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STUDIES DIRECTED TOWARDS THE TOTAL SYNTHESIS OF MORPHINE ALKALOIDS

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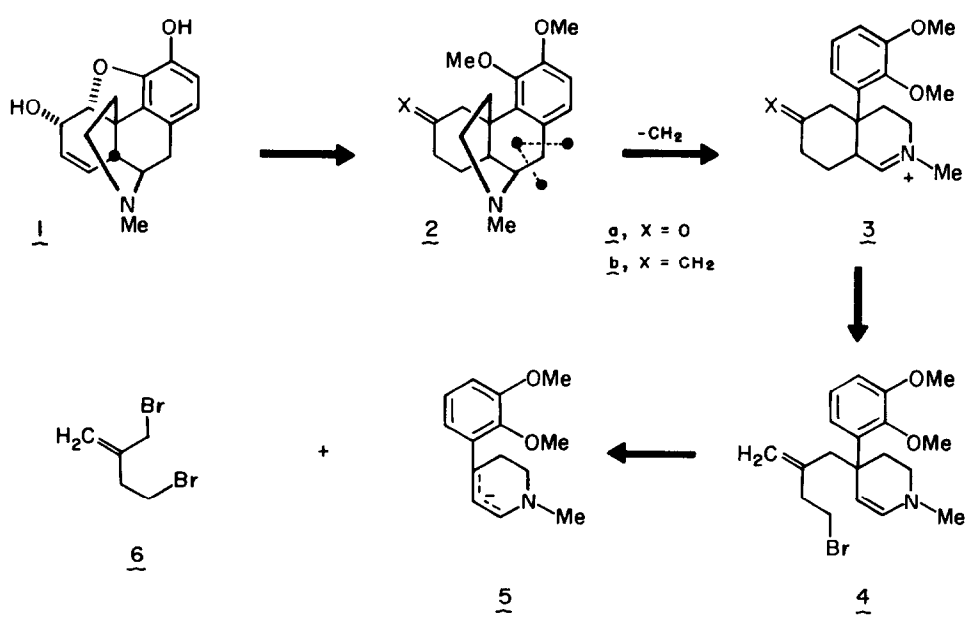
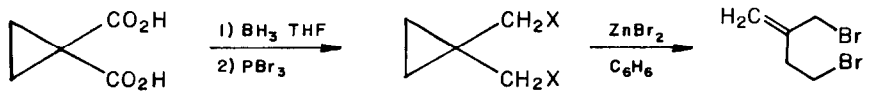
Abstract: Application of metallated enamines to the synthesis of morphine related congeners is reported. A formal total synthesis of (±)-morphine has been completed.

A recent publication from this laboratory outlined an efficient approach to the construction of simple morphinan derivatives.[1] The purpose of this communication is to expand upon the scope of our earlier studies which have been directed toward the development of a morphine total synthesis according to the plan outlined in Scheme I.

Scheme I

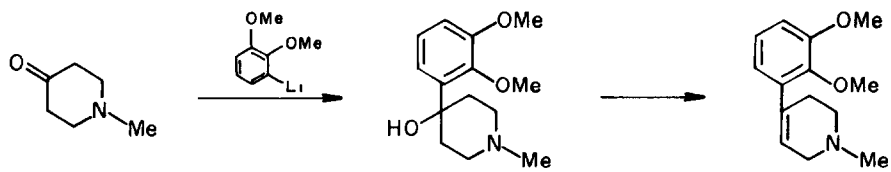


Pursuant to executing the desired synthesis plan, the illustrated structural components were constructed in the following fashion. The requisite dibromide **6** was conveniently synthesized in three steps from cyclopropane dicarboxylic acid[2] as illustrated below (eq 1). Borane reduction of **7** (BH_3, THF, 25°C, 75%) and subsequent bromination[3] of diol **8a** (1.1 molar equiv PBr_3, 0.1 equiv 48% HBr, CH_2Cl_2, 96 h) afforded the dibromide **8b** in 75% yield. The requisite allylic dibromide **6** was prepared via Lewis Acid catalyzed cyclopropylcarbinyl rearrangement[4] of **8b** (1.0 equiv. $ZnBr_2$, C_6H_6, 80°C, 36 h) in 80% yield.[5] The synthesis



(1)

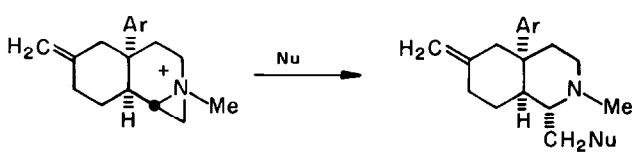
7 8a, X = OH; b, X = Br [60%] 6 [75%]



(2)

9

of the required tetrahydropyridine **9** was executed by the addition of 2,3-dimethoxyphenyllithium[6] to N-methyl 4-piperidone (Et_2O, 0°C, 45-50%) followed by acid catalyzed dehydration (3 equiv. TsOH, toluene, 110°C, 2 h, 95%) of the resultant alcohol (eq 2). The annelation process leading to the bicyclic enamine **10** was carried out by metallation of tetrahydropyridine **9** (n-BuLi,THF, -10°C, 30 min) and subsequent cannulation of the anion into 2 equiv of dibromide **6** (Et_2O, -78°C). The resultant monocyclic enamine **4** (c.f. Scheme I) was then cyclized to the bicyclic enamine **10** in the presence of sodium iodide (MeCN, K_2CO_3 80°C, 2 h). In complete analogy with earlier studies,[1] kinetic protonation of **10** ($HClO_4$-MeOH, Et_2O) afforded the crystalline (mp 149-151°C) trans-fused immonium salt which, upon dissolution in MeOH (50°C, 24 h), equilibrated to the thermodynamically preferred cis-isomer **11** (cis:trans = 95:5) as an amorphous powder in an overall yield of 60% from **9**. Conversion of the cis-fused immonium perchlorate **11** to the morphinan skeleton was accomplished in 72% yield by the following three-step sequence. The reaction of **11** (CH_2Cl_2, 25°C) with an ethereal solution of diazomethane afforded the diastereomerically pure aziridinium salt **12** (mp 186-188 C, 95%) which was readily transformed into the α-amino aldehyde **13** in virtually quantitative yield upon its dissolution in anhydrous dimethyl sulfoxide (25°C). This exceptionally efficient "Kornblum oxidation" of aziridinium salts deserves further attention as a potentially generalizable method for the construction of α-amino aldehydes.

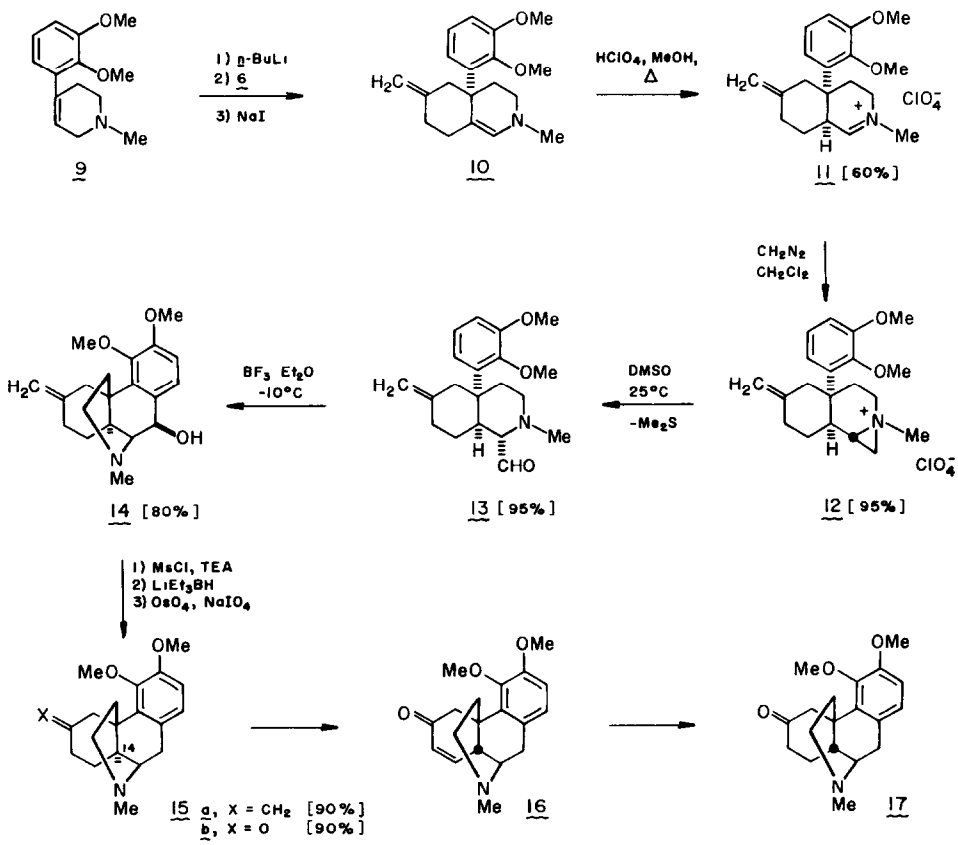


12

Nu = Cl^-, ^-OH, $^-O\text{-}\overset{+}{S}(Me)_2$ (3)

In the present instance, the oxidative cleavage of aziridinium perchlorate **12** by DMSO was suggested by the facile regioselective substitution reactions of this salt by both hydroxide and chloride ions (eq 3). The conversion of **13** to the morphinan carbinol **14** was affected by Lewis Acid catalyzed cyclization (2.5 equiv BF_3 Et_2O, toluene, -10°C, 3 h) in 80% yield. Successive methanesulfonation and reduction of the mesylate derived from **14** ($LiBEt_3H$) afforded morphinan **15a** in excellent yield.

Scheme II



From our earlier studies precedent had been established for the direct conversion of immonium salt **11** to morphinan **15a** upon diazomethane treatment.[1] With a sample of the direct cyclization product **15a** in hand, a careful examination of the reaction of **11** with diazomethane revealed the presence of approximately 1% of **15a**. The small percentage of morphinan noted in this instance is in marked contrast to our earlier observations that this ring system could be directly constructed from immonium ions related to **11** upon diazomethane treatment.[1]

The completion of a formal total synthesis of (±)-morphine was accomplished by Lemieux-Johnson oxidation (OsO_4, $NaIO_4$) of **15a** under acidic conditions ($THF:H_2O:HOAc$, 3:1:1)[7] to ketone **15b** which was previously employed by Gates in his pioneering total synthesis of morphine.[8] Verification of the structure of **15b** was accomplished by its conversion to the C_{14}-epimer **17** via base catalyzed equilibration and subsequent reduction of unsaturated ketone **16**.[9] The ^1H, ^{13}C NMR and infrared spectra of **17** were found to be identical with authentic **17** obtained from natural sources, generously provided by A. Brossi and H. Schmidhammer.[10]

Acknowledgement. This work has been supported by the National Institutes of Health (GM-26111) and the Eli Lilly Company. The use of the Southern California Regional NMR Facility (NSF-7916324A1) is also acknowledged.

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Selected ^{13}C NMR Data: (22.5 MHz)

17: ($CDCl_3$) δ 210.5, 151.5, 148.9, 130.4, 130.2, 122.9, 111.4, 60.3, 57.0, 55.8, 51.3, 46.5, 45.6, 42.6, 41.5, 41.1, 40.0, 27.0, 24.0.

15b: (C_6D_6) δ 209.6 (s), 151.9 (s), 148.7 (s), 136.8 (s), 131.1 (s), 123.2 (d), 111.8 (d), 60.0 (q), 57.8 (d), 55.6 (q), 51.9 (t), 47.9 (t), 42.8 (q), 41.7 (d), 40.8 (t), 40.4 (s), 31.3 (t), 28.5 (t), 26.9 (t).

14: (C_6D_6) δ 152.7, 147.4, 137.0, 136.3, 123.8, 111.8, 110.1, 69.7, 63.3, 60.1, 55.4, 47.0, 46.7, 45.5, 42.4, 40.3, 35.4, 30.2, 25.4.

11 trans: (CD_3CN) δ 182.4, 154.6, 148.8, 145.1, 131.2, 123.9, 122.3, 113.7, 111.8, 61.3, 56.5, 52.4, 48.8, 45.7, 43.0, 35.2, 34.7, 27.0.

11 cis: (CD_3CN) δ 181.4, 154.6, 148.9, 144.6, 136.2, 124.8, 120.2, 113.7, 111.9, 61.2, 56.5, 52.2, 49.3, 43.1, 42.6, 39.3, 33.2, 27.6, 27.1.

12: (CD_3CN) δ 154.5, 148.8, 145.7, 138.3, 124.1, 121.3, 113.3, 111.4, 60.8, 56.5, 53.5, 50.8, 50.7, 46.2, 43.3, 39.4, 34.8, 30.8, 30.4, 27.6.

10: ($CDCl_3$) δ 153.2, 147.7, 147.3, 138.9, 133.7, 125.1, 122.0, 112.8, 110.9, 108.4, 60.2, 55.7, 46.7, 46.2, 44.5, 42.7, 37.8, 36.1, 31.8.

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