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AROMATIC ANNELATION. A SYNTHESIS OF (±)-3-METHYL-8,14-DEHYDROMORPHINAN.

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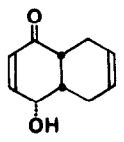
Summary: (±)-3-Methyl-8,14-dehydromorphinan has been prepared by forming the aromatic ring in the late stages of the synthesis.

Since the pioneering work of Gates,[1a] the synthesis of morphine and of morphinans has continued to attract the attention of organic chemists. The inspired syntheses by Evans[1b] and by Rice[1c] are the latest of many directed toward this family of alkaloids. Syntheses of morphinans by Boger[1d] and by Meyers[1e] have also been disclosed. There are two reasons for the continuing research effort: first, the bridged polycyclic structure provides a challenge to chemists' ingenuity. Second, there continues to be a need for synthetic opiates for use in research and as analgesics.

In all but one[1d] of the syntheses reported to date, the aromatic ring of the final product was present in the early intermediates. In this communication a preparation of (±)-3-methyl-8,14-dehydromorphinan (1) will be described which follows the alternative strategy of introducing the aromatic ring toward the end of the synthesis. Such a strategy is made possible by the availability of efficient methods for the introduction of aromatic rings onto non-aromatic precursors.[2]

The starting material for the synthesis of 1 was ketoalcohol 2 which was prepared in 82% yield from the Diels-Alder adduct of butadiene and p-benzoquinone by reduction with tetra-n-butylammonium borohydride in dichloromethane. The bridgehead alkylation of 2 was unexpectedly challenging, and failed for unreactive alkyl halides. It was interesting to note that the success of the alkylation reaction depended upon the choice of alcohol protecting group.[3] Treatment of a dichloromethane solution of 2 with 10 equiv of ethyl vinyl ether and a trace of tosic acid produced the protected material in quantitative yield. Enolate generation with lithium 2,2,6,6-tetramethylpiperidide in THF, followed by quenching with allyl bromide gave 3 in 85% yield. Enone 3 was converted to α-hydroxymethylene derivative 4[4] in four steps: treatment at -70°C in THF with a solution of K-Selectride (92% yield);[5] hydrolytic removal of the ethoxyethyl protecting group with aqueous HCl in THF (95% yield); protection of the alcohol as the tert-butyldimethylsilyl ether in dichloromethane with the silyl triflate[6] and triethylamine (86% yield), and treatment in anhydrous ether with ethyl formate and sodium methoxide (100% yield). Hydroxymethylene 4 was converted to hydrolytically labile vinylogous ester 5 which was



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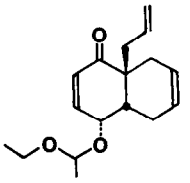

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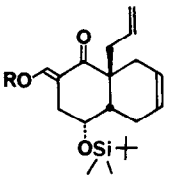
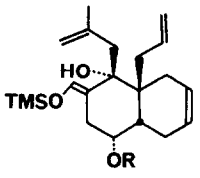


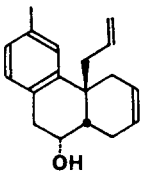
4 R=H

5 R=TMS



6 R=TBDMS

7 R=MOM



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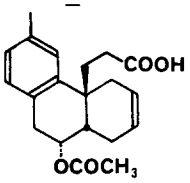

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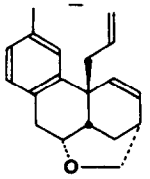

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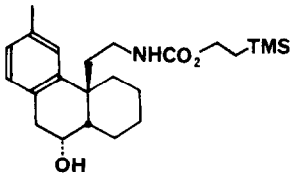

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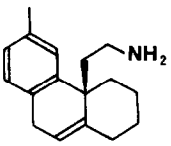

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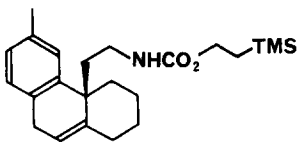

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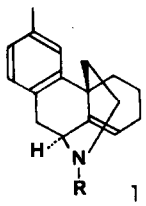

1 R=H

14 R=Ac

treated with methallylmagnesium chloride to produce 6. The cyclization of 6 to 8[7] in refluxing degassed benzene containing catalytic tosic acid took place in 77% yield.[8] The cyclization was also carried out in similar yield by treating 6 in benzene at 23°C for 12 h with 0.2 N pyridinium tosylate. This is an extraordinarily mild procedure for an aromatic annelation reaction. The cyclization of 7 in refluxing benzene containing tosic acid had produced the beautifully crystalline ether 9 (mp 130°C), in which the methoxymethyl protecting group had led to a second cationic cyclization to a tetrahydropyran. This unforeseen product proved that the ring junction stereochemistry was cis.

The next task was to convert the bridgehead allyl to an aminoethyl group. Alcohol 8 was protected as the acetate (93% yield) and the terminal alkene was converted to the primary alcohol by hydroboration with dicyclohexylborane (86% yield). Swern oxidation (96% yield) followed by Jones reagent in acetone (73% yield) furnished carboxylic acid 10 which was subjected to Overman's conditions for the Curtius rearrangement.[9] Treatment of 10 with methyl chloroformate and Hünig's base in acetone followed by aqueous sodium azide produced an acyl azide which was decomposed in refluxing benzene in the presence of an excess of 2-trimethylsilylethanol (84% yield). A methanolic solution of the carbamate was treated with 1 atm of hydrogen over 5% Pd on carbon and the acetate was removed with potassium carbonate in aqueous methanol. The overall yield of 11 was 82%.

Attempts to form a piperidine ring by displacement of the hydroxy group of 11 by the carbamate nitrogen or by the free amine were uniformly unsuccessful. Accordingly, an indirect approach was followed. Treatment of 11 with Ph_3P/diethylazodicarboxylate[10] produced a chromatographically separable 4.2:1 mixture of 12 and the corresponding styrene in 86% yield. The carbamate was removed with aqueous HF in THF (77% yield). Amine 13[11] was treated with 1 equiv of bromine in chloroform.[12] Replacement of the reaction solvent by DMF and treatment for 15 min at 23°C with 1 equiv of solid $NaHCO_3$ produced an aziridinium salt which rearranged to 1 upon heating at 100°C for 30 min. The reaction product was converted to acetamide 14[13] in 57% overall yield with acetic anhydride in pyridine.

In summary, (±)-3-methyl-8,14-dehydromorphinan has been prepared using an aromatic annelation reaction. This strategy will be useful for the synthesis of aromatic ring analogs of the morphine alkaloids.

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References and Notes

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3. The alkylation reaction was successful only when the alcohol was protected as the methoxymethyl or ethoxyethyl ether. See: M. Yamazaki, M. Shibasaki and S. Ikegami, J. Org. Chem., 48, 4402 (1983).

4. 4: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1 H), 5.7 (m, 1 H), 5.6 (m, 1 H), 5.10 (br s, 1 H), 5.05 (dd, J = 4.0, 1.0 Hz, 1 H), 4.27 (ddd, J = 6.1, 6.1, 2.8 Hz, 1 H), 2.63 (m, 1 H), 2.57 (dd, J = 15.3, 6.7 Hz, 1 H), 2.45 (dd, J = 14.0, 6.8 Hz, 1 H), 2.37 (dd, J = 14.0, 7.0 Hz, 1 H), 2.2-2.35 (m, 2 H), 2.05-1.9 (m, 3 H), 0.84 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H); IR (neat) 2960, 2880, 1630, 1580, 1250, 1080, 820, 760 cm^{-1}; mass spectrum m/e 348 (M^+), 307 (M^+ - allyl), 291 (M^+ - t-butyl); exact mass calcd for $C_{17}H_{27}O_3Si$ 307.1707, found 307.1729.

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7. t-Butyldimethylsilyl ether of 8: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.0 (s, 1 H), 6.9 (s, 2 H), 5.65 (m, 1 H), 5.57 (s, 2 H), 4.96-5.06 (m, 2 H), 4.51 (ddd, J = 7.3, 7.3, 4.0 Hz, 1 H), 3.06 (dd, J = 17.5, 7.2 Hz, 1 H), 2.80 (dd, J = 17.5, 7.6 Hz, 1 H), 2.59 (dd, J = 17.0, 3.5 Hz, 1 H), 2.27 (s, 3 H), 2.3-1.8 (m, 6 H), 0.87 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H); IR (neat) 2930, 1667, 1640, 1617, 1253, 997 cm^{-1}; mass spectrum m/e 368 (M^+), 327 (M^+ - allyl), 311 (M^+ - t-butyl), 273, 251, 235; exact mass calcd for $C_{21}H_{32}OSi$ 327.2134, found 327.2144.

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10. O. Mitsunobu, Synthesis, 1 (1981).

11. 13: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (s, 1 H), 6.93 (s, 2 H), 5.68 (br s, 1 H), 3.27 (br s, 2 H), 2.68 (t, J = 9.0 Hz, 2 H), 2.29 (s, 3 H), 2.19 (t, J = 9.0 Hz, 2 H), 2.0-1.2 (m, 8 H); IR (neat) 3360, 2940, 1640, 1507, 1445, 1399, 1144 cm^{-1}; mass spectrum m/e 241 (M^+), 239, 199, 197, 155; exact mass calcd for $C_{14}H_{15}N$ 197.1204, found 197.1321; mp 121°C.

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13. 14 (spectra show evidence for amide rotamers): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (s, 1 H), 6.93 (s, 2 H), 5.75 (t, J = 4.0 Hz, 1 H) and 5.70 (t, J = 4.0 Hz, 1 H), 5.21 (d, J = 5.5 Hz, 1 H) and 4.45 (d, J = 5.8 Hz, 1 H), 4.39 (dd, J = 13.3, 4.3 Hz, 1 H) and 3.51 (dd, J = 13.3, 4.3 Hz, 1 H), 3.26 (dd, J = 17.2, 5.5 Hz, 1 H) and 3.18 (dd, J = 17.2, 5.6 Hz, 1 H), 3.15 (ddd, J = 13.2, 13.2, 3.5 Hz, 1 H) and 2.56 (ddd, J = 13.7, 13.7, 3.5 Hz, 1 H), 2.91 (d, J = 17.3 Hz, 1 H) and 2.88 (d, J = 17.2 Hz, 1 H), 2.30 (s, 3 H), 2.24 (m, 1 H), 2.16 (s, 3 H) and 2.03 (s, 3 H), 2.0-1.5 (m, 5 H); IR (neat) 2910, 1651, 1645, 1622, 1616, 1605, 1499, 1414, 1370, 1322, 1265, 1250, 1221, 1053, 1022, 945, 877 cm^{-1}; mass spectrum m/e 281 (M^+), 238 (M^+ - acetyl), 196, 195; exact mass calcd for $C_{19}H_{23}NO$ 281.1780, found 281.1772.

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