DOI 10.5012/bkcs.2010.31.11.3382

Total Synthesis of (±)-Aspidospermidine Starting from 3-Ethyl-5-bromo-2-pyrone

Hyun-Kyu Cho, Nguyen Thanh Tam, and Cheon-Gyu Cho*

*Department of Chemistry, Hanyang University, Seoul 133-791, Korea. *E-mail: ccho@hanyang.ac.kr*
Received September 8, 2010, Accepted September 21, 2010

A new synthetic route to (±)-aspidospermidine was devised, starting from the cycloadduct of 3-ethyl-5-bromo-2-pyrone with vinyl sulfide through a tandem conjugate addition-alkylation sequence. The requisite 3-ethyl-5-bromo-2-pyrone was prepared *via* the C3-selective Pd-catalyzed coupling reaction with Et_3Al-dimethylaminoethanol complex.

Key Words: Total synthesis, Aspidospermidine, Diels-Alder reaction, 3,5-Dibromo-2-pyrone, Tandem reaction

Introduction

As a part of our ongoing research program on 3,5-dibromo-2-pyrone and its derivatives as novel enophile synthons, we have explored the potential utility of the resultant densely functionalized cycloadducts in the target-oriented synthesis.[1] Such endeavors have resulted in the successful total synthesis of several bioactive alkaloid natural products including *trans*-dihydronarciclasine,[1e] joubertinamine,[1f] crinine,[1c] crinamine[1d] and galanthamine.[1b]

Bearing a pentacyclic ABCDE framework in common, the aspidosperma alkaloid comprises one of the largest groups of indole alkaloids with more than 250 members (Figure 1). The unique molecular architecture and a vast array of important biological activities featured by many of its members have led to intense investigation over the years. Aspidospermidine **1**, the parent compound of this alkaloid family,[2] has received the most attention and driven the development of many efficient and elegant synthetic methods and strategies.[3]

We have previously demonstrated that the key pentacyclic framework of the aspidosperma alkaloid could be readily forged from the cycloadduct of 3-aryl-5-bromo-2-pyrone.[1a] In this report, the rings D and E, in particular, were constructed by the intramolecular imino Diels-Alder reaction of the appropriately functionalized cyclohexenone precursor. Alternatively, the same ring system could be assembled by a tandem conjugate addition-alkylation sequence. Inspired by this envision, we decided to study the tandem reaction and subsequently the total synthesis of aspidospermidine.

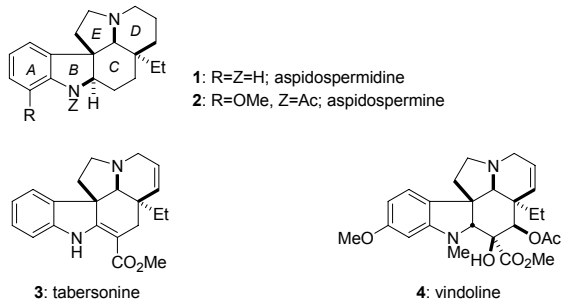


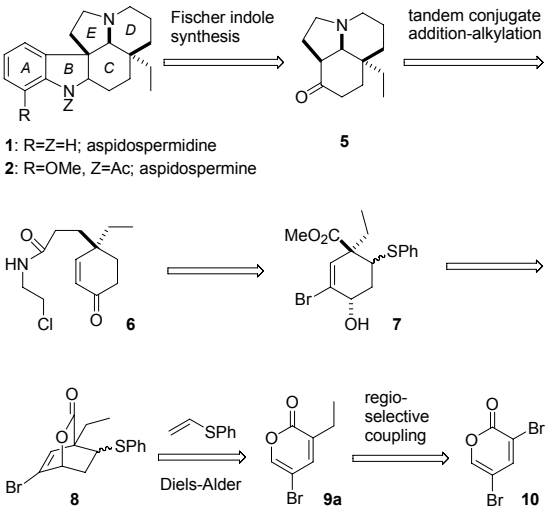
Figure 1. Selected examples of aspidosperma alkaloids.

Results and Discussion

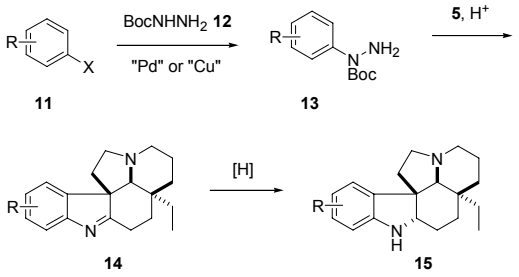
Our synthetic study of (±)-aspidospermidine **1** was conceived by the retrosynthesis illustrated in Scheme 1. The initial disconnection of the indoline unit led to ketone **5**, identical to the Stork's approach and others,[4] with respect to the employment of the Fischer synthesis for its assembly. For the construction of the D and E rings, we adopted the tandem conjugation-alkylation strategy reported by Marino and coworkers,[3f] in our case, retrosynthetically translated to the cyclohexenone **6** bearing all necessary functional groups. The final and key elaboration called for bicyclolactone **8**, the Diels-Alder adduct of 2-pyrone **9a** and phenyl vinyl sulfide.

We found this route particularly appealing because it allows the late stage variation of aromatic ring system *via* the use of our modified Fischer cyclization protocol (Scheme 2).[5] The starting *N*-Boc-aryl hydrazines **13** are conveniently prepared from *t*-butyl carbazate **12** and aryl halides **11** under Pd or Cu(I)-catalysis to warrant the structural and functional diversity of the indoline aryl unit.[6]

The synthesis commenced with the Pd-catalyzed incorporation of ethyl group onto the C3 position of 3,5-dibromo-2-pyrone **10**.[7] The use of Et_3Al-dimethylaminoethanol complex gave the



Scheme 1. Retrosynthesis of (±)-aspidospermidine **1**



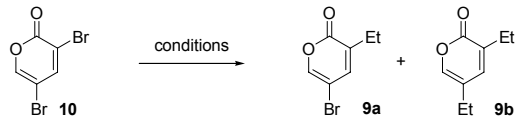
Scheme 2. Late-stage variation of aromatic subunit *via* the Fischer indolization with aryl hydrazide.

best results in terms of yield and selectivity (entry 1, Table 1).[1i,8] Other less successful trials are also listed in the Table for a comparison.

Upon securing multi-gram quantity of the 2-pyrone **9a**, we conducted the Diels-Alder reaction with phenyl vinyl sulfide which gave bicyclolactone **8** as a mixture of *endo*/*exo* isomers (3:2, 68% combined yield, Scheme 3). Much similar to the cycloaddition reactions of other C3-substituted-2-pyrones, the ethyl group at C3 position is presumed to destabilize otherwise favored *endo*-transition state, resulting in moderate *endo*/*exo* selectivity.[9] Although both isomers are tactically equivalent (phenylthio group is removed later in the sequence, **17** → **18**), the *endo*- and *exo*-cycloadducts were separated and carried individually through the reaction sequence for the handiness in the spectroscopic characterizations (only the reactions with *endo*-isomer is shown).[10]

Lactone opening of the bicyclolactone and protection of the resultant hydroxyl group as a TBS ether afforded **16** in good overall yield. The methyl ester was reduced to give alcohol **17**,

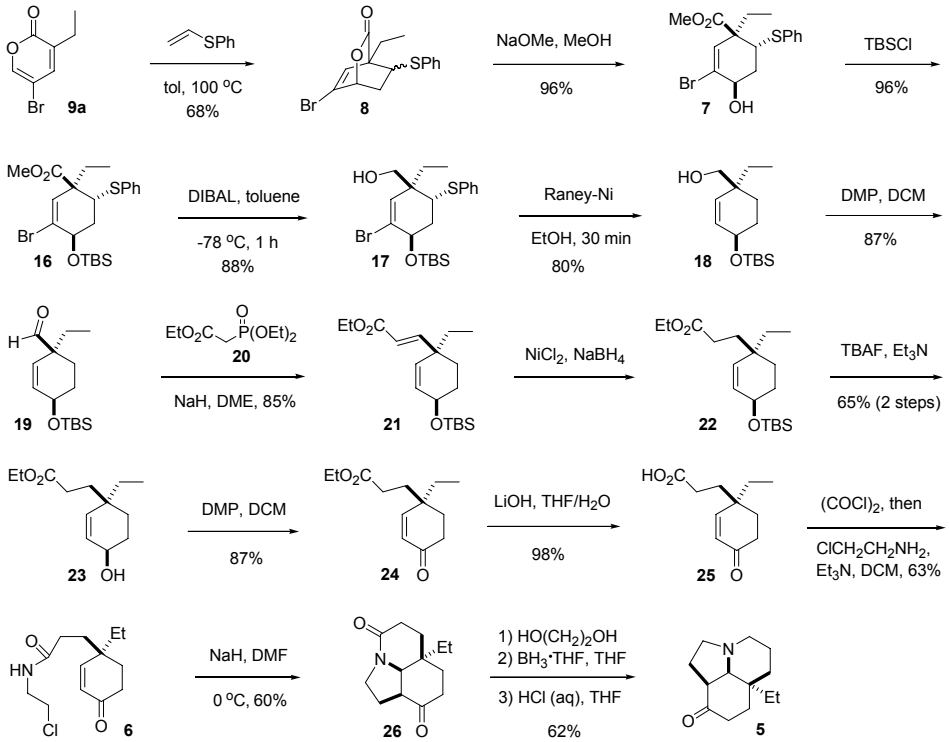
Table 1. Preparation of 3-ethyl-5-bromo-2-pyrone **9a**



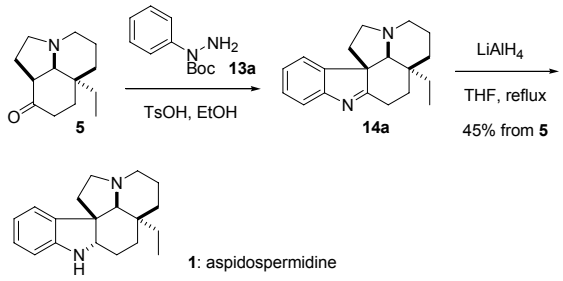
entry	conditions	**9a**:**9b**[a] (yield[b])
1	0.4 eq. Et_3Al-$Me_2N(CH_2)_2OH$ $PdCl_2(PPh_3)_2$, tol, 100 °C, 1 h	> 99:1 (55%)
2	0.4 eq. Et_3Al, $PdCl_2(PPh_3)_2$, tol, 100 °C, overnight	no reaction
3	0.4 eq. Et_3Al-$Et_2N(CH_2)_2OH$ $PdCl_2(PPh_3)_2$, tol, 100 °C, 1.5 h	> 99:1 (27%)
4	$EtBF_3K$, $Pd(OAc)_2$, RuPhos, Cs_2CO_3, tol, 80 °C	trace
5	$EtB(OH)_2$, $PdCl_2(PPh_3)_2$, tol, 100 °C, 48 h	6:4 (25%)
6	Et_2Zn, $PdCl_2(PPh_3)_2$, dioxane, 100 °C, 1 h	7:3 (34%)

[a] ^{1}H NMR ratio on crude products. [b]combined yield.

prior to the reductive removal of both vinyl bromide and phenylthio groups with Raney Nickel, to obtain cyclohexene **18**. Dess-Martin oxidation to aldehyde **19** followed by the Wittig olefination with phosphonate **20** gave ethyl enoate **21**. Selective conjugate reduction of the enoate double bond afforded ester **22** along with inseparable over-reduced product in the ratio of 6 to 1 (see supporting information for details). Removal of the TBS protecting group allowed the separation, providing pure alcohol **23** in 65% yield over 2 steps. Oxidation of the allylic alcohol to



Scheme 3. Synthesis of ketone **5**



Scheme 4. End-game synthesis

ketone **24** and hydrolysis of the methyl ester afforded the corresponding acid **25**[11] in good overall yield. Formation of acid chloride followed by the coupling reaction with chloroethylamine furnished amide **6** in 63% yield. When treated with NaH in DMF, enone **6** readily proceeded the tandem conjugate addition-alkylation cascade to give the tricyclic ketone **26** in 60% yield. Its amide group was then reduced to produce ketone **5** by following the known three-step reaction sequence involving ketalization, amide reduction and ketal unmasking.[12]

With sufficient quantity of ketone **5** in hand, we investigated the Fischer cyclization reaction with *N*-Boc-phenyl hydrazine **13a** (Scheme 4). When heated in EtOH with TsOH, ketone **5** provided the imine **14a**. Subsequent reduction with $LiAlH_4$ afforded aspidospermidine **1** in 45% overall yield from **5**.

In summary, we have devised a new synthetic route to (±)-aspidospermidine from 3,5-dibromo-2-pyrone, *via* the regioselective synthesis of 3-ethyl-5-bromo-2-pyrone and its Diels-Alder cycloaddition. Although the overall sequence may not be as efficient as others, we have demonstrated our Fischer cyclization protocol with aryl hydrazide could be highly effective in the generation of its congeners and various other analogs.

Experimentals

All information regarding experimental procedures and spectroscopic data is available in the supporting information.

(±)-Aspidospermidine (1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, J = 6.8 Hz, 1H), 7.01 (t, J = 7.2 Hz, 1H), 6.72 (t, J = 7.2 Hz, 1H), 6.63 (d, J = 7.6 Hz, 1H), 3.51 (dd, J = 10.8, 6.4 Hz, 1H), 3.14-3.10 (m, 1H), 3.06 (d, J = 10.8 Hz, 1H), 2.33-2.25 (m, 2H), 2.22 (s, 1H), 1.98-1.90 (m, 2H), 1.79-1.61 (m, 3H), 1.52-1.35 (m, 4H), 1.11 (td, J = 13.6, 4.4 Hz, 1H), 1.08-1.04 (m, 1H), 0.91-0.82 (m, 1H), 0.63 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 135.8, 127.1, 122.9, 119.1, 110.4, 71.4, 65.8, 54.0, 53.4, 53.1, 38.9, 35.7, 34.6, 30.1, 28.2, 23.1, 21.8, 6.9.

Acknowledgments. This work was supported by a grant of Hanyang University (2005). CHK and NTT thank the BK21 fellowship.

References

1. (a) Tam, N. T.; Jung, E.-J.; Cho, C.-G. *Org. Lett*. **2010**, *12*, 2012. (b) Chang, J.; Kang, H.-U.; Jung, I.-H.; Cho, C.-G. *Org. Lett*. **2010**, *12*, 2016. (c) Tam, N. T.; Cho, C.-G. *Org. Lett*. **2008**, *10*, 601. (d) Tam, N. T.; Chang, J.; Jung, E.-J.; Cho, C.-G. *J. Org. Chem*. **2008**, *73*, 6258. (e) Shin, I.-J.; Choi, E.-S.; Cho, C.-G. *Angew. Chem. Int. Ed*. **2007**, *46*, 2303. (f) Tam, T.; Cho, C.-G. *Org. Lett*. **2007**, *9*, 3391. (g) Kim, H.-Y.; Cho, C.-G. *Prog. Heterocycl. Chem*. **2007**, *18*, 1. (h) Shin, J.-T.; Hong, S.-C.; Shin, S.; Cho, C.-G. *Org. Lett*. **2006**, *8*, 3339. (i) Ryu, K.; Cho, Y.-S.; Cho, C.-G. *Org. Lett*. **2006**, *8*, 3343. (j) Chung, S.-I.; Seo, J.; Cho, C.-G. *J. Org. Chem*. **2006**, *71*, 6701.
2. (a) Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, Chapter 1. (b) Saxton, J. E. *Indoles, Part 4: The Monoterpenoid Indole Alkaloids*; Wiley: Chichester, 1983.
3. For a recent synthesis, see: (a) Coldham, I.; Burrell, A. J. M.; White, L. E.; Adams, H.; Oram, N. *Angew. Chem. Int. Ed*. **2007**, *46*, 6159. (b) Sharp, L. A.; Zard, S. Z. *Org. Lett*. **2006**, *8*, 831. (c) Iyengar, R.; Schildknegt, K.; Morton, M.; Aube, J. *J. Org. Chem*. **2005**, *70*, 10645. (d) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc*. **2002**, *124*, 4628. (e) Banwell, M. G.; Smith, J. A. *J. Chem. Soc., Perkin Trans 1* **2002**, *23*, 2613. (f) Marino, J. P.; Rubio, M. B.; Cao, G.; de Dios, A. *J. Am. Chem. Soc*. **2002**, *124*, 13398. (g) Patro, B.; Murphy, J. A. *Org. Lett*. **2000**, *2*, 3599. (h) Iyengar, R.; Schildknegt, K.; Aube, J. *Org. Lett*. **2000**, *2*, 1625. (i) Toczko, M. A.; Heathcock, C. H. *J. Org. Chem*. **2000**, *65*, 2642. (j) Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A. *J. Chem. Soc., Perkin Trans 1: Organic and Bio-Organic Chem*. **1999**, 995. (k) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc*. **1998**, *120*, 13523.
4. Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc*. **1963**, *85*, 2872.
5. (a) Park, I.-K.; Suh, S.-E.; Lim, B.-Y.; Cho, C.-G. *Org. Lett*. **2009**, *11*, 5454. (b) Johnson, P. D.; Sohn, J.-H.; Rawal, V. H. *J. Org. Chem*. **2006**, *71*, 7899. (c) Lim, Y.-K.; Cho, C.-G. *Tetrahedron Lett*. **2004**, *45*, 1857.
6. (a) Lim, Y.-K.; Lee, K.-S.; Cho, C.-G. *Org. Lett*. **2003**, *5*, 979. (b) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett*. **2002**, *4*, 581.
7. Kim, W.-S.; Kim, H.-J.; Cho, C.-G. *J. Am. Chem. Soc*. **2003**, *125*, 14288.
8. Blum, J.; Gelman, D.; Baidossi, W.; Shakh, E.; Rosenfeld, A.; Aizenshtat, Z. *J. Org. Chem*. **1997**, *62*, 8681.
9. Kim, W.-S.; Lee, J.-H.; Kang, J.; Cho, C.-G. *Tetrahedron Lett*. **2004**, *45*, 1683.
10. **7-exo** provided **13** in similar overall yield.
11. Meyers, A. I.; Berney, D. *J. Org. Chem*. **1989**, *54*, 4673.
12. Literature yield (ref 1c): 67%.