An Efficient Palladium Mediated Synthesis of (±)-γ-Lycorane

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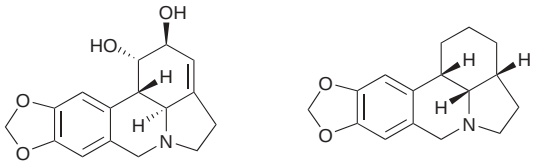
Abstract: An intramolecular approach incorporating a Michael addition followed by a palladium-mediated arylation of ketone towards the synthesis of Amaryllidaceae alkaloid (±)-γ-lycorane was reported.

Key words: synthesis, (±)-γ-lycorane, palladium, intramolecular arylations, alkaloids

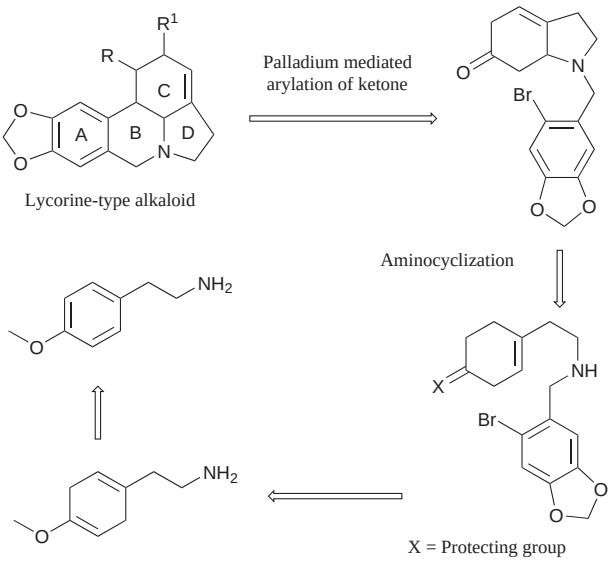
The lycorine-type alkaloids, which are characterized by the presence of the galanthan (tetracyclic pyrrolo[*d*,*e*]phenanthridine) ring system, are an important class of natural products isolated from the plants of the Amaryllidaceae family.[1] Many members of this group of alkaloids exhibit potent biological activities including antitumor,[2] antiviral and insect antifeedant activities.[3] The pentacyclic structure as well as its interesting biological activities have long attracted the attention of numerous research groups. Synthetic efforts directed towards lycorine (**1**) and γ-lycorane (**2**) have generated a great deal of creative total synthesis and a wide variety of methodologies (Figure 1).[4] Recent examples in the synthesis of lycorine-type alkaloids were documented in Padwa's elegant intramolecular [4+2] cycloaddition and rearrangement cascade of furanyl carbamates,[4b] Zard's radical cyclization of xanthates[5] and Tomioka's nitro-Michael cyclization of unsaturated esters.[6]



Lycorine (**1**) γ-Lycorane (**2**)

Figure 1 Representative lycorine-type alkaloids

As part of our ongoing program in pursuit of efficient while flexible strategy for the synthesis of Amaryllidaceae alkaloids, we recently disclosed a highly stereoselective aminocyclization approach towards the synthesis of the core N-heterocyclic center for a number of natural alkaloids.[7] It appeared to us that lycorine-type alkaloids such as lycorine and γ-lycorane were the immediate target by employing this aminocyclization protocol. As shown in our retrosythetic analysis in Scheme 1, one of the key issues in our synthetic pathway is the palladium-mediated arylation of ketone to afford the galathan ring system for lycorine-type alkaloids.



Scheme 1 Retrosythetic analysis of lycorine-type alkaloids

Although palladium mediated arylation of ketones has been well documented in the literature[8] and has the potential to be used for the synthesis of complex natural products, few methodologies involving this powerful reaction has been developed towards the synthesis of natural products.[9] In order to demonstrate the efficiency of such an intramolecular approach as depicted in Scheme 2, a synthesis towards the less complicated lycorine-type alkaloid, namely the (±)-γ-lycorane was initiated.

Starting from commercially available 2-(4-methoxyphenyl)-ethylamine, a Birch reduction furnished the diene **4** in 98% yield. The diene **4** was then treated with 6-bromopiperonal followed by reduction with $NaBH_4$ in ethanol afforded the secondary amine **5**. After treatment with 4 N HCl in methanol at 35 °C, an intramolecular Michael addition provided the octahydro-indol-6-one (**6**) in 80% overall yield for the two reactions. It is noteworthy that only *cis*-C,D-ring junction for the octahydro-indol-6-one (**6**) was observed.[10] The intramolecular arylation of compound **6** was initially conducted in anhydrous THF with $Pd_2(dba)_3$ and racemic BINAP in the presence of sodium *tert*-butoxide. The reaction did proceed, however, in low yield. To our delight, variation of the solvent to toluene afforded the desire cyclization in 81% yield. The stereo-

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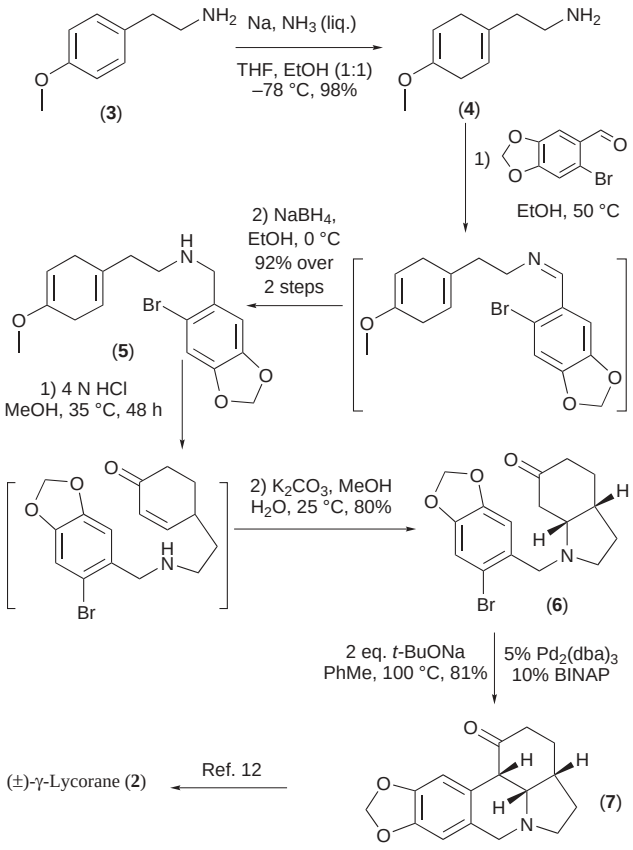
chemistry of this reaction is quite remarkable, *cis*-fused B,C-ring junction was exclusively formed.[11] The NOE experiment for this compound was conducted and the results were consistent with a *cis*-B,C,D-ring system. In the literature,[12] ketone **7** has already been converted to (±)-γ-lycorane, therefore a formal synthesis of (±)-γ-lycorane was completed.



Scheme 2 Formal synthesis of (±)-γ-lycorane

In summary, we have developed a concise method towards the synthesis of (±)-γ-lycorane. A convenient four step-sequence leaded to the (±)-α-dihydrocaronone in an overall 58% yield. The intramolecular approach including a Michael addition followed by a palladium mediated arylation of ketone demonstrated herein represents a highly efficient while stereoselective strategy and are valuable for the preparation of lycorine related compounds. Synthesis of lycorine by utilizing this protocol is in progress.

Acknowledgment

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(11) Compound **4**: IR (KBr): ν_{max} = 1696 (w), 1664 (m), 1389 (m), 1216 (s), 1173 (s)cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.36 (1 H, s), 4.53 (1 H, s), 3.46 (3 H, s, OMe), 2.69 (2 H, t, *J* = 6.7 Hz), 2.67–2.62 (4 H, brs), 2.05 (2 H, t, *J* = 6.7 Hz), 1.26 (2 H, brs). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.23, 133.15, 119.52, 90.54, 54.05, 41.09, 40.17, 29.40. GC-MS: *m/z* (%) = 153.4 (2) [M$^+$], 152.3 (1), 138.4 (1), 136.4 (3), 135.3 (17), 125.5 (15), 123.7 (100), 121.4 (16), 120.3 (5), 109.4 (39), 108.3 (35), 105.2 (16), 103.2 (11), 91.3 (46), 79.4 (35), 77.3 (38). Compound **5**: IR (KBr): ν_{max} = 1665 (w), 1502 (w), 1477 (s), 1413 (w), 1390 (w), 1241 (s), 1216 (s), 1172 (m), 1038 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.96 (1 H, s), 6.87 (1 H, s), 5.93 (2 H, s), 5.43 (1 H, s), 4.58 (1 H, s), 3.74 (2 H, s), 3.52 (3 H, s, OMe), 2.80–2.60 (6 H, m), 2.20 (2 H, t, *J* = 6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.31, 147.69, 147.61, 133.46, 133.01, 119.47, 114.38, 113.00, 110.39, 102.01, 90.65, 54.18, 53.91, 47.05, 37.36, 29.60, 29.51. GC-MS: *m/z* (%) = 364.4 (7) [M$^+$ – 1], 362.4 (6) [M$^+$ – 1], 284.4 (10), 244.2 (61), 242.2 (58), 216.3 (22), 215.0 (100), 213.1 (82), 182.9 (8), 162.4 (13), 157.2 (21), 155.2 (16), 136.5 (9), 135.2 (72), 124.4 (67), 123.3 (26), 121.4 (17), 108.4 (7), 105.4 (32). Compound **6**: IR (KBr): ν_{max} = 1713 (s), 1503 (w), 1478 (s), 1411 (w), 1360 (m), 1223 (s) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.92 (1 H, s), 6.83 (1 H, s), 5.92 (1 H, d, *J* = 1.0 Hz), 5.91 (1 H, d, *J* = 1.0 Hz), 3.76 (1 H, d, *J* = 13.8 Hz), 3.28 (1 H, d, *J* = 13.8 Hz), 2.91 (1 H, dd, *J* = 8.3, 17.0 Hz), 2.87 (1 H, dd, *J* = 4.3, 10.3 Hz), 2.55 (1 H, td, *J* = 4.2, 15.8 Hz), 2.52 (1 H, td, *J* = 4.2, 15.8 Hz), 2.51 (1 H, dd, *J* = 4.3, 15.7 Hz), 2.44 (1 H, ddd, *J* = 4.7, 10.3, 18.0 Hz), 2.18 (1 H, ddd, *J* = 4.5, 6.5, 18.0 Hz), 2.10 (1 H, dd, *J* = 9.7, 17.0 Hz), 2.02–1.90 (2 H, m), 1.76–1.68 (1 H, m), 1.55–1.45 (1 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.74, 147.73, 147.53, 131.93, 114.33, 112.71, 110.71, 101.96, 62.20, 57.20, 53.50, 41.93, 36.48, 35.52, 29.83, 26.71. GC-MS: *m/z* (%) = 353.4 (37) [M$^+$], 351.2 (42)

[M^+], 296.3 (45), 294.1 (54), 281.3 (6), 272.3 (8), 213.3 (100), 185.0 (11), 159.2 (8), 157.1 (34), 154.9 (15), 148.4 (11), 135.3 (47). Compound **7**: IR (KBr): ν_{max} = 2927 (w), 2788 (w), 1730 (m), 1715 (s), 1645 (w), 1503 (m), 1484 (s), 1448 (w), 1373 (w), 1241 (s), 1145 (w), 1100 (w), 1039 (s), 935 (m), 807 (m)cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.60 (1 H, s), 6.50 (1 H, s), 5.91 (1 H, d, *J* = 1.3 Hz), 5.90 (1 H, d, *J* = 1.3 Hz), 3.99 (1 H, d, *J* = 14.5 Hz, PhCH), 3.46 (1 H, d, *J* = 3.6 Hz), 3.28 (1 H, d, *J* = 14.5 Hz, PhCH), 3.22 (1 H, dd, *J* = 7.9, 8.6 Hz), 2.83 (1 H, dd, *J* = 3.6, 7.8 Hz), 2.71–2.63 (1 H, m), 2.53 (1 H, ddd, *J* = 4.3, 10.8, 15.4 Hz), 2.39 (1 H, ddd, *J* = 4.5, 6.5, 10.8 Hz), 2.22 (1 H, dd, *J* = 8.6, 17.4 Hz), 2.13–2.03 (2 H, m), 1.85–1.76 (1 H, m), 1.69–1.60(1 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.84, 147.02, 146.04, 128.40, 125.04, 111.81, 106.42, 101.19, 64.39, 56.19, 54.12, 51.46, 36.59, 34.97, 29.35, 27.20. GC-MS: m/z (%) = 271.4 (64) [M^+], 270.4 (100), 255.5 (5), 254.4 (35), 243.4 (3), 242.4 (18), 241.4 (3), 228.4 (7), 225.4 (2), 215.4 (6), 214.4 (21), 212.3 (15), 207.3 (11), 200.4 (5), 188.4 (7), 187.4 (17), 184.4 (5), 174.3 (13), 173.3 (6), 162.4 (14), 154.3 (9), 148.3 (12), 147.3 (10), 130.4 (11), 116.4 (8), 115.3 (10), 106.4 (5), 102.3 (12), 91.4 (7), 89.3 (17), 78.3 (10), 77.4 (24).

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