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General Method of Synthesis for Naloxone, Naltrexone, Nalbuphone, and Nalbuphine by the Reaction of Grignard Reagents with an Oxazolidine Derived from Oxymorphone

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Abstract: The *N*-oxide of *O*-acyloxymorphone, when treated with the Burgess reagent, provides the corresponding oxazolidine in a one-pot sequence and in excellent yield. The oxazolidine derived from oxymorphone, temporarily protected at O-3 and C-6, reacts with Grignard reagents to provide directly *N*-allyl, *N*-cyclopropylmethyl, and *N*-cyclobutylmethyl derivatives that are further converted to the title compounds, namely naltrexone, naloxone, nalbuphone, and nalbuphine in excellent yields. Each of these medicinal agents is obtained from the oxazolidine in a one-pot sequence. Complete spectral and experimental data are provided for all compounds.

Keywords: N-demethylation; morphinans; nucleophilic opening; oxazolidine; oxymorphone

Opiate-derived antagonists such as naloxone (**1**), naltrexone (**2**), nalbuphone (**3**) and nalbuphine (**4**) are prepared by semi-synthesis from the natural opiates such as morphine (**5**), thebaine (**6**), or oripavine (**7**) (Figure 1).[1] These medicinally useful products are used extensively as antagonists (naltrexone and naloxone) or mixed agonist/antagonist (nalbuphine).[2] The most common commercial route to the title compounds involves alkylation of noroxymorphone with either an alkyl halide in the presence of an acid scavenger[3] or reductive alkylation with the appropriate aldehyde.[4] The synthesis of these compounds requires the oxidation of natural opiate alkaloids (such as thebaine or oripavine) at the C-14 position and the eventual replacement of an *N*-methyl group with allyl, cyclopropylmethyl, cyclobutylmethyl, or other alkyl groups. Of these two processes the latter is much more arduous than the former.

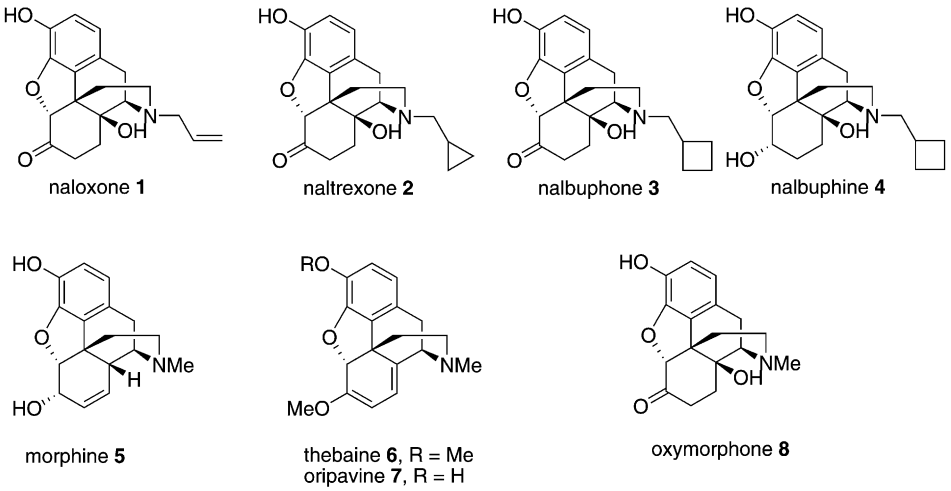


Figure 1. Opiate-derived medicinal agents and their natural sources.

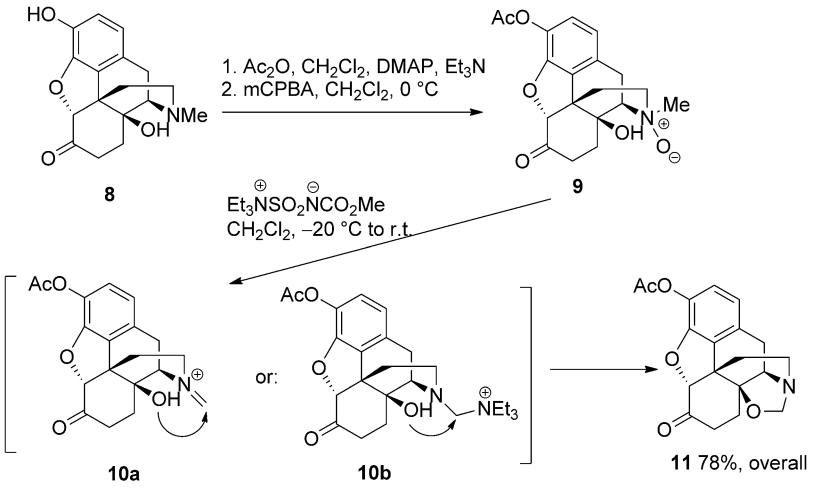


Figure 2. One-pot synthesis of oxazolidine derived from oxymorphone.

Many protocols are known for the *N*-demethylation of morphine alkaloids.[5–14] Recently, we discovered that the *N*-oxide of oxymorphone is easily demethylated with the Burgess reagent and that the intermediate iminium ion is trapped to form oxazolidine **11** in excellent yield and in a one-pot sequence from oxymorphone **8**, as shown in Figure 2.[2,15]

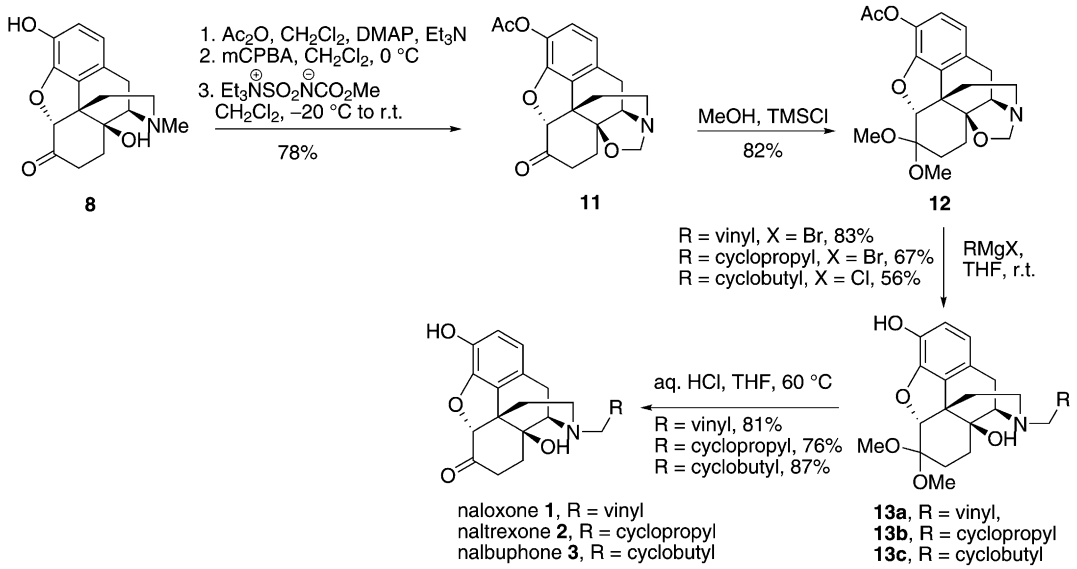
Our program in this area was implemented in order to discover more efficient and environmentally friendly methods for the replacement of the *N*-methyl group in natural opiates with other alkyl groups needed for the various medicinal agents. Having prepared each of the derivatives **1**–**4** shown in Figure 1 by several methods, we compared them for overall efficiency and the potential for scale-up by process groups. Our *N*-demethylation protocols for naltrexone and methylnaltrexone were deemed suitable for process scale-up. However, *N*-demethylation of quaternary salts containing an *N*-allyl group, as required for the synthesis of naloxone, was not possible as the treatment of such salts with nucleophiles led to *N*-deallylation rather than *N*-demethylation. Similarly, attempts to apply the palladium catalyzed *N*-demethylation/acylation protocol to the synthesis of naloxone necessitated the use of acrylic esters and the eventual selective reduction of acrylamide to the *N*-allyl group. Preliminary investigations of such protocols met with failure.[16]

We therefore investigated nucleophilic cleavage of oxazolidines[17] of type **11**, containing a suitably protected C-6 ketone. We reasoned that if the oxazolidine could be cleaved by a Grignard or alkyllithium reagent then the original carbon of the *N*-methyl group would remain in the product and the process for the synthesis of naloxone and other derivatives would be, by definition, more economical. This approach offers some advantage over the previously reported syntheses where the oxazolidine in **11** was hydrolyzed and the various derivatives were prepared from the secondary amine by alkylation.[2] In this paper we report a general method of synthesis for naloxone, naltrexone, nalbuphone, and nalbuphine *via* oxazolidines **11** derived from oxymorphone.

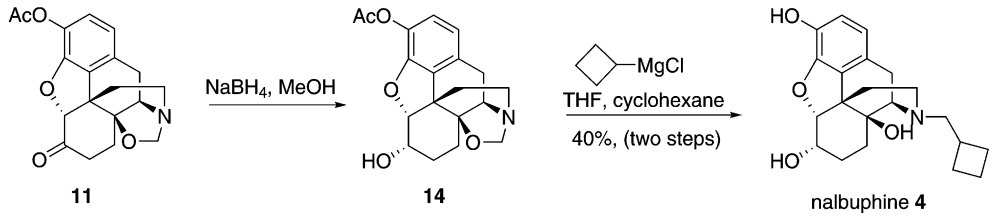
Oxymorphone was converted to its *O*-acetate and subjected to oxidation and Burgess reagent induced *N*-demethylation to produce **11** in a one-pot operation as previously described.[2] Protection of the C-6 ketone under mild conditions provided ketal **12** in 82% yield, as shown in Scheme 1. This compound was treated with excess Grignard reagent derived from allyl bromide, cyclopropylmethyl bromide, or cyclobutylmethyl chloride to yield the corresponding *N*-alkylated products **13a**–**c** in good to excellent yields. The lower yield of **13c** is likely the function of the less reactive Grignard reagent derived from cyclobutylmethyl chloride, which was used instead of the corresponding bromide because of its lower cost.

Hydrolysis of the ketal moiety in **13a**–**c** then produced naloxone, naltrexone, and nalbuphone, respectively, in high yields. The synthesis of nalbuphine was accomplished in a more direct manner by reduction of the C-6 ketone in **11** and treatment of alcohol **14** with excess cyclobutylmethyl Grignard reagent as shown in Scheme 2. In this way all four title compounds were synthesized from the same precursor. In addition, the naloxone synthesis was reduced to a one-pot preparation. Oxazolidine **11** was converted to naloxone in 75% overall yield without isolation of intermediates (see the Supporting Information for the experimental procedure).

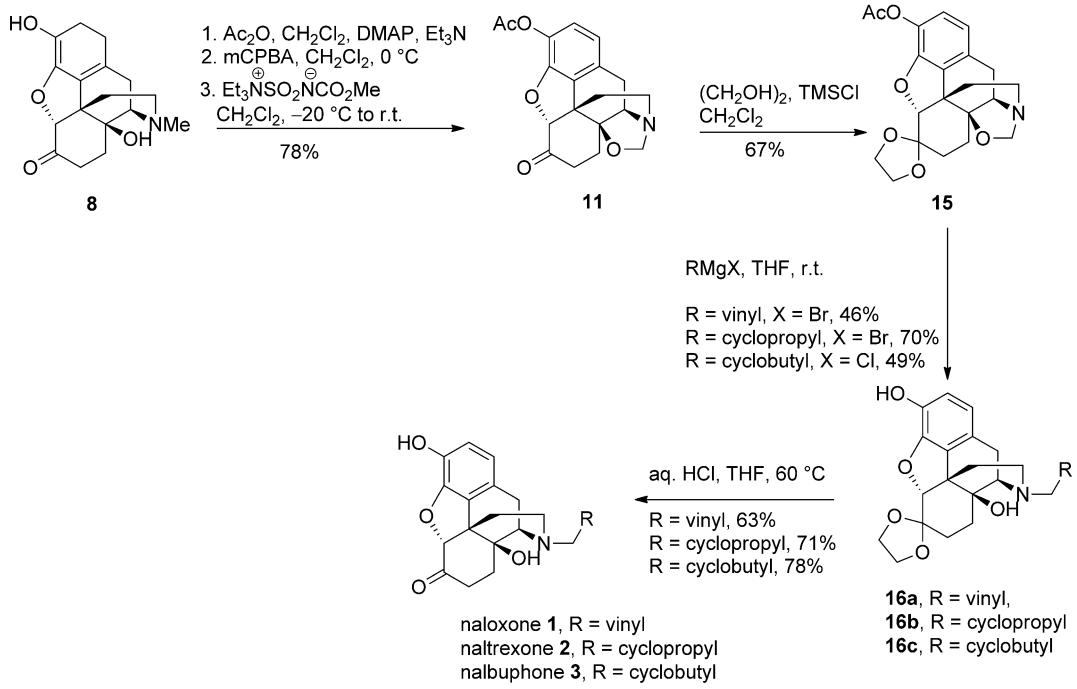
In addition, we investigated the conversion of oxazolidine to the title compounds *via* ketal **15**, derived by protection of the C-6 ketone with ethylene glycol. The results of these transformations are shown in Scheme 3. In general, the yields were somewhat lower than those in the series employing ketal **12**. The hy-



Scheme 1.



Scheme 2.



Scheme 3.

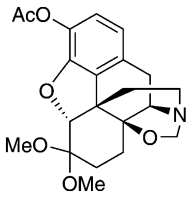
drolysis of the more robust ketal in **16a–c** proceeded also in lower yields.

In conclusion, we have synthesized the title compounds in two one-pot operations from oxymorphone by taking advantage of the electrophilic nature of the oxazolidine carbon in **11** and its tendency to react with the Grignard reagents. The synthesis of these compounds is made more economical as the carbon of the original *N*-methyl group remains in the final products. The sequence of reactions from oxymorphone to compounds **1–4** proceeds in good to excellent yields and should be subjected to further optimization and scale-up.

Experimental Section

For the rest of the procedures see the Supporting Information

(5a*R*,6*R*,8a*S*,11a*R*,11b*S*)-2-Acetoxy-5,5a,9,10-tetrahydro-11,11-dimethoxy-6,11b-ethano-7*H*-furo[2′,3′,4′,5′:4,5]phenanthro[9,8a-*d*]oxazole (12)

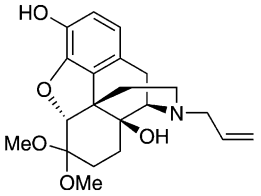


To a stirred suspension of oxazolidine acetate **11**[2] (60 mg, 0.18 mmol) in MeOH (5 mL) was added TMSCl (0.50 mL). After the addition of TMSCl a homogenous yellowish solution was observed. The mixture was allowed to stir at room temperature for 2 h, at which time TLC monitoring of reaction mixture using $CHCl_3$/MeOH/NH_4OH (5:1:0.01) as eluent indicated that the reaction was complete. The reaction mixture was diluted with dichloromethane (10 mL) and the resulting solution was washed with saturated $NaHCO_3$ (5 mL). The organic layer was dried with $MgSO_4$, filtered and evaporated to dryness *via* rotary evaporation to afford **12** as an oil, which was used in the next step without further purification; yield: 50 mg (82%).

General Procedure for the Preparation of 13a–c from 12

To a stirred solution of oxazolidine **12** (1 mmol) in THF (10 mL) at 0 °C was added the Grignard reagent (5 mmol) dropwise. The mixture was allowed to warm up to room temperature and stirred for a further 2 h, then it was quenched with saturated NH_4Cl solution (10 mL) and was diluted with EtOAc (10 mL). The layers were separated and the aqueous layer was extracted further with EtOAc (2× 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated using a rotary evaporation to afford crude **13**. Chromatography on silica gel using mixtures of CH_2Cl_2 and MeOH afforded **13a–c** as white solids; yields: 56–83%.

17-Allyl-4,5α-epoxy-3,14-dihydroxy-6,6-dimethoxymorphinan (13a): Yield: 83%; mp 178–179 °C (toluene); $[\alpha]_D^{20}$: −92.3 (c = 0.8, $CHCl_3$); R_f = 0.26 (7:2; CH_2Cl_2/MeOH); IR

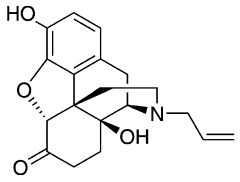


($CHCl_3$): ν = 3435, 2957, 2834, 1642, 1458, 1333, 1141, 1110, 1047, 989, 908, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.71 (d, J = 8.1 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 5.77–5.86 (m, 1H), 5.21 (d, J = 18.0 Hz, 1H), 4.60 (s, 1H), 3.38 (s, 3H), 3.03–3.11 (m, 2H), 3.12 (s, 3H), 3.03 (s, 1H), 2.94 (d, J = 5.7, 1H), 2.62 (d, J = 5.7 Hz, 1H), 2.53–2.57 (m, 1H), 2.31 (ddd, J = 12.3, 12.0, 3.0 Hz, 1H), 2.19 (ddd, J = 12.3, 12.0, 3.0 Hz, 1H), 1.87–1.96 (m, 1H), 1.40–1.59 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.8 (C), 137.7 (C), 135.4 (CH=CH_2), 130.8 (C), 124.5 (C), 118.4 (C), 117.8 (CH), 116.8 (CH_2=CH), 99.8 (O−C−O), 91.8 (O−CH), 69.9 (HO−C), 62.7 (N−CH), 57.7 (N−CH_2CH), 49.1 (C), 48.2 (OCH_3), 48.1 (OCH_3), 43.6 (NCH_2CH), 31.9 [$C(OCH_3)_2CH_2$], 27.9 (HO−C−CH_2), 24.6 (NCH_2CH_2), 22.5 ($PhCH_2$); MS (EI^+): m/z (%) = 373 (5), 358 (10), 342 (28), 341 (100), 326 (12), 139 (12), 101 (14), 57 (21), 56 (20), 43 (25); HR-MS (EI^+): m/z = 373.1891, calcd. for $C_{21}H_{27}NO_5$: 373.1889.

General Procedure for Hydrolysis of 13a–c

To a stirred solution of **13** (0.10 mmol) in THF (2 mL) was added 3 N HCl (1 mL). The resulting solution was heated to 60 °C for 2 h. The mixture was concentrated *via* rotary evaporation to remove THF. A saturated solution of $NaHCO_3$ was added to adjust the pH of the mixture to 8. It then was extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were dried, filtered and concentrated *via* rotary evaporation to afford the target compounds **1–3** as white solids; yields: 76–87%.

Naloxone (1): Yield: 81%; mp 179–180 °C (EtOAc/hexane) (lit.[18] 179.5 °C (toluene); R_f = 0.35 (7:2 CH_2Cl_2/MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ = 6.75 (d, J =



7.8 Hz, 1H), 6.63 (d, J = 7.8 Hz, 1H), 5.84 (m, 1H), 5.22 (m, 2H), 4.73 (s, 1H), 3.19 (m, 2H), 3.15 (m, 1H), 3.04 (m, 2H), 2.58–2.64 (m, 2H), 2.46 (ddd, J = 12.0, 6.0, 4.2 Hz, 1H), 2.33 (d, J = 11.4 Hz, 1H), 2.19 (ddd, J = 12.0, 8.4, 3.6 Hz, 1H), 1.90 (d, J = 13.8 Hz, 1H), 1.66 (td, J = 13.8, 3.0 Hz, 1H), 1.58 (d, J = 13.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 209.7 (C=O), 143.5 (C), 138.8 (C), 135.1 (CH=CH_2), 129.0 (C), 124.2 (C), 119.9 (CH), 118.2 (CH_2=CH), 117.9 (CH), 90.6

(O−CH), 70.4 (HO−C), 62.3 (N−CH), 57.7 (N−CH_2CH), 51.0 (C), 43.3 (N−CH_2CH_2), 36.2 (O=C−CH_2), 31.3 (HO−C-−CH_2), 30.5 (NCH_2CH_2), 22.7 ($PhCH_2$).

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