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Construction of the ABC-ring System of Delnudine through Free Radical Cyclization and Alkylidene Carbene C-H Insertion†

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Delnudine isolated from seeds of *Delphinium Delnudatum* by Götz and Wiesner[1] belongs to the aconite alkaloids[2] with a complex pentacyclic structure[3] that is thought to be biogenetically related to hestine and denudatine.[4]

Recently, we developed a novel synthetic strategy to construct tricyclo[4.3.2.0^{1,5}]-undecane structures through a tandem radical cyclization reactions and a rearrangement. The efficiency of this strategy was demonstrated by the total synthesis of suberosenone.[5] Since a tricyclo[4.3.2.0^{1,5}]-undecane structure was imbedded in the core structure of delnudine (Figure 1), we became interested in the total synthesis of delnudine.

A synthetic strategy toward delnudine was devised based on the tandem radical cyclization reaction route as one might be able to attach the A and D-rings of delnudine onto the BC-ring system that could be obtained from radical cyclization reaction. That strategy requires functionalization of unactivated carbon centers for further elaboration of the ring system into the delnudine skeleton. To functionalize the carbon centers for appending the A and D-rings on to the BC-ring skeleton, a regioselective alkylidene carbene C-H insertion to construct the A-ring and a similar strategy using radical or carbene mediated functionalization of the dimethylene bridge of the B-ring are required (Scheme 1). In this paper, we would like to report a successful construction of the ABC-ring system of delnudine from a readily prepared unfunctionalized BC-ring system of delnudine **5**[5] using regioselective carbene C-H insertion reaction.

From the tricyclic compound **5**,[6] construction of the A-ring of delnudine was explored through intramolecular alkylidene carbene insertion reaction strategy. Execution of that strategy required a selective functionalization between two double bonds of **5** to introduce a carbonyl group as the precursor of the alkylidene carbene. After protecting the two alcohols of **5** as benzyl ethers, mCPBA epoxidation proceeded selectively as anticipated to produce **7** as a single diastereomer. Treatment of **7** with $BF_3{\cdot}Et_2O$ produced the aldehyde **8** as a mixture of diastereomers (α:β = 1:8). The minor α-isomer was converted to the β-aldehyde through equilibration using sodium methoxide in methanol. Addition of lithiated ethyl vinyl ether[7] to **8** produced two isomeric α-siloxyketones **9a** and **9b** (1:5) after protection of α-hydroxy groups as silyl ethers. Reductive deoxygenation of the silyl ethers of **9a** or **9b** using SmI_2[8] produced **10** (Scheme 2). Compound **11** was prepared from **10** by ozonolysis with an anticipation of the selective reaction at only the desired carbonyl center.

With **9a**, **9b**, **10** and **11** in hand, we examined the scope of the crucial alkylidene carbene C-H insertion reaction, especially the regioselectivity between tertiary and secondary C-H bonds for the construction of the A-ring.[9] Treatment of each **9a**, **9b**, **10**, and **11** with (trimethylsilyl)-diazomethane anion[10] efficiently generated alkylidene carbenes from ketones and underwent selective C-H insertion reaction. The result of C-H insertion reaction was summarized in the Table 1. Alkylidene carbenes underwent the insertion reaction into the tertiary C-H bond with a complete selectivity in all cases except **9a**. For **9a**, selectivity of the insertion reaction reversed completely in favour of the secondary C-H bond to form **16**. This reversal of selectivity of

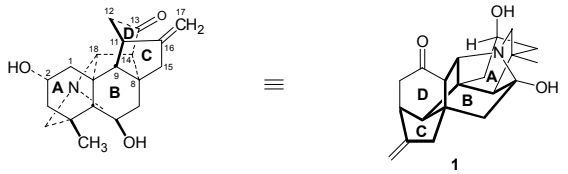
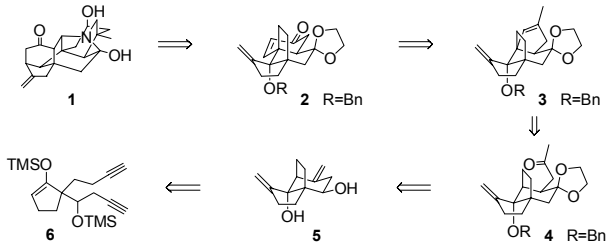
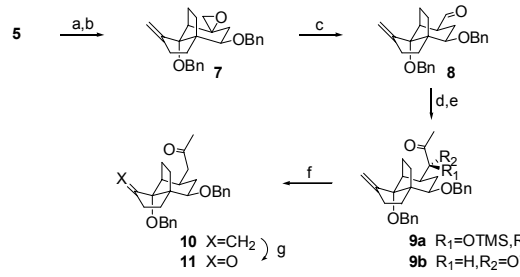


Figure 1. Structure of delnudine.

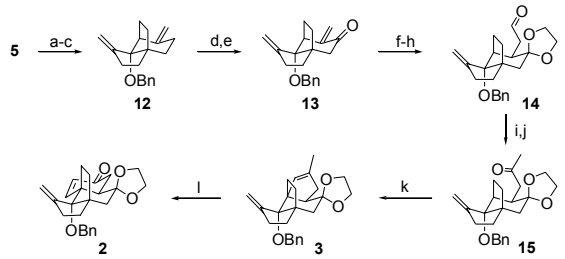


Scheme 1. Retrosynthetic analysis of delnudine



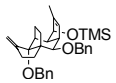
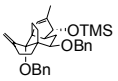
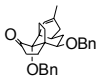
Scheme 2. Reagents and conditions: (a) BnBr, NaH, $Bu_4N^+I^-$, DMF, quant. (b) mCPBA, CH_2Cl_2, 80%. (c) $BF_3{\cdot}Et_2O$ (0.1 eq), Toluene, 0 °C, 78%. (d) Ethyl vinyl ether/*t*-BuLi, THF, −78 °C; 5% HCl (aq), 90%. (e) DIPEA, TMSCl, CH_2Cl_2, 85%. (f) SmI_2, MeOH/THF (1/2), −78 °C, 83%. (g) O_3, CH_2Cl_2, −78 °C; Me_2S, 52%

†This paper is dedicated to Professor Sunggak Kim on the occasion of his honorable retirement.



Scheme 3. Reagents and conditions: (a) Phenylchlorothionoformate, DMAP, CH_2Cl_2, 92%. (b) Bu_3SnH, AIBN, benzene, reflux, 94%. (c) BnBr, NaH, $Bu_4N^+I^-$, DMF, 0 °C, quant. (d) SeO_2, *t*-BuOOH, CH_2Cl_2, 76%. (e) TPAP, NMO, CH_2Cl_2, 84%. (f) Et_2AlCN, toluene, 0°C, 90%. (g) ethylene glycol, *p*-TsOH, benzene, reflux, 90%. (h) DIBAL-H, toluene, −78 °C, 86%. (i) MeMgBr, ether, 0 °C, 97%. (j) TPAP, NMO, CH_2Cl_2, 95%. (k) $TMSN_2CLi$, 87%. (l) O_3; PPh_3; 10% KOH/MeOH, 58%

Table 1. Alkylidene carbene C-H insertion[a]

substrate	**9a**	**9b**	**10**	**11**
product				
	16	**17**	**18**	**19**
isolated yield	45%	78%	73%	31%

[a]condition: [(trimethylsilyl)diazomethyl]lithium, THF, 0 °C.

C-H insertion reaction is presumed to be due to strong eclipsing interaction of OTMS group with the B-ring in a conformation for the desired C-H insertion reaction into the tertiary C-H bond to form the cyclopentene ring. This result was quite intriguing since this is the first example of complete regioselective C-H insertion reaction[11] and even **10** that had no conformational bias during the insertion reaction showed the complete selectivity toward the tertiary C-H bond.

With the successful exploitation of the selective C-H insertion reaction, we prepared the substrate with proper functionalization pattern of the B-ring for the construction of the A-ring of delnudine. First, the secondary alcohol of **5** was removed using a radical deoxygenation protocol.[12] Selective formation of thiocarbonate of the secondary alcohol of **5** with phenylchlorothionoformate in the presence of DMAP followed by reduction using Bu_3SnH and AIBN produced **12** after protection of the remaining alcohol as the benzyl ether. Then, **12** was converted to the enone **13** through selective allylic oxidation of exocyclic olefin in the B-ring using SeO_2 followed by TPAP oxidation.[13] Conjugate addition of diethylaluminum cyanide[14] to the enone of **13** produced the cyano ketone as a single diastereomer. Since direct methylation of the nitrile did not proceed at all, the nitrile was reduced to the corresponding aldehyde **14** with DIBAL-H[15] after protection of the ketone as ethylene ketal. Addition of methylmagnesiumbromide to **14** followed by TPAP oxidation afforded the methylketone **15** (Scheme 3). Alkylidene carbene insertion reaction of **15** using the same protocol produced cyclopentene **3** in 87% yield. The cyclopentene ring of **3** was converted into the six-membered A-ring of delnudine through ozonolysis, aldol condensation and dehydration sequence[16] to furnish the ABC-ring system of delnudine with adequately introduced functional groups (Scheme 3).

In summary, we have demonstrated that free radical cyclization reaction and alkylidene carbene C-H insertion reaction were shown to be powerful tools in the construction of complex natural product skeletons through a synthesis of the ABC-ring system of delnudine with proper functionalization of the ring system. Currently we are working on the introduction of the final D-ring of delnudine through another radical mediated selective C-H activation of the dimethylene bridge of the B-ring.

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6. All new compounds were fully characterized by physical and spectroscopic methods. Spectral data for **2**, **3**, and **5** were given below. **5**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10-1.18 (m, 1H), 1.32-1.39 (m, 1H), 1.50 (br s, 1H), 1.55 (br s, 1H), 1.66-1.81 (m, 3H), 1.88-1.95 (m, 1H), 2.09-2.16 (m, 1H), 2.48-2.59 (m, 2H), 2.64-2.70 (m, 1H), 2.73 (d, *J* = 5.8 Hz, 1H), 3.98 (dd, *J* = 5.5, 6.4 Hz, 1H), 4.84 (m, 2H), 5.04 (m, 1H), 5.09 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.67, 25.48, 28.66, 28.72, 37.31, 50.22, 55.36, 72.87, 86.87, 108.14, 111.03, 148.34, 153.88. IR (thin film) 3411, 2944, 1651, 1086, 1041 cm^{-1}. HRMS calcd for $C_{13}H_{18}O_2$: 206.1307 found: 206.1307. **3**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (m, 1H), 1.38 (m, 1H), 1.46 (m, 1H), 1.57-1.70 (m, 3H), 1.73 (s, 3H), 1.87-2.00 (m, 2H), 2.18 (dd, *J* = 13.1, 1.8 Hz, 1H), 2.23-2.28 (m, 1H), 2.45-2.60 (m, 2H), 3.07 (dd, *J* = 10.4, 7.70 Hz, 1H), 3.75-4.05 (m, 4H), 4.49 (d, *J* = 3.0 Hz, 2H), 5.18 (m, 1H), 5.28 (m, 1H), 5.76 (s, 1H), 7.18-7.30 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.65, 26.61, 28.72, 29.69, 30.73, 31.70, 41.80, 49.43, 55.81, 58.42, 63.42, 64.87, 65.59, 89.13, 109.68, 110.27, 126.64, 126.73, 127.68, 128.03, 139.91, 140.06, 149.82. IR (thin film) 2955, 1455, 1308, 1271, 1166, 1119, 1039 cm^{-1}. HRMS calcd for $C_{25}H_{30}O_3$: 378.2195 found: 378.2184. **2**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41-1.69 (m, 3H), 1.72 (d, *J* = 13.3 Hz, 1H), 1.87 (m, 1H), 2.16 (m, 1H), 2.22 (d, *J* = 13.4 Hz, 1H), 2.42 (m, 1H), 2.52-2.60 (m, 3H), 3.14 (m, 1H), 3.76-3.99 (m, 4H), 4.38-4.55 (dd, *J* = 41.8, 11.4 Hz, 2H), 5.34 (m, 1H), 5.47 (m, 1H), 5.92 (d, *J* = 10.2 Hz, 1H), 7.19-7.29 (m, 5H), 7.50 (d, *J* = 10.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.19, 29.12, 30.57, 31.10, 33.77, 40.71, 43.00, 50.66, 55.03, 63.89, 65.26, 65.82, 89.82, 108.75, 112.46, 126.75, 127.08, 127.83, 128.19, 138.79, 149.46, 152.85, 200.12. IR (thin film) 2946, 1681, 1455, 1267, 1170, 1126, 1095 cm^{-1}. HRMS calcd for $C_{25}H_{28}O_4$: 392.1988 found: 392.1995.
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