

A CONVENIENT OXIDATION METHOD OF THE BENZYLIC 10-POSITION IN 4,5-EPOXYMORPHINAN

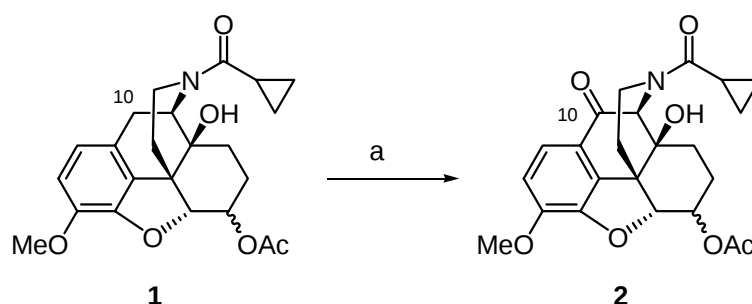
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Abstract – A convenient oxidation method of the benzylic 10-position in 4,5-epoxymorphinan to obtain its 10-oxo derivatives is described. The reaction by using potassium permanganate proceeds in good yield and can be performed in large scale.

Three types of opioid receptors (μ , δ , κ) are now well established by not only pharmacological studies but also molecular biological studies.¹⁻³ Especially, the κ -opioid receptor has been of interest because its activation produces analgesia with minimum physical dependence and respiratory depression.⁴ Thus, a highly selective κ -opioid agonist may provide a useful analgesic free from abuse potential and the adverse effects of a μ -agonist like morphine.^{4,5} Oxo derivatives at the benzylic position of 4,5-epoxymorphinan and benzomorphan were described to possess more κ -receptor selectivity than the corresponding parent compounds, respectively.⁶⁻⁸ In our research program searching for opioid receptor-type selective compounds, we focused on the 10-oxo derivatives of 4,5-epoxymorphinan compounds. In the field of opioid chemistry, several oxidation methods at the benzylic position are well known using various oxidants and reaction conditions such as chromic acid,⁹⁻¹⁹ selenium dioxide,^{8,20} oxygen,²¹ electrochemical oxidation,²² and photo-oxidation.²³ It is interesting to note that the benzylic oxidation using a common oxidant, chromic acid, affords the oxo derivative at the benzylic position in morphinan¹³⁻¹⁵ or benzomorphan^{16,17} series in good yields, but the same oxidant affords 10-hydroxylated derivative in 4,5-epoxymorphinan series concomitant with a trace amount of its 10-oxo derivative.^{9-12, 18, 19} Selenium dioxide is the only oxidant which can directly convert 4,5-epoxymorphinan into its 10-oxo derivative. In our 4,5-epoxymorphinan substrate, the oxidation proceeds in moderate yield by using selenium dioxide (Figure 1). However, in general, the reaction requires drastic conditions (sealed tube at 180 °C) so that it is difficult to apply to large-scale synthesis. Herein, we wish to report a more convenient oxidation method of 4,5-epoxymorphinans by using potassium permanganate which can easily be scaled up and

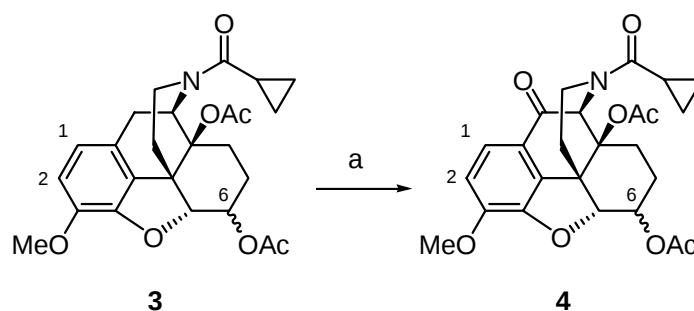
afford 10-oxo derivatives in good yields.



a) SeO_2 (3 eq.), 1,4-dioxane, 180 °C (sealed tube), 24 h (60-70%)

Figure 1. SeO_2 oxidation of compound (**1**)

It is well known that potassium permanganate is one of the strongest oxidants and that it is difficult to control the oxidation stage of products.²⁴ On the other hand, 10-oxo derivatives of 4,5-epoxymorphinan could not enolize so that we considered further oxidation at the 10-position of 10-oxo derivatives would not proceed. On the basis of this hypothesis, we attempted to apply potassium permanganate for oxidation at the 10-benzylic position of 4,5-epoxymorphinans to obtain their 10-oxo derivatives. To the best of our knowledge, this is the first example of application of potassium permanganate to the 10-position oxidation in 4,5-epoxymorphinan.



a) KMnO_4 (1+2 eq.), MgSO_4 , aq. NaOH, *t*-BuOH, rt (74%) (6 α /6 β = 1/1)

Figure 2. KMnO_4 oxidation of compound (**3**)

First, compound (**3**) was subjected to potassium permanganate oxidation to investigate whether the 10-oxo derivative could be obtained or the 10-hydroxy derivative could be obtained (Figure 2). Thus, potassium permanganate (1 eq.) was added to a solution of compound (**3**) in *t*-BuOH under basic conditions (2.5 M aq. NaOH) at room temperature and stirring was continued for 12 h. At this point, the reaction mixture was worked up and the resulting residue was checked by ^1H -NMR spectrum to show that the residue was constructed of *ca.* 1:1 mixture of the starting material (**3**) and 10-oxo derivative (**4**). Further oxidation of the crude mixture with potassium permanganate (2 eq.) under the same conditions

was carried out for 15.5 h. After work-up and chromatographic separation, the desired 10-oxo derivative (**4**) was obtained in 74% yield without any 10-hydroxy compound.²⁵ The above results suggest that potassium permanganate could be a useful oxidant to directly obtain 10-oxo-4,5-epoxymorphinans. Next, suitably protected 4,5-epoxymorphinans (**5**) and (**6**) as shown in Figure 3 were used as the starting materials for potassium permanganate oxidation. Oxidation of these substrates having 6-ketal and 17-*N*-*tert*-butoxycarbonyl groups could afford 10-oxo derivatives favorable for further derivatization to κ -selective opioid ligands.

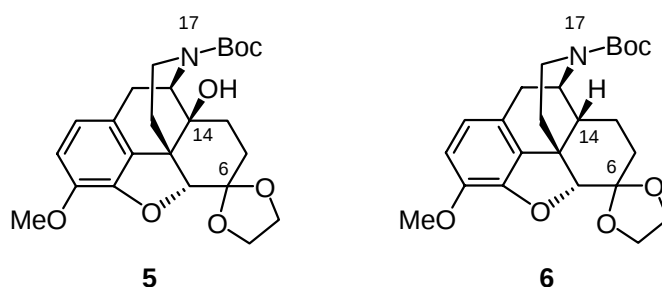
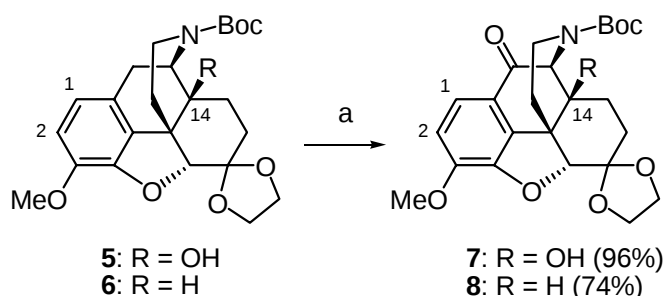


Figure 3. Protected 4,5-epoxymorphinan as oxidation substrates

In this benzylic oxidation, 5 equivalents or more of potassium permanganate were used to complete the oxidation reaction. As the results, the oxidation of compound (**5**) proceeded completely to give the corresponding 10-oxo derivative (**7**)²⁶ in 96% isolated yield after chromatographic separation. Similarly, the oxidation of compound (**6**) also gave the corresponding 10-oxo derivative (**8**)²⁷ in 74% isolated yield (Figure 4).



a) KMnO_4 (5.2 eq. for **5**, 7.4 eq. for **6**), MgSO_4 , aq. NaOH, *t*-BuOH/Py (10/1), rt

Figure 4. KMnO_4 oxidation of compounds (**5**) and (**6**)

In these reactions, *t*-BuOH and pyridine (10/1 v/v) were used as co-solvents because compound (**5**) and (**6**) were hardly dissolved only in *t*-BuOH. When only pyridine was used as solvent²⁸, the oxidation resulted in poor yield (35%) in the case of substrate (**5**). The solvent ratio (*t*-BuOH/pyridine = 10/1) was an important factor to attain good yield in this reaction system.²⁹

The structures of 10-oxo derivatives (**4**, **7**, **8**) were confirmed mainly by ¹H-NMR spectral analyses. It is known that the chemical shifts of protons of the 1- and 2-positions in 10-oxo derivatives shift to more down-field²⁰ than those of their parent compounds (**3**, **5**, **6**). The chemical shift values of the 1- and 2-positions are in good agreement with those of literature.²⁰

As the results described above, potassium permanganate is a useful reagent to oxidize 4,5-epoxymorphinans having a hydrogen, hydroxy or acetoxy group on angular 14-position. The oxidation of compound (**5**) was carried out in 15 g scale under the same reaction conditions and its 10-oxo derivative (**7**) was obtained in high yield again (92%).

In conclusion, potassium permanganate is proved to be an efficient and more convenient oxidant than selenium dioxide for oxidation of the benzylic 10-position of 4,5-epoxymorphinan and this procedure can easily be scaled up. After oxidizing the 10-position, the obtained compounds (**7**) and (**8**) which possess convertible functional groups at the 6-, 10-, and 17-positions would be appropriate starting materials for a variety of new opioid ligands especially those having κ-receptor selectivity.

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25. The analytical and spectral data of compound (**4**): White powder, mp 190 °C; ¹H-NMR (300 MHz, CDCl₃) δ: 0.86-1.00 (4H, m), 1.40-1.93 (5H, m), 1.95 (1.5H, s), 2.11 (1.5H, s), 2.25 (1.5H, s), 2.26 (1.5H, s), 2.40-2.80 (3H, m), 3.99 (1.5H, s), 4.01 (1.5H, s), 4.45-4.55 (1H, m), 4.70-4.80 (1H, m), 4.91 (0.5H, d, *J* = 4.8 Hz), 5.30-5.40 (0.5H, m), 5.46-5.48 (1H, m), 6.94 (0.5H, d, *J* = 8.4 Hz), 6.95 (0.5H, d, *J* = 8.4 Hz), 7.47 (0.5H, d, *J* = 8.4 Hz), 7.50 (0.5H, d, *J* = 8.4 Hz); IR (KBr) cm⁻¹: 1737, 1687, 1617, 1509. HRMS (EI) *m/z* Calcd for C₂₅H₂₇NO₈: 469.1737 (M⁺). Found: 469.1711.
26. The analytical and spectral data of compound (**7**): Amorphous solid, ¹H-NMR (300 MHz CDCl₃) δ: 1.39-1.80 (5H, m), 1.50 (9H, s), 2.03-2.12 (1H, m), 2.47 (1H, m), 2.71 (1H, m), 3.12 (1H, m), 3.76-3.89 (1H, m), 3.91-4.06 (2H, m), 3.97 (3H, s), 4.13-4.17 (1H, m), 4.56 (1H, s), 6.92 (1H, d, *J* = 8.4 Hz), 7.45 (1H, d, *J* = 8.4 Hz). IR (KBr) cm⁻¹: 3444, 1691, 1619, 1507, 1286. HRMS (EI) *m/z* Calcd for C₂₄H₂₉NO₈: 459.1893 (M⁺). Found: 459.1913.
27. The analytical and spectral data of compound (**8**): Amorphous solid, ¹H-NMR (300 MHz, CDCl₃) δ: 1.22-1.30 (3H, m), 1.45-1.62 (2H, m), 1.50 (9H, s), 1.66-1.80 (2H, m), 2.24-2.30 (1H, m), 2.75-2.95 (1H, m), 3.79-3.93 (2H, m), 3.95-4.04 (1H, m), 3.97 (3H, s), 4.15-4.20 (1H, m), 4.52 (1H, s), 4.60-4.85 (1H, m), 6.90 (1H, d, *J* = 8.4 Hz), 7.44 (1H, d, *J* = 8.4 Hz). IR (KBr) cm⁻¹: 1691, 1620, 1506. HRMS (EI) *m/z* Calcd for C₂₄H₂₉NO₇: 443.1944 (M⁺). Found: 443.1928.
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29. The general procedure for potassium permanganate oxidation of compound (**5**): To a stirred solution of compound (**5**) (3.33 g, 7.47 mmol) in 120 mL of *t*-BuOH and 12 mL of pyridine was added MgSO₄ (20.9 g, 173 mmol) at rt. To this suspension, a solution of KMnO₄ (6.18 g, 39.1 mmol) in a 2.5M aq. NaOH solution (30 mL, 75 mmol) and 120 mL of water was added, and the mixture was stirred at rt. After stirring for 12 h, 10% sodium thiosulfate solution was added to the suspension, and the mixture

was filtered through hyflo super-cell[®] and washed with CHCl₃ followed by water. The organic layer was separated and the water layer was extracted with CHCl₃. The combined organic layer was dried over Na₂SO₄ and concentrated *in vacuo* to give 3.31 g of crude products. This was chromatographed on silica gel (86 g). Elution with *n*-hexane/EtOAc (1/1) gave 3.30 g (96%) of desired compound (7) as an amorphous solid.