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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Received November 19, 1999

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

Several synthetic efforts directed toward stenine (1) and tuberostemonine (2) have been reported.6 Among them, Hart’s elegant synthesis6a,b of stenine (1) utilized an intramolecular Diels-Alder strategy to build the B ring. Then, D, A, C rings were constructed in sequence. Kozikowski6c 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 (1) 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 triene 6.

Triene 6 was synthesized starting from the readily available vinyl iodide 7 and vinylstannane 8 (Scheme 1). A Stille coupling9 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 lithiomyethylphosphonate followed by Horner-Emmons coupling10 of the resulting ketophosphonate with the aldehyde 11 under Masamune-Roush conditions12 completed the synthesis of 6 (79% from 10). With triene 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 1H NMR spectroscopic data. The observed 1H-1H coupling constants (12: \( J_{ab} = 5.2 \) Hz, \( J_{ac} = 8.3 \) Hz; 13: \( J_{ab} = J_{ac} = 10.7 \) Hz) are related closely 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-fused cyclic skeleton 4 in 89% yield. 1H NMR data (appearance of -NHCO peak: \( \delta 5.96, d, J = 6.05 \) Hz; downfield shift of H4, peak at 3.42 ppm compared to H4 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 retroactively 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...
50 °C, the alcohol underwent smooth cyclization via its mesylate to provide the tertiary lactam 3\textsuperscript{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.

Acknowledgment. This research was supported by the Korea Science and Engineering Foundation (Grant No. 961-0302-020-2) and the Korea Research Foundation (Grant No. 1998-015-D00190). Authors thank Dr. Kang-Bong Lee at KIST for obtaining 600 MHz ¹H NMR spectra of 12, 13 and 3.

References

8. Obtained from the reaction of 5-pentyn-1-ol with n-Bu₃H in the presence of AIBN (90% yield).
15. All new compounds gave spectral data consistent with the assigned structure. Spectral data for selected compounds are as follows: 12: ¹H NMR (600 MHz, CDCl₃) δ 7.67-7.68 (m, 4H), 7.33-7.42 (m, 2H), 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), 3.74 (m, 1H), 3.31 (m, 1H), 2.14 (m, 1H), 2.34 (dd, J = 5.2, 8.3 Hz, 1H), 2.28 (dd, J = 5.5, 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); ¹³C NMR (50 MHz, CDCl₃) δ 131.7, 131.0, 130.3, 109.7, 129.8, 128.3, 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) 2295, 1706 cm⁻¹, 1513 cm⁻¹.
16. ³¹P NMR (200 MHz, CDCl₃) δ 7.58-7.72 (m, 4H), 7.32-7.37 (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, 3H), 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) 3000 (N-H), 2925, 1666 (C=O), 1620, 1513, 1467, 1427, 1248, 1102, 704 cm⁻¹. ³¹P NMR (600 MHz, CDCl₃) δ 8.64-7.60 (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, 2861, 1466, 1272, 7117, 753, 714 cm⁻¹.