundamental research and drug development.[4] However, more efficient and general approaches to theses alkaloids are still desirable, especially for challenging construction of polycyclic aza-quaternary skeletons.

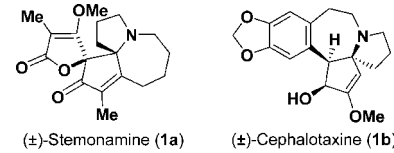


FIGURE 1. Selected polycyclic aza-quaternary alkaloids.

In connection with our previous investigations,[5] we have recently reported the first total synthesis of (±)-stemonamine (**1a**) based on the tandem semipinacol rearrangement/Schmidt reaction.[6] This achievement encouraged us to develop alternatively more general and efficient new strategies for this type and other kinds of complex aza-quaternary alkaloids syntheses. Herein, we wish to present a concise tactic for formal syntheses of (±)-stemonamine (**1a**) and (±)-cephalotaxine (**1b**) using the key Schmidt reaction of the 2-quaternary-1,3-cyclodione substrates.

As shown in Scheme 1, our synthetic plan focused on the construction of crucial tricyclic enone **8** and tetracyclic enone **23**, which could be achieved from **6** and **19** through several transformations including oxidation and aldol cyclization. As the key strategy level step, intramolecular Schmidt reaction[7] of symmetric azido diones **5** and **18** would provide the desired aza-quaternary pyrrolo[1,2-*a*]azepine **6** and aza-quaternary indolizine **19**, respectively.

Initially, we selected stemonamine (**1a**) possessing the basic structural element of interest as an optimal target to test our methodology. As shown in Scheme 2, dione **2** was obtained

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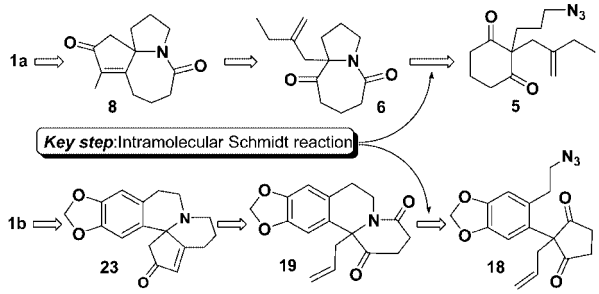
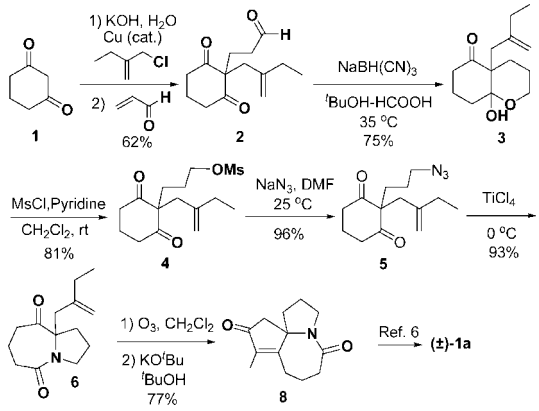
10.1021/jo900113s CCC: $40.75 © 2009 American Chemical Society
Published on Web 03/25/2009

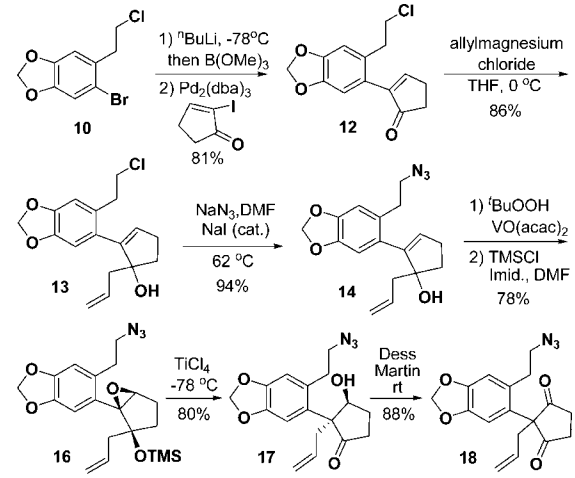
SCHEME 1



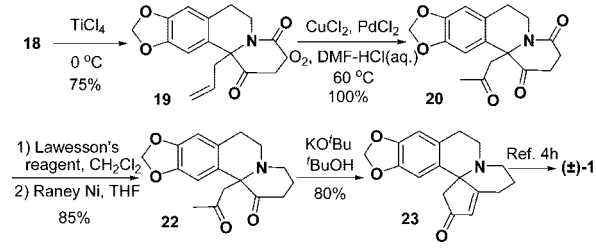
SCHEME 2



SCHEME 3



SCHEME 4



from commercially available cyclohexane-1,3-dione **1** in 62% overall yield via two steps involving allylation and Michael addition. Reduction of **2** with $NaBH(CN)_3$ gave rise to the corresponding hemiketal **3**, which was converted to mesylate and treated with NaN_3[8] to afford azido dione **5** in 58% yield over three steps. With **5** in hand, the key intramolecular Schmidt reaction was investigated. As expected, treatment of **5** with 2.05 equiv of $TiCl_4$ in CH_2Cl_2 at 0 °C successfully gave the desired aza-quaternary pyrrolo[1,2-*a*]azepine **6** in 93% yield, which could conveniently convert to **1a** according to our reported produce. [6]

The successful formal synthesis of **1a** above encouraged us to develop another formal synthesis of more challenging molecular **1b**. Initially, we envisioned that the key substrate **18** could be achieved through Pd-catalyzed arylation of cyclopentane-1,3-dione with **10** and successive allylation according to the Buchwald procedure;[9] however, we could not obtain the desired 2-aryl-1,3-dione product **18** under our reaction conditions. Thus, we had to develop other method for preparation of **18**. As depicted in Scheme 3, our project commenced with Suzuki−Kumada coupling[10] of aryl boracic acid (prepared from **10**) and 2-iodocyclopentenone[11] to afford enone **12** in 81% overall yield from **10**. The Grignard addition of the resulting enone **12**, followed by substitution with NaN_3, epoxidation, and protection with TMSCl, afforded siloxy epoxy azide **16** in 63% overall yield from **12**. Treatment of epoxide **16** with $TiCl_4$ at −78 °C gave *β*-hydroxy ketone **17**,[12] and subsequent oxidation of **17** with Dess−Martin reagent afforded the desired **18** in 70% yield over two steps.

With a reliable route to **18** in hand, we turned our attention to the key intramolecular Schmidt reaction. To our delight, we obtained the desired product **19** in 75% yield using the same procedure as for **5** (Scheme 4). Wacker oxidation of **19** furnished the methyl ketone **20** in quantitative isolated yield.[4h] To complete the synthesis, treatment of lactam **20** with Lawesson's reagent and reduction of thiolactam using W-2 Raney Ni in THF gave the tertiary amine **22** in 85% yield over two steps. Finally an easy aldol cyclization of **22** gave the key tetracyclic aza-quaternary intermediate **23** in 80% yield, whose spectral chracteristics were identical to those reported by Li and co-worker.[4h−j] The intermediate **23** has been used for the total synthesis of cephalotaxine by Li's groups, and therefore, we completed successfully a formal synthesis of cephalotaxine.

In summary, we have accomplished simple and efficient formal total syntheses of stemonamine and cephalotaxine via a facile intramolecular Schmidt reaction of symmetric azido dione precursor. This concise Schmidt reaction may be applicable in other alkaloids syntheses. Currently, we are carrying on an investigation of this reaction from asymmetric vision in our laboratory.

Experimental Section

Azido Diketone 5. The diketone **4** (6.64 g, 21.0 mmol) was treated with NaN_3 (4.1 g, 63.0 mmol) in DMF (30 mL) at room temperature under argon. After 15 h, the mixture was diluted with ether. The organic phase was washed with water twice, dried over $MgSO_4$, concentrated, and chromatographed (R_f = 0.6, 1:1 hexane/

(8) **CAUTION!** Alkyl azides are potential explosion hazards in substrate synthesis.

(9) Joseph, M. F.; Xiaohua, H.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.

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(11) Krafft, M. E.; Cran, J. W. *Synlett* **2005**, 1263.

(12) Here, compound **17** failed to give an N-insertion product via the Schmidt reaction under these conditions.

ethyl acetate; dense liquid) to give the desired diketone **5** (5.30 g, 96% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90−1.00 (t, 3H), 1.20−1.40 (m, 2H), 1.75−2.10 (complex, 6H), 2.45−2.65 (m, 6H), 3.10−3.25 (t, 2H), 4.54 (s, 1H), 4.80 (s, 1H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 12.2, 16.6, 24.6, 30.0, 33.7, 39.8, 44.1, 51.3, 68.0, 112.9, 146.3, 210.8; MS (EI) *m*/*z* 178, 164, 150, 136, 55, 41; HRMS (ESI) calcd for $C_{14}H_{25}N_4O_2$ (M + NH_4) 281.1972, found 281.1969. Error: 1.1 ppm.

Amide Compound 6. To a solution of the azido dione **5** (363 mg, 1.38 mmol) in dry CH_2Cl_2 (6 mL) under argon was added $TiCl_4$ (1.45 mL, 1 M in CH_2Cl_2) at −78 °C. The resulting mixture was stirred for 15 min under these conditions. The mixture was then warmed to room temperature and quenched with 3 mL of water. The resulting mixture was partitioned between water and CH_2Cl_2. The organic layer was collected, dried over $MgSO_4$, filtered, concentrated, and chromatographed (R_f = 0.1, 1:1 hexane/ethyl acetate; dense liquid) to afford **6** (300 mg, 93% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90−1.00 (m, 3H), 1.80−2.15 (complex, 9H), 2.20−2.60 (complex, 4H), 2.70−2.90 (m, 2H), 3.50−3.80 (m, 2H), 4.75−4.90 (m, 2H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 12.1, 20.7, 22.6, 29.4, 32.8, 34.8, 37.5, 39.4, 47.1, 74.2, 114.2, 146.2, 170.8, 210.7; IR (neat) 1649, 1714 cm^{-1}; MS (EI) *m*/*z* 235, 178, 166, 150, 138, 123; HRMS (ESI) calcd for $C_{14}H_{22}O_2N$ (M^++ H) 236.1645, found 236.1648. Error: 1.3 ppm.

Amide Compound 19. To a solution of **18** (40 mg, 0.12 mmol) in CH_2Cl_2 (3 mL) under argon was added $TiCl_4$ (0.24 mL, 1 M in CH_2Cl_2) at 0 °C. The resulting mixture was stirred for 40 min under these conditions. The mixture was then quenched with 2 mL of water. The resulting mixture was partitioned between water and CH_2Cl_2. The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated. Chromatography (R_f = 0.5, ethyl acetate; dense liquid) afforded **19** (27.4 mg, 75% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40−2.80 (complex, 6H), 2.85−3.05 (m, 2H), 3.15−3.30 (m, 1H), 4.85−4.95 (m, 1H), 5.10−5.20 (m, 2H), 5.50−5.70 (m, 1H), 5.90−5.95 (m, 2H), 6.57 (s, 1H), 6.95 (m,1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.0, 29.8, 35.4, 35.7, 43.7, 71.6, 101.2, 105.9, 109.1, 121.0, 126.5, 128.3, 131.5, 146.5, 147.2, 168.9, 204.7; IR (neat) 1235, 1406, 1485, 1655, 1728 cm^{-1}; MS (EI) *m*/*z* 299, 258, 230, 84; HRMS (ESI) calcd for $C_{17}H_{18}NO_4$ (M^+ + H) 300.1230, found 300.1229. Error: 0.3 ppm.

Tertiary Amine Compound 22. A solution of thiolactam (60 mg, 0.18 mmol) in THF (3 mL) was treated with W2-Raney Ni at room temperature. The reaction mixture was stirred for 1 h and filtered. The solvent was removed under reduced pressure, and the residue was chromatographed (R_f = 0.2, 2:1 hexane/ethyl acetate; colorless dense liquid) to give **22** (46 mg, 85% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85−1.95 (m, 1H), 2.06 (s, 3H), 2.07−2.30 (complex, 3H), 2.35−2.45 (m, 1H), 2.55−2.65 (m, 2H), 2.85−3.20 (complex, 6H), 3.30−3.40 (m, 1H), 3.55−3.60 (d, 1H), 5.85−5.90 (m, 2H), 6.55−6.60 (d, 2H); ^{13}C NMR (100.6 MHz,$CDCl_3$) δ 22.4, 23.0, 38.1, 45.6, 47.4, 53.3, 70.6, 100.9, 106.2, 109.5, 126.4, 127.1, 146.4, 146.8, 205.4, 207.0; IR (neat) 1038, 1235, 1483, 1706 cm^{-1}; MS (EI) *m*/*z* 273, 230, 189, 115, 43; HRMS (ESI) calcd for $C_{17}H_{20}NO_4$ (M^+ + H) 302.1387, found 302.1383. Error 1.3 ppm.

Pentacyclic Enone Compound 23. To a solution of **22** (30 mg, 0.1 mmol) in *t*-BuOH (3 mL) was added KO^{t}Bu (13.4 mg, 0.12 mmol) at 40 °C under argon. After 30 min, the solvent was removed under reduced pressure, and the residue was taken in 50 mL of $CHCl_3$. The organic phase was washed with water and brine, dried over $MgSO_4$, concentrated, and chromatographed (R_f = 0.05, 1:1 hexane/ethyl acetate; colorless dense liquid) to give cyclic enone **23** (23 mg, 80% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75−1.95 (complex, 2H), 2.05−2.18 (m, 1H), 2.40−2.58 (m, 2H), 2.65−2.90 (complex, 4H), 3.00−3.15 (m, 2H), 3.30−3.42 (m, 1H), 5.85−5.90 (m, 2H), 6.10−6.20 (d,1H), 6.37 (s,1H), 6.59 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.2, 26.7, 27.1, 46.6, 46.9, 67.1, 100.8, 104.9, 109.3, 126.1, 129.2, 129.7, 146.6, 146.8, 178.9, 205.6; IR (neat) 1038, 1236, 1482, 1713, 2932 cm^{-1}; MS (EI) *m*/*z* 283, 254, 240, 226, 196, 115, 41; HRMS calcd for $C_{17}H_{18}NO_3$ (M^+ + H) 284.1281, found 284.1284. Error: 1.1 ppm.

Acknowledgment. We gratefully acknowledge financial support from the NSFC (Nos. 20621091, 20672048, and 20732002) and the "111" program of Chinese Education Ministry.

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

JO900113S