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A Model Study toward the Total Synthesis of *N*-Deacetyllappaconitine

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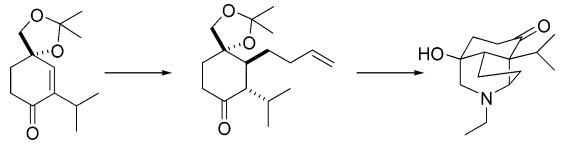
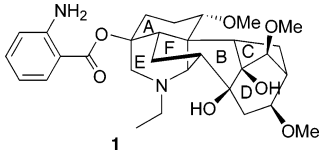


A model study leading to the preparation of the AEF rings of *N*-deacetyllappaconitine is described. The conjugate addition to the α-alkyl cyclohexenone **10** proceeded with high diastereocontrol. The Mannich cyclization of **16** to **4** was accomplished by heating with Rexyn-300 and Na_2SO_4.

Introduction

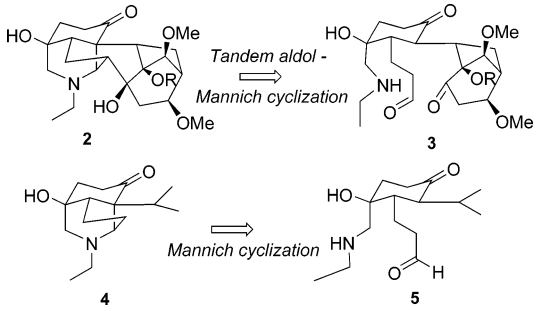
The hexacyclic *N*-deacetyllappaconitine **1** is a cardioactive agent that is representative of the diterpenoid *Delphinium* alkaloids.[1] This intriguing skeleton, which includes 6 rings and 12 stereogenic centers, is a substantial challenge for organic synthesis. Despite the potent physiological activity of this class of alkaloids,[2] only a little progress[3] has been reported toward a practical preparation of this family of alkaloids since the landmark (56 steps) synthesis of the first aconite by Wiesner[4] more than 25 years ago.



1

The intramolecular Mannich reaction is a powerful strategy for the assembly of complex ring systems.[5] For the synthesis of the diterpene alkaloid **1** (Scheme 1), our plan is to use a tandem aldol/Mannich cyclization (**3** → **2**) as the key step. To explore the proposed Mannich cyclization, we have carried out a model study (**5** → **4**) using an isopropyl group as a surrogate for the right bicyclic fragment of **3**. The compound **4** incorporates the A, E, and F rings of *N*-deacetyllappaconitine.

SCHEME 1



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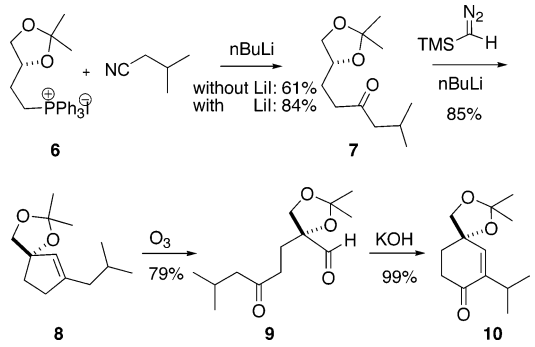
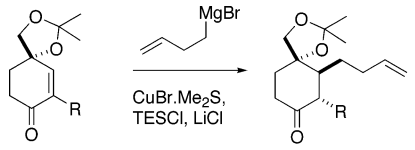
SCHEME 2



SCHEME 3

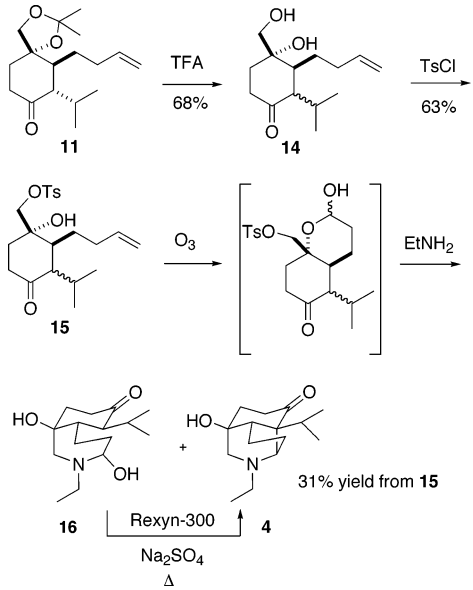


Results and Discussion

Intramolecular Alkylidene Carbene Insertion To Form 10. The route toward the Mannich precursor **5** began with the phosphonium salt **6** (Scheme 2), which is easily prepared in large scale from racemic 1,2,4-butanetriol (both enantiomerically pure 1,2,4-butanetriols are also commercially available).[6] Recently, we reported the preparation of ketones by the condensation of phosphonium salts with nitriles,[7] following an improvement of the McEwen procedure.[8] We have since found (Supporting Information) that including an additional stoichiometric amount of LiI improved the yield of the ketone **7** from 61% to 84%. The ketone **7** was cyclized via intramolecular alkylidene carbene C−H insertion to give **8**.[9] Ozonolysis followed by aldol condensation then gave the cyclohexenone **10**.

Conjugate Addition to the α-Alkyl Cyclohexenone 10. Several years ago, we reported that excellent diastereoselectivity could be achieved for the chlorotriethylsilane-promoted conjugate addition of cuprates to the cyclohexenone **12** to give **13** (Scheme 3, diastereomer ratio 93:7).[10] The presence of the alkyl group on the α-position of the enone makes the conjugate addition to **10** more difficult. To our delight, Cu-mediated addition of the Grignard reagent derived from 4-bromo-1-butene proceeded smoothly to give **11** as a single diastereomer, in 78% yield from **10**, under the same conditions as described before. The relative configuration achieved was that needed for the Mannich cyclization. This unique conjugate addition forms two stereocenters in one step with high stereoselectivity. Thus, *intramolecular carbene insertion and conjugate addition combine to form a powerful approach for the stereoselective synthesis of such multisubstituted cyclohexanones*.

SCHEME 4



Mannich Cyclization. With the correct relative configuration of **11** in hand, deprotection (Scheme 4) with trifluoroacetic acid (TFA) gave the diol **14** as an inconsequential mixture of two diastereomers. Monotosylation of **14** afforded **15**. Ozonolysis of **15** gave an aldehyde that subsequently cyclized with the tertiary alcohol to form a hemiacetal intermediate. This intermediate was used for the Mannich cyclization without further purification.

Our initial attempts at Mannich cyclization were not encouraging. On exposure to ethylamine, the hemiacetal was converted to the Mannich base **16** (90%), but only a trace amount of the desired product **4** (2%) could be isolated. Dehydration of the Mannich base **16** to form the cyclized product **4** proved elusive. TsOH is a very efficient reagent for the intermolecular Mannich reaction,[11] but no reaction was observed even when a stoichiometric amount of TsOH was added to **16**, with or without heating. Lewis acids, such as $LiClO_4$ or $Al(Et)_2Cl$, can prompt a Mannich base to form the cyclized product.[12] However, Lewis acids also did not effect the dehydration of **16**.

Fortunately, we found that Rexyn-300, a commercial resin that contains both strong acid and strong base

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(11) Bobowski, G.; Shavel, J. J. *J. Heterocycl. Chem.* **1980**, *17*, 519.

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groups, converted **16** into the cyclized product **4**. High temperatures were required (sealed tube, 170 °C, 8 h), as well as the addition of Na_2SO_4 as a water sequestering agent. In addition to **4**, a small quantity of **16** (10% based on **15**) was recovered from the cyclization.

Conclusion

The synthesis of the model intermediate cyclohexanone **11** has been successfully accomplished using an alkylidene carbene insertion/ozonolysis/aldol/conjugate addition sequence. The conjugate addition to the α-alkyl cyclohexenone proceeded with high diastereocontrol, so this strategy can be used for the construction of multisubstituted cyclohexanones. The Mannich cyclization was realized in the presence of Rexyn-300 and Na_2SO_4 at elevated temperature by dehydration of the intermediate Mannich base **16**. The synthesis of the Mannich product **4** containing the A, E, and F rings of *N*-deacetyllappaconitine took nine steps with 6.9% overall yield, starting from ketone **7**. Our efforts toward the enantioselective total synthesis of *N*-deacetyllappaconitine are continuing.

Experimental Section

Cyclohexanone (11). A mixture of CuBr·Me_2S (1.77 g, 8.6 mmol) and LiCl (364 mg, 8.6 mmol) in THF (33 mL) was purged with N_2 for 15 min. The mixture was chilled to −78 °C, and 3-butenylmagnesium bromide (0.65 M in THF, 13 mL, 8.45 mmol) was added. After a few minutes, TESCl (1.5 mL, 8.6 mmol) was added, followed immediately by the addition of the cyclohexenone **10** (1.00 g, 4.4 mmol) in THF (0.5 mL). The reaction mixture was stirred at −78 °C for 15 min and then warmed to −30 °C over 0.5 h. After being stirred at −30 °C for 15 min, the mixture was partitioned between saturated aqueous NH_4Cl and Et_2O. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was redissolved in THF (10 mL), and TBAF (1.0 M in THF, 5 mL, 5 mmol) was added. After being stirred for 0.5 h at rt, the mixture was partitioned between saturated aqueous NH_4Cl and Et_2O. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford cyclohexanone **11** (960 mg, 3.4 mmol, 78% yield) as a colorless oil: TLC R_f = 0.44 (10% Et_2O/petroleum ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.79 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 6.4 Hz, 3H), 1.05−1.15 (m, 2H), 1.39 (s, 3H), 1.48 (s, 3H), 1.83−1.96 (m, 3H), 2.05−2.15 (m, 4H), 2.52−2.58 (m, 1H), 2.82−2.90 (m, 1H), 3.78−3.83 (m, 2H), 4.99−5.04 (m, 2H), 5.65−5.73 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ u 116.3, 110.2, 82.8, 73.8, 35.6, 34.3, 32.5, 30.9, 6.2; d 137.9, 63.0, 46.4, 28.7, 26.6, 22.0, 21.7, 7.0; IR (cm^{-1}) 1708, 1370, 1211, 1059; HRMS calcd for $C_{17}H_{28}O_3$ (M) 280.2038, found 280.2035.

Diol (14). To the cyclohexanone **11** (500 mg, 1.79 mmol) in THF/H_2O (4:1, 10 mL) was added trifluoroacetic acid (1 mL). The mixture was warmed to reflux for 4 h and then cooled. Et_3N (2 mL) was added, and the mixture was partitioned between saturated aqueous $NaHCO_3$ and ethyl acetate. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give an inseparable mixture of diols **14** (2:1 mixture of diastereomers, 260 mg, 1.1 mmol, 68% yield based on 90% conversion) as a colorless oil, TLC R_f = 0.15 (50% Et_2O/petroleum ether). Starting material **11** (50 mg, 0.18 mmol, 10%) was also recovered. For **14**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.80 (major) (d, J = 6.7 Hz, 2 of 3H), 0.85 (minor) (d, J = 6.8 Hz, 1 of 3H), 0.92 (minor) (d, J = 6.3 Hz, 1 of 3H), 1.00 (major) (d, J = 6.5 Hz, 2 of 3H), 1.02−1.07 (m, 1H), 1.34−1.43 (m, 1H), 1.75−2.21 (m, 7H), 2.44 (s, 1H), 2.61−2.72 (m, 2H), 2.85−2.92 (m, 1H), 3.50 (t, J = 12.4 Hz, 1H), 3.64 (t, J = 12.4 Hz, 1H), 4.95−5.04 (m, 2H), 5.67−5.77 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ u (major) 216.6, 115.8, 73.9, 68.5, 34.8, 32.0, 31.7, 29.5; (minor) 214.4, 115.3, 74.3, 67.5, 38.6, 34.3, 32.3, 25.8; d (major) 137.9, 62.3, 43.8, 29.6, 21.9, 21.8; (minor) 138.3, 56.3, 46.7, 23.6, 22.5, 19.8; IR (cm^{-1}) 3433, 1693, 1045; HRMS calcd for $C_{14}H_{24}NaO_3$ (M + Na) 263.1623, found 263.1614.

Monotosylate (15). A mixture of the diol **14** (300 mg, 1.25 mmol), DMAP (15.3 mg, 0.125 mmol), and Et_3N (0.52 mL, 3.75 mmol) in CH_2Cl_2 (6.3 mL) was cooled to 0 °C. TsCl (357.5 mg, 1.88 mmol) was added in portions over 15 min, and the resulting mixture was stirred at rt for 24 h. The mixture was partitioned between saturated aqueous $NaHCO_3$ and Et_2O. The combined organic extract was dried (Na_2SO_4) and then concentrated. The residue was chromatographed to provide monotosylate **15** (inseparable 2:1 mixture of diastereomers, 232 mg, 0.59 mmol, 63% yield based on 75% conversion) as a colorless oil: TLC R_f = 0.37 (50% Et_2O/petroleum ether). Starting material **14** (75 mg, 0.19 mmol, 25%) was also recovered. For **15**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.78 (major) (d, J = 6.6 Hz, 2 of 3H), 0.81 (minor) (d, J = 6.8 Hz, 1 of 3H), 0.90 (minor) (d, J = 6.2 Hz, 1 of 3H), 1.00 (major) (d, J = 5.6 Hz, 2 of 3H), 1.02−1.07 (m, 1H), 1.12−1.32 (m, 1H), 1.71−2.20 (m, 7H), 2.47−2.80 (m, 5H), 2.87−2.94 (m, 1H), 3.92−4.03 (m, 2H), 4.86−4.98 (m, 2H), 5.57−5.65 (m, 1H), 7.30−7.40 (m, 2H), 7.80−7.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ u (major) 214.7, 145.5, 132.3, 115.8, 75.7, 73.0, 34.2, 31.5, 31.4, 25.9; (minor) 212.8, 145.6, 132.2, 115.3, 74.8, 73.0, 38.0, 34.1, 31.9, 29.5; d (major) 137.4, 130.2, 128.1, 61.6, 43.4, 29.5, 23.5, 21.8, 19.7; (minor) 137.6, 130.2, 128.0, 55.8, 46.9, 29.5, 22.5, 21.7, 19.7; IR (cm^{-1}) 3508, 1704, 1598, 1362, 1176; HRMS calcd for $C_{21}H_{30}NaO_5S$ (M + Na) 417.1712, found 417.1720.

Mannich Cyclized Amine (4). The monotosylate **15** (150 mg, 0.38 mmol) and Sudan-III (1 mg) in CH_2Cl_2 (20 mL) was chilled to −78 °C. Ozone was passed through the solution until the pink color faded, and then N_2 was passed through for 15 min. Dimethyl sulfide (0.056 mL, 0.74 mmol) was added, and the mixture was stirred for another 2 h. The mixture was concentrated in vacuo and transferred into a thick-wall tube. THF (1.4 mL) was added, and the mixture was purged with N_2 for 15 min. Ethylamine (70% H_2O solution, 5.6 mL) was added, and the tube was sealed and put into a 65 °C oil bath for 4 h. The mixture was cooled and and partitioned between H_2O and ethyl acetate. The combined organic extract was dried (Na_2SO_4) and then concentrated in vacuo. The residue was transferred into a thick-wall tube (Aldrich), and Rexyn-300 (Fisher, 700 mg), Na_2SO_4 (563 mg), and *o*-xylene (2.8 mL) were added. The solution was purged with N_2 for 15 min, and then the tube was sealed and put into 170 °C oil bath for 8 h (safety shield!). The mixture was cooled, and Et_3N (1.5 mL) was added. The mixture was stirred for 0.5 h and filtered. The filter cake was washed with ethyl acetate, and the filtrate was concentrated. The residue was chromatographed to give the cyclized product **4** (30 mg, 0.12 mmol, 31% yield from **15**) as a pale yellow oil: TLC R_f = 0.45 (50% Et_2O/petroleum ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (d, J = 6.9 Hz, 3H), 0.95 (t, J = 7.1 Hz, 3H), 1.16 (d, J = 6.9 Hz, 3H), 1.43−1.53 (m, 3H), 1.66−1.82 (m, 3H), 1.96−2.05 (m, 2H), 2.21−2.33 (m, 5H), 2.51−2.58 (m, 1H), 2.69 (d, J = 10.8 Hz, 1H), 3.34 (d, J = 4.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ u 214.1, 69.6, 63.7, 58.1, 48.7, 40.2, 36.6, 24.1, 19.7; d 66.6, 49.5, 30.2, 18.1, 17.5, 13.0; IR (cm^{-1}) 3450, 1697, 1153, 1093; HRMS calcd for $C_{15}H_{26}NO_2$ (M + H) 252.1964, found 252.1965.

The uncyclized Mannich base **16** (10 mg, 0.037 mmol, 10% yield from **15**) was also isolated: TLC R_f = 0.22 (50% Et_2O/petroleum ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.99 (d, J = 7.1 Hz, 3H), 1.06 (d, J = 7.0 Hz, 3H), 1.11 (t, J = 7.2 Hz, 3H), 1.43−1.61 (m, 2H), 1.71−1.83 (m, 3H), 1.94−2.05 (m, 4H), 2.18−2.24 (m, 2H), 2.36−2.41 (m, 2H), 2.66−2.71 (m, 1H), 2.81−2.86 (m, 1H), 3.56 (d, J = 9.9 Hz, 1H), 4.79 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ u 210.3, 81.5, 59.0, 52.0, 40.1, 35.8, 31.6, 23.7; d 93.3, 56.7, 43.9, 25.6, 20.6, 17.4, 14.6; IR (cm^{-1}) 3558, 1715, 1456, 1070; HRMS calcd for $C_{15}H_{25}NO_2$ (M − H_2O) 251.1885, found 251.1874.

In a separate run, chromatography after the 65 °C heating gave **16** in 90% yield and **4** in 2% yield from **15**. On exposure to the Rexyn-300 conditions, purified **16** gave a 30% yield of **4**.

Acknowledgment. We thank Dr. John Dykins for recording mass spectra and the NIH (GM60287) for financial support.

Supporting Information Available: General experimental procedures, experimental procedures for the preparation of **7**−**10**, and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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