Synthetic Studies on the *Stemona* Alkaloids: Construction of BCD Tricyclic Ring Skeleton of Stenine Based on an IMDA/Beckmann Rearrangement Strategy

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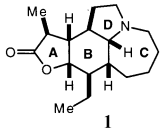
Stenine (**1**) and tuberostemonine (**2**) are the structurally related alkaloids isolated from *Stemona* species whose extracts have long been used in China and Japan both as drugs for the treatment of respiratory disease and anthelmintics.[1-3] The structures of stenine and tuberostemonine were determined by chemical degradation and spectrometric methods, with the full absolute configuration being elucidated by X-ray crystallographic analysis.[4,5]



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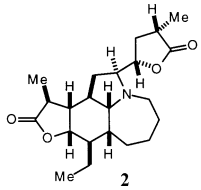

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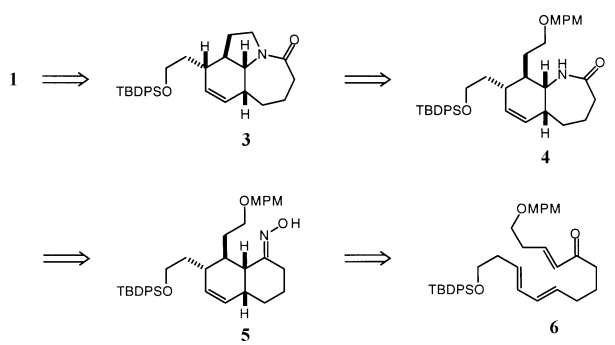
Several synthetic efforts directed toward stenine (**1**) and tuberostemonine (**2**) have been reported.[6] Among them, Hart's elegant synthesis[6a,6b] of stenine (**1**) utilized an intramolecular Diels-Alder strategy to build the B ring. Then, D, A, C rings were constructed in sequence. Kozikowski[6c] also used an intramolecular Diels-Alder reaction to install the B ring of tuberostemonine (**2**), in which $PhSe^+$-induced C ring formation was failed. As part of our studies in *Stemona* alkaloid synthesis, we designed an alternative intramolecular Diels-Alder approach to stenine (**2**) in which the Beckmann rearrangement was combined to construct the BC ring framework. We now report a novel construction of the BCD tricyclic ring skeleton of stenine (**2**) based on an intramolecular Diels-Alder/Beckmann rearrangement strategy.

As outlined in Scheme 1, we envisaged that the tertiary lactam **3** would serve as a suitable intermediate to stenine (**1**) and the five-membered D ring could be easily formed from the lactam **4** by a sequence of deprotection and cyclization process. The seven-membered C ring was expected to be built by the Beckmann rearrangement of the oxime **5**. The precursor ketone to oxime **5** was envisioned to be obtained through a Diels-Alder reaction of trienone **6**.

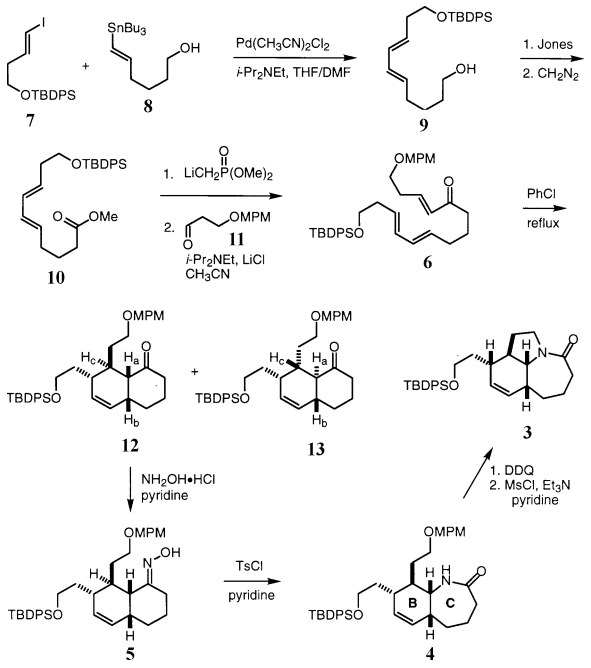


Scheme 1

Trienone **6** was synthesized starting from the readily available vinyl iodide **7**[7] and vinylstannane **8**[8] (Scheme 2). A Stille coupling[9] of **7** and **8** provided the targeted (*E*,*E*)-diene alcohol **9** in 62% yield. The alcohol **9** was converted into ester **10** in 80% yield by Jones oxidation and diazomethane treatment. Reaction of **10** with dimethyl lithiomethylphosphonate followed by Horner-Emmons coupling[10] of the resulting ketophosphonate with the aldehyde **11**[11] under Masamune-Roush conditions[12] completed the synthesis of **6** (79% from **10**). With trienone **6** in hand, the key intramolecular Diels-Alder reaction was explored. When heated to reflux in chlorobenzene for 48h, **6** underwent cyclization to produce two diastereomeric adducts. The desired *cis*-fused adduct **12** was obtained *via* the *endo* transition state in 40% yield along with 19% of *trans*-fused adduct **13**. The stereochemical assignments of cycloadducts **12** and **13** were made on the basis of analysis of ^{1}H NMR spectroscopic data. The observed ^{1}H-^{1}H coupling constants (**12**: J_{ab} = 5.2 Hz, J_{ac} = 8.3 Hz; **13**: J_{ab} = J_{ac} = 10.7 Hz) are related closly to known data of similar systems.[13]

Treatment of **12** with hydroxylamine hydrochloride in pyridine gave a 10 : 1 mixture of two stereoisomeric oximes in 93% yield. A Beckmann rearrangement of the major oxime **5** by tosyl chloride in pyridine at room temperature readily assembled the C ring skeleton to provide the seven-membered *cis*-lactam **4** in 89% yield. ^{1}H NMR data (appearance of -NHCO peak: δ 5.96, d, J = 6.05 Hz; downfield shift of H_a peak at 3.42 ppm compared to H_a peak at 2.34 ppm in **12**) and IR data (3,300 cm^{-1}, N-H stretch; 1,666 cm^{-1}, amide I; 1,620 cm^{-1}, amide II) are in accord with the structure of **4**. Because the Beckmann rearrangement proceeds with *anti* migration, the structure of **4** retrospectively verified the stereochemistry of the *anti*-oxime **5**.

The D ring could be constructed in two steps. The MPM group of **4** was removed with DDQ (89%). Installation of the D ring required a bond formation between amide nitrogen and hydroxy-containing carbon. Initially, we anticipated that such one-step cyclization should be possible by the Mitsunobu reaction.[14] However, many attempts to bring about cyclization using the Mitsunobu reaction were unsuccessful. We next tried to make a cyclization through a sequence of mesylate formation followed by base treatment. To our delight, it was found that this process could be performed in a single pot. Thus, treating with mesyl chloride and triethylamine in pyridine at room temperature and then heating at



Scheme 2

50 °C, the alcohol underwent smooth cyclization *via* its mesylate to provide the tertiary lactam **3**[15] in 70% yield. It was observed that the cyclization also took place at room temperature with or without the use of triethylamine, although it was slow. Addition of triethylamine and heating facilitated the ring closure.

In summary, we have demonstrated that the intramolecular Diels-Alder/Beckmann rearrangement strategy should be amenable to the construction of BCD ring skeleton of stenine.

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15. All new compounds gave spectral data consistent with the assigned structure. Spectral data for selected compounds are as follows. **12**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62-7.68 (m, 4H, aromatic), 7.33-7.42 (m, 6H), 7.20 (d, J = 8.3 Hz, 2H) , 6.83 (d, J = 8.3 Hz, 2H), 5.55 (s, 2H), 4.34 (ABq, 2H), 3.77 (s, 3H), 3.76 (m, 1H), 3.72 (m, 1H), 3.41 (m, 2H), 2.43 (m, 1H), 2.34 (dd, J = 5.2, 8.3 Hz, 1H), 2.28 (ddd, J = 5.6, 10.7, 13.8 Hz, 1H), 2.16 (m, 1H, 2.03-2.10 (m, 2H), 1.83-1.93 (m, 2H), 1.67-1.77 (m, 2H), 1.51-1.65 (m, 3H), 1.48 (m, 1H), 1.06 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 214.4, 135.9, 134.0, 131.3, 130.8, 129.7, 129.3, 128.8, 127.7, 113.8, 112.4, 72.6, 67.5, 61.6, 55.4, 54.9, 40.0, 38.0, 37.3, 36.5, 32.9, 32.1, 29.2, 27.0, 25.0, 19.3; IR (neat) 2925, 1706 (C=O), 1513 cm^{-1}. **4**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.58-7.72 (m, 4H), 7.32-7.47 (m, 6H), 7.23 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.96 (d, J = 6.5 Hz, 1H), 5.42-5.60 (m, 2H), 4.38 (ABq, 2H), 3.79 (m, 3H), 3.74 (m, 2H), 3.50 (m, 2H), 3.42 (m, 1H), 2.50 (m, 1H), 2.16-2.37 (m, 2H), 1.98 (m, 1H), 1.40-1.98 (m, 9H), 1.04 (s, 9H). IR (neat) 3300 (N-H), 2925, 1666 (C=O), 1620, 1513, 1467, 1427, 1248, 1102, 704 cm^{-1}. **3**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64-7.60 (m, 4H), 7.44-7.38 (m, 6H), 5.57 (m, 1H), 5.51 (m, 1H), 3.73 (t, J = 6.4 Hz, 2H), 3.52 (m, 1H), 3.50-3.43 (m, 2H), 2.72 (m, 1H), 2.63 (m, 1H), 2.58 (m, 1H), 2.16 (m, 1H), 2.08-2.16 (m, 2H), 2.00-2.10 (m, 1H), 1.68-1.83 (m, 2H), 1.58-1.66 (m, 2H), 1.40-1.57 (m, 2H), 1.30 (s, 9H). IR (neat) 2927, 1641, 1466, 1272, 1117, 753, 714 cm^{-1}.