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Chinese Chemical Letters 23 (2012) 1378–1380

CHINESE CHEMICAL LETTERS

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Efficient synthesis of the C/D rings of atisine-type C_{20}-diterpenoid alkaloids

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Received 20 September 2012
Available online 16 November 2012

Abstract

A bicyclo[2.2.2]octane C/D ring system, with a lactonic ring at C-8 and C-9, of the atisine-type C_{20}-diterpenoid alkaloids, was successfully synthesized, using an oxidative dearomatization/intramolecular Diels–Alder reaction.

Keywords: C_{20}-diterpenoid alkaloids; Oxidative dearomatization/intramolecular Diels–Alder reaction

C_{20}-diterpenoid alkaloids, featuring polycyclic, highly bridged, and heavily substituted structures, constitute the most structure types group of diterpeniod alkaloids [1]. The architectural features and the important pharmacological activities of the C_{20}-diterpenoid alkaloids pose an alluring target for synthetic chemists and medicinal chemists. The atisine-type C_{20}-diterpenoid alkaloids possess a relative simplicity and extensive structural data, made it an ideal first synthesis target, such as atisine **1** (Fig. 1) was the first total synthesis of the diterpenoid alkaloids respectively by Nagata group [2], Masamune group [3], Wiesner group [4], Fukumoto group [5]. Recently, we reported the total synthesis of (±)-atisine and (±)-isoazitine [6], as well as constructing A/E ring systems [7], A/E/F ring systems [8] and B/C/D ring systems of the C_{19}-diterpenoid alkaloids [9].

So far, five different approaches to Pelletier's synthetic intermediate (Fig. 1) for atisine has been reported [2–6], we also expect to efficiently and convergently construct it. Our retrosynthetic analysis of the Pelletier's synthetic intermediate is shown in Scheme 1. The target compound **2** was proposed to proceed from the tetracyclic compound **3**, which constructed nitrogen heterocyclic ring through the double Mannich reaction [10]. The tetracyclic **3** could be gained, using an intramolecular aldol condensation reaction of ketone **4** to form the key C9–C10 bond. The other key C6–C7 bond was builded to afford the ketone **4** by a Witting reaction of phosphonium salt **5** with aldehyde **6**. The aldehyde **6** could be obtained through several steps from lactone **7**. Here, we hope to report an efficient approach of constructing the [2.2.2]octane C/D ring systems of atisine-type C_{20}-diterpenoid alkaloids, using an oxidative dearomatization/intramolecular Diels–Alder reaction, which was developed by Liao and co-workers in 2001 [11].

Lactone **7** was prepared as shown in Scheme 2. Reduction of commercially available aromatic aldehyde **8** with $NaBH_4$ under 0 °C provided benzyl alcohol **9**, which reacted with acryloyl chloride to afford ester **10** in 70% yield over

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1001-8417/$ – see front matter
http://dx.doi.org/10.1016/j.cclet.2012.11.004

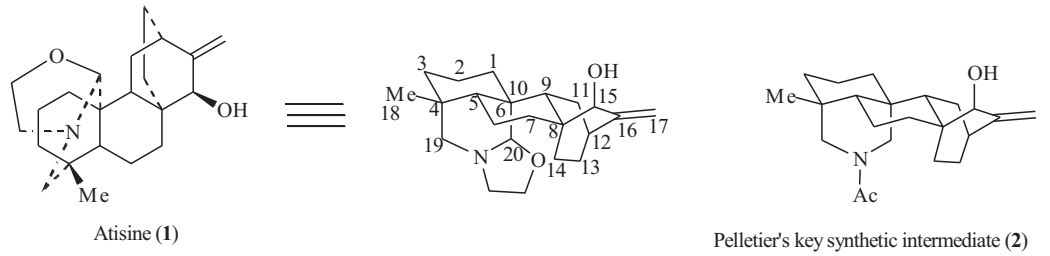
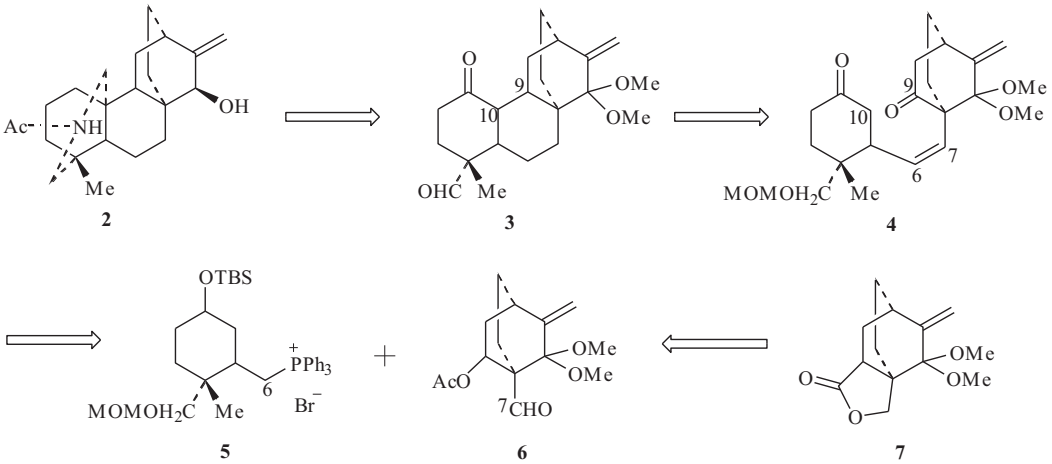
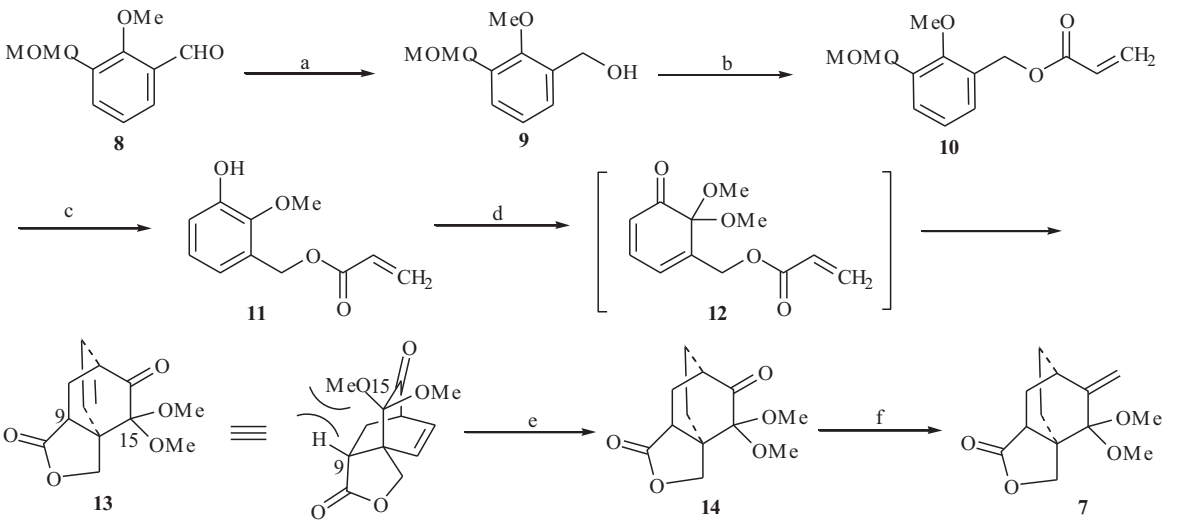


Fig. 1. Structures of atisine and Pelletier's intermediate.



Scheme 1. Retrosynthetic analysis for Pelletier's intermediate.



Scheme 2. Construction of C/D ring system of C_{20}-diterpenoid alkaloids. Conditions and reagents: (a) $NaBH_4$, MeOH, 0 °C, 90%; (b) acryloyl chloride, Py, CH_2Cl_2, 0 °C, 78%; (c) CF_3COOH, CH_2Cl_2, rt, 85%; (d) PIDA, MeOH, 0 °C, then xylene, reflux, 67%; (e) H_2, Pd/C, MeOH, rt, 87%; (f) Ph_3PCH_3Br, t-BuOK, Et_2O, 40 °C, 53%.

2 steps. Using trifluoroacetic acid, was the MOM group removed to give phenol precursor **11** in 85% yield. With phenol **11** in hand, we next explored the key oxidative dearomatization/intramolecular Diels–Alder reaction. Since a significant amount of undesired intermolecular dimerization product was produced using the literature procedure [11], we slightly modified the procedure as follows: the precursor **11** was oxidized with $PhI(OAc)_2$ using methanol as solvent in an ice-water bath, after 30 min switching the solvent from methanol to xylene, the resulting masked *ortho*-quinone **12** was heated at 160 °C to provide the lactone **13** [12] in 67% yield. Compound **13** was assigned as the desired endo product of the Diels–Alder reaction due to the critical correlation between H-9 and the methoxyl of C-15 in the NOESY spectrum of the hydrogenation product **14** [13]. Finally, the lactone **7** [14] was yielded from ketone **14** through a Wittig methylenation.

In conclusion, an efficient construction of highly functionalized C/D rings of atisine-type C_{20}-diterpenoid alkaloids has been successfully accomplished within 6 steps from a know aromatic aldehyde **8**, using oxidative dearomatization/intramolecular Diels–Alder reaction, which demonstrate a convergent strategy to construct highly functionalized bicyclo[2.2.2]octane systems by Liao and co-worker. Further elaboration into the A-, B-, E-rings base on the lactonic ring of compound **7** are under investigated in our laboratory and will be published in due course.

Acknowledgment

We are grateful for the financial support provided by the National Science Foundation of China (No. 81273387).

References

[1] (a) F.P. Wang, Q.H. Chen, X.Y. Liu, Nat. Prod. Rep. 27 (2010) 529;
(b) F.P. Wang, X.T. Liang, in: G.A. Cordell (Ed.), The Alkaloids: Chemistry and Biology, vol. 59, Elsevier Science, New York, 2002, p. 1.
[2] (a) W. Nagata, T. Sugasawa, M. Narisada, et al. J. Am. Chem. Soc. 85 (1963) 2342;
(b) W. Nagata, T. Sugasawa, M. Narisada, et al. J. Am. Chem. Soc. 89 (1967) 1483.
[3] S. Masamune, J. Am. Chem. Soc. 86 (1964) 291.
[4] (a) R.W. Guthrie, Z. Valenta, K. Wiesner, Tetrahedron Lett. 7 (1966) 4645;
(b) R.W. Guthrie, W.A. Henry, et al. Collect Czech. Chem. Commun. 31 (1966) 602.
[5] (a) M. Ihara, M. Suzuki, K. Fukumoto, et al. J. Am. Chem. Soc. 110 (1988) 1963;
(b) M. Ihara, M. Suzuki, K. Fukumoto, et al. J. Am. Chem. Soc. 112 (1990) 1164.
[6] X.Y. Liu, H. Cheng, F.P. Wang, et al. Org. Biomol. Chem. 10 (2012) 1411.
[7] Z.K. Yang, Q.H. Chen, F.P. Wang, Tetrahedron 67 (2011) 4192.
[8] Z.G. Liu, L. Xu, F.P. Wang, et al. Tetrahedron 68 (2012) 159.
[9] H. Cheng, L. Xu, F.P. Wang, et al. Tetrahedron 68 (2012) 1171.
[10] F.F. Blicke, F.J. McCarty, J. Org. Chem. 24 (1959) 1069.
[11] (a) Y.K. Chen, R.K. Peddinti, C.C. Liao, Chem. Commun. 2001 (2001) 1340;
(b) H.Y. Shiao, H.P. Hsieh, C.C. Liao, Org. Lett. 10 (2008) 449.
[12] Spectra data of compound **13**: IR (KBr, cm^{-1}): 2978, 2911, 1776, 1738, 1466, 1053, 986; ^1H NMR (400 MHz, $CDCl_3$): δ 1.78–1.84 (m, 1H), 2.22–2.29 (m, 1H), 3.16 (s, 3H), 3.20 (t, 1H, J = 2.8 Hz), 3.41 (dd, 1H, J = 6.8, 10.4 Hz), 3.50 (s, 3H), 4.50 (d, 1H, J = 8.8 Hz), 4.69 (d, 1H, J = 8.4 Hz), 6.21 (d, 1H, J = 8.4 Hz), 6.53 (t, 1H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9 (CH_2), 39.8 (CH), 47.8 (CH), 50.3 (CH_3), 51.5 (CH_3), 53.7 (C), 69.6 (CH_2), 93.7 (C), 132.7(CH), 133.8 (CH), 175.0 (C), 201.7 (C); HR-ESIMS: *m/z*: $C_{12}H_{14}O_5$ $[M+Na]^+$ 261.0738 (calcd. 261.0739).
[13] Spectra data of compound **14**: IR (KBr, cm^{-1}): 2950, 2987, 1782, 1739, 1370, 1065, 976; ^1H NMR (400 MHz, $CDCl_3$): δ 1.78–1.91 (m, 5H), 2.16 (dt, 1H, J = 2.0, 4.4 Hz), 2.42 (s, 1H), 3.14 (t, 1H, J = 10.0 Hz), 3.18 (s, 3H), 3.57 (s, 3H), 3.95 (d, 1H, J = 8.4 Hz,), 4.59 (d, 1H, J = 8.8 Hz,); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2 (CH_2), 21.9 (CH_2), 22.8 (CH_2), 39.5 (CH), 42.4 (CH), 48.1 (C), 51.0 (CH_3), 51.9 (CH_3), 70.2 (CH_2), 96.9 (C), 175.8 (C), 208.0 (C); HR-ESIMS: *m/z*: $C_{12}H_{16}O_5$ $[M+Na]^+$ 263.0890 (calcd. 263.0895).
[14] Spectra data of compound **7**: IR (KBr, cm^{-1}): 2924, 1648, 1514, 1104; ^1H NMR (400 MHz, $CDCl_3$): δ 1.61–1.72 (m, 4H), 1.83–1.95 (m, 2H), 2.47 (d, 1H, J = 2.8 Hz), 3.10–3.13 (m, 1H), 3.16 (s, 3H), 3.38 (s, 3H), 3.96 (d, 1H, J = 8.4 Hz), 4.60 (d, 1H, J = 8.4 Hz), 5.21 (s, 1H), 5.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7 (CH_2), 25.2(CH_2), 26.4 (CH_2), 38.2 (CH), 40.7 (CH), 47.9 (C), 50.0 (CH_3), 50.6 (CH_3), 71.2 (CH_2), 100.0 (C), 113.3 (CH_2), 148.9 (C), 177.4 (C); HR-ESIMS: *m/z*: $C_{13}H_{18}O_4$ $[M+Na]^+$ 261.1101 (calcd. 261.1103).