Supporting Information for *Organic Letters*

Investigation of phenolic bioisosterism in opiates: 3-Sulfonamido analogues of naltrexone and oxymorphone

Christopher R. McCurdy, Robert M. Jones, and Philip S. Portoghese
Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455, USA.

Materials

Naltrexone hydrochloride and oxymorphone hydrochloride were obtained from Mallinkrodt. All other reagents used were obtained from Aldrich Chemical Company (Milwaukee, WI) unless otherwise noted. Reactions sensitive to air or moisture were performed under a nitrogen atmosphere, in oven-dried glassware. Dry tetrahydrofuran was obtained from a potassium metal still. ^{1}H NMR spectra were taken on either a Varian Inova 300 MHz or Varian Unity 300 MHz instruments . Chemical shifts are expressed in ppm of the δ scale with TMS as an internal reference (δ=0.00) . All spectra were recorded at ambient temperature. Gravity and low-pressure column chromatrography were performed over silica gel (200-400 mesh, BET surface area 500 m2/g, pore volume 0.75 cm3/g, Adrich Chemical company) as the stationary phase under nitrogen with run solvents containing: dichloromethane, methanol, and ammonium hydroxide (C:M:A). TLC was performed on Analtech silica gel GF plates. Infra-red (IR) spectra were recorded on a Perkin-Elmer PE-281 spectrophotometer on potassium bromide (KBr) discs. Low resolution (LRFABMS) and high resolution (HRFABMS) mass spectra were obtained on a VG-707EHF spectrometer using a m-nitro benzyl alcohol (MNOBA) matrix.

17-Cyclopropylmethyl-6,6-[2-(1,3-dioxolanyl)]-4,5-a-epoxy-14 dihydroxymorphinan. (2a)

A mixture of naltrexone hydrochloride (10.00g, 0.005 mol, 1eq) and para-toluenesulfonic acid (2.00g) in ethylene glycol (200ml) was heated at 65˚C for 4 hours at 0.1 mmHg pressure to remove water and some ethylene glycol. The solution was cooled and poured with stirring into a saturated aqueous solution of sodium bicarbonate (300ml). The product was extracted with ethyl acetate (3 x 250ml). The combined organic extracts were washed with water and then brine, dried over sodium sulfate, filtered and concentrated to afford the desired compound (**2a**) as a white crystaline solid. The product was recrystallized in absolute methanol. (9.50g, 93.1 %). ^{1}H NMR 300 MHz $DMSOd_6$ δ (ppm): 8.875 (bs, 1H, phenolic OH); 6.486 (d, 1H, H2, J = 8.0 Hz); 6.384 (d, 1H, H1, J = 8.0 Hz); 4.877 (bs, 1H, OH14); 4.301 (s, 1H, H5); 4.011 (m, 1H, O-CH2-CH2-O); 3.870 (m, 1H, O-CH2-CH2-O); 3.693 (m, 2H, O-CH2-CH2-O); 2.947 (m, 1H); 2.473 (m, 3H); 2.288 (m, 2H); 1.622 (m, 3H); 1.351 (m, 3H); 1.156 (m, 1H); 0.788 (m, 1H); 0.422 (m, 2H); 0.064 (m, 2H).

17-Cyclopropylmethyl-6,6-[2-(1,3-dioxolanyl)]-4,5-a-epoxy-3-O [(trifluoromethyl)sulphonyl]-14-dihydroxymorphinan. (3a)

To a solution of **2a** (9.5g, 0.025mol) in 200ml of dichloromethane was added 5ml of triethylamine with stirring. The solution was cooled to 0˚C at which time 12.8g (1.44 eq)

of N-phenyltrifluoromethanesulfonimide was added. The solution was allowed to stir while the temperature gradually rose to ambient. The reaction stirred at room temperature under a nitrogen atmosphere overnight. The solution was then concentrated under reduced pressure to a white soild and subjected to column chromtography (97.5:2.0:0.5; C:M:A). The first compound isolated was the desired product, **3a**, which was a white crystalline solid. (12.21g, 95.8%). ^{1}H NMR 300 MHz DMSOd_6 δ (ppm): 7.067 (d, 1H, H2, J = 8.0 Hz); 6.733 (d, 1H, H1, J = 8.0 Hz); 4.948 (bs, 1H, OH14); 4.623 (s, 1H, H5); 3.980 (m, 1H, O-CH2-CH2-O); 3.689 (m, 3H, O-CH2-CH2-O); 3.044 (m, 1H); 2.454 (m, 2H); 2.461 (s, 1H); 2.247 (m, 3H); 1.889 (m, 2H); 1.327 (m, 3H), 1.144 (m, 1H); 0.803 (m, 1H); 0.429 (m, 2H); 0.078 (m, 2H).

17-Cyclopropylmethyl-6,6-[2-(1,3-dioxolanyl)]-4,5-α-epoxy-3-carbomethoxy-14 dihydroxymorphinan. (4a)

In a 500ml round bottom flask was placed 8.00g (0.016 mol) of compound **3a**. The compound was dissolved in a mixture of DMSO and methanol (120ml:80ml). To this solution was added palladium acetate (0.38g, 0.1 eq), dppf (2.00g, 0.21 eq) and TEA (5.16ml, 2.2 eq). The mixture was stirred at room temperature while carbon monoxide gas was bubbled through it for 10 minutes. The reaction vessel was then sealed under a carbon monoxide atmosphere and heated to 65˚C for 3 hours. The reaction mixture was cooled to room temperature and excess methanol was evaporated under reduced pressure. The resulting solution was poured into 1200ml of water and extracted (4 x 500ml) with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered and concentrated to a brown oil. This was placed on a silica gel column and the desired product was eluted with 94.5:5.0:0.5; C:M:A. The first compound eluted (**4a**) was isolated as a white solid (5.13g, 77.7%). ^{1}H NMR 300 MHz DMSOd_6 δ (ppm): 7.482 (d, 1H, H2, J = 8.0 Hz); 6.708 (d, 1H, H1, J = 8.0 Hz); 4.930 (bs, 1H, OH14); 4.506 (s, 1H, H5); 4.049 (m, 2H, O-CH2-CH2-O); 3.661 (m, 2H, O-CH2-CH2-O); 3.127 (m, 3, OCH3); 3.041 (m, 1H); 2.568 (m, 2H); 2.461 (m, 1H); 2.300 (m, 2H); 2.163 (m, 1H); 2.023 (m, 1H); 1.836 (m, 1H); 1.356 (m, 3H); 1.134 (m, 1H); 0.800 (m, 1H); 0.427 (m, 2H); 0.071 (m, 2H). IR KBr: 1712.

17-Cyclopropylmethyl-6,6-[2-(1,3-dioxolanyl)]-4,5-α-epoxy-3-hydrazide-14 dihydroxymorphinan. (5a)

Compound **4a** (3.00g, mol) was added to 10 ml of hydrazine monohydrate which had been cooled to 0˚C. This mixture was allowed to come to ambient temperature and was then heated to 50˚C for 4 hours to ensure complete transformation. It was cooled to room temperature and then poured into 200 ml of water and the product was extracted with dichloromethane (3 x 150ml). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated to afford the desired product as a white solid. (1.80g, 60.2%). ^{1}H NMR 300 MHz DMSOd_6 δ (ppm): 8.511 (bs, 1H, CO<u>NH</u>NH_2); 7.464 (d, 1H, H2, J = 8.0 Hz); 6.726 (d, 1H, H1, J = 8.0 Hz); 4.945 (bs, 1H, OH14); 4.586 (s, 1H, H5); 4.497 (bd, 2H, CONH<u>NH_2</u>); 4.105 (m, 1H, O-CH2-CH2-O); 3.760 (m, 1H, O-CH2-CH2-O); 3.619 (m, 2H, O CH2-CH2-O); 3.020 (m, 2H); 2.592 (m, 1H); 2.534 (m, 1H); 2.306 (m, 3H); 2.205 (m, 1H); 1.992 (m, 1H); 1.858 (m, 1H); 1.364 (m, 2H); 1.179 (m, 1H); 0.814 (m, 1H); 0.430 (m, 2H); 0.079 (m, 2H). IR KBr: 1683, 1669, 1646, 1635.

17-Cyclopropylmethyl-6,6-[2-(1,3-dioxolanyl)]-4,5-α-epoxy-3-acylazide-14 dihydroxymorphinan. (6a)

Compound **5a** (1.00g, 2.34 mmol) was dissolved in 20 ml of THF and cooled to 0˚C. To the stirring solution was added t-butyl nitrite (0.31ml, 1.1 eq). Then 20 ml of a 1:1 v/v mixture of 2N-HCl/H2O was added to form nitric acid in situ. This solution stirred at 0˚C for 10 minutes. The reaction was quenched by the addition of 20 ml of TEA. The reaction solution was then added to a 500ml separatory funnel containing 100 ml of methylene chloride and 100 ml of water. The compound was extracted into the organic layer and dried over sodium sulfate. The solvent was then filtered and concentrated under reduced pressure at room temperature to afford the desired azide (**6a**) as an off-white solid which required no further purification. (1.02g, 99.3%). ^{1}H NMR 300 MHz $DMSOd_6$ δ (ppm): 7.475 (d, 1H, H1, J= 8.0 Hz); 6.743 (d, 1H, H2, J= 8.0 Hz); 4.940 (bs, 1H, OH14); 4.572 (s, 1H, H5); 4.030 (m, 1H, O-CH2-CH2-O); 3.710 (m, 2H, O-CH2 CH2-O); 3.613 (m, 1H, O-CH2-CH2-O); 3.040 (m, 2H); 2.581 (m, 2H); 2.247 (m, 3H); 2.027 (m, 1H); 1.817 (m, 1H); 1.353 (m, 2H); 1.150 (m, 2H); 0.796 (m, 1H); 0.429 (m, 2H); 0.071 (m, 2H). IR KBr: 2143.

17-Cyclopropylmethyl-6,6-[2-(1,3-dioxolanyl)]-4,5-α-epoxy-3 amino(benzyloxycarboxylate)-14-dihydroxymorphinan. (7a)

Compound **6a** (1.00g, 2.28 mmol) was dissolved in 5 ml of benzene containing 4 eq of triethylamine. This solution was allowed to reflux for 2 hours during which time the azide underwent Curtius rearrangement. The solution was cooled below reflux and benzyl alcohol (0.94ml, 4.0 eq) was added. The solution was again heated to reflux and was held there for 24 hours. The solution was cooled to room temperature and washed with water (4 x 25ml), and the organic layer was dried over anhydrous potassium carbonate, filtered and concentrated under reduced pressure to a light brown oil. This was placed on a silica gel column and eluted with CMA (94.5:5.0:0.5). The desired compound (**7a**) was the first to elute and was isolated as a yellowish solid. (0.450g, 38.0%). ^{1}H NMR 300 MHz $DMSOd_6$ δ (ppm): 9.034 (bs, 1H, carbamate NH); 7.313 (m, 5H, Ar), 7.076 (m, 1H, Ar); 6.539 (m, 1H, Ar); 5.063 (bd, 2H, benzylic CH2); 4.894 (bs, 1H, OH14); 4.362 (s, 1H, H5); 3.960 (m, 1H); 3.699 (m, 2H); 3.562 (m, 1H); 2.935 (m, 3H); 2.543 (m, 1H); 2.298 (m, 2H); 2.023 (m, 3H); 1.358 (m, 2H); 1.159 (m, 2H); 0.796 (m, 1H); 0.466 (m, 2H); 0.071 (m, 2H). IR KBr: 1734.

17-Cyclopropylmethyl-6,6-[2-(1,3-dioxolanyl)]-4,5-α-epoxy-3-amino-14 dihydroxymorphinan. (8a)

Compound **7a** (220mg, 0.42 mmol) was dissolved in 10 ml of methanol in a parr flask. To this was added 40mg of 10% palladium on charcoal. The flask was placed on the parr hydrogenator at 55 p.s.i. of hydrogen for 1 hour. Afterwhich time, 50 ml of dichloromethane was added and the solution was filtered through celite, and concentrated to a white foam. (160mg, 98.2%).

17-Cyclopropylmethyl-6,6-[2-(1,3-dioxolanyl)]-4,5-α-epoxy-3 methanesulfonamido-14-dihydroxymorphinan. (9a)

Compound **8a** (160mg, 0.430 mmol) was dissolved in 5 ml of methylene chloride containing 1.1 eq of TEA. This solution was cooled to 0˚C. Next, 1.1 eq of

methanesulfonyl chloride was added. After 4 hours the reaction was quenched with 2 eq of TEA. The mixture was transfered to a separatory funnel and washed with water and then brine. The organic phase was dried over magnesium sulfate, filtered and concentrated to a white solid (97mg, 50%). ^{1}H NMR 300 MHz DMSOd_6 δ (ppm): 9.109 (bs, 1H, SO_2NH); 6.881 (d, 1H, H2, J = 8.0 Hz); 6.575 (d, 1H, H1, J = 8.0 Hz); 4.919 (bs, 1H, OH14); 4.427 (s, 1H, H5); 3.971 (m, 1H); 3.848 (m, 1H); 3.743 (m,1H); 3.622 (m, 1H); 3.127 (m, 1H); 3.006 (m, 1H); 2.950 (s, 3H, SO_2CH_3); 2.536 (m, 2H); 2.303 (m, 2H); 2.150 (m, 1H); 1.932 (m, 2H); 1.378 (m, 3H); 1.132 (m, 1H); 0.790 (m, 1H); 0.429 (m, 2H); 0.075 (m, 2H).

17-Cyclopropylmethyl-4,5-α-epoxy-3-methanesulfonamido-14-dihydroxymorphinan. (10a)

Compound **9a** (80mg, 0.173mmol) was dissolved in 10 ml of absolute alcohol and the solution was made acidic with the addition of conc. HCl. This mixture was heated to reflux for 8 hours at which time the reaction was cooled to room temperature. The solvent evaporated and the solution dissolved in aqueous saturated sodium bicarbonate solution and extracted with ethylacetate (3x25) to afford **10a** in the free base form as a white solid (51mg, 70.3%). ^{1}H NMR 300 MHz DMSOd_6 δ (ppm): 9.261 (bs, 1H, SO_2NH); 6.868 (d, 1H, H2, J = 8.0 Hz); 6.670 (d, 1H, H1, J= 8.0 Hz); 5.119 (bs, 1H, OH14); 4.972 (s, 1H, H5); 3.141 (m, 1H); 3.040 (s, 3H, SO_2CH_3); 2.924 (m, 2H); 2.587 (m, 2H); 2.363 (m, 3H); 2.082 (m, 1H); 1.834 (m, 2H); 1.447 (m, 1H); 1.261 (m, 1H); 0.839 (m, 1H); 0.439 (m, 2H); 0.094 (m, 2H). IR KBr: 1725. HRFABMS MNOBA matrix for C21H26N2O5S: calculated 418.1562, observed 419.1609 [M+H]+.

17-Methyl-6,6-[2-(1,3-dioxolanyl)]-4,5-α-epoxy-14-dihydroxymorphinan. (2b)

A mixture of oxymorphone hydrochloride (9.00g, 0.027 mol, 1eq) and para-toluenesulfonic acid (2.00g) in diethylene glycol (200ml) was heated at 65˚ C for 4 hours at 0.1 mmHg pressure to remove water and some diethylene glycol. The solution was cooled and poured with stirring into a saturated aqueous solution of sodium bicarbonate (300ml). The solution turned brown. The product was extracted with ethyl acetate (3 x 250ml). The combined organic extracts were washed with water and then brine, dried over sodium sulfate, filtered and concentrated to afford the desired compound (25b) as a white crystaline solid. The product was recrystallized in absolute methanol. (7.10g, 77.2%). ^{1}H NMR 300 MHz DMSOd_6 δ (ppm): 8.883 (bs, 1H, phenolic OH); 6.488 (d, 1H, 2H, J= 8.0 Hz); 6.403 (d, 1H, H1, J= 8.0 Hz); 4.782 (bs, 1H, OH14); 4.284 (s, 1H, H5); 4.030 (m, 1H, O-CH2-CH2-O); 3.864 (m, 1H, O-CH2-CH2-O); 3.691 (m, 2H, O-CH2-CH2-O); 2.982 (d, 1H, J = Hz); 2.668 (d, 1H, J = Hz); 2.428 (m, 1H); 2.330 (m, 1H); 2.254 (s, 3H, N CH3); 2.122 (m, 1H); 1.956 (m, 2H); 1.338 (m, 3H); 1.139 (m, 1H). HRFABMS MNOBA matrix for C19H23NO5: calculated 345.1576, observed 346.1889 [M+H]+.

17-Methyl-6,6-[2-(1,3-dioxolanyl)]-4,5-α-epoxy-3-O-[(trifluoromethyl)sulphonyl]-14-dihydroxymorphinan. (3b)

To a solution of **2b** (6.5g, 0.mol) in 200ml of dichloromethane was added 2.88ml (1.1 eq) of triethylamie with stirring. The solution was cooled to 0˚C at which time 7.39g (1.1 eq) of N phenyltrifluoromethanesulfonimide was added. The solution was allowed to stir

while the temperature gradually rose to ambient. The reaction stirred at room temperature under a nitrogen atmosphere overnight. The solution was then concentrated under reduced pressure to a white soild and subjected to column chromtography (97.5:2.0:0.5; C:M:A). The first compound isolated was the desired product, **3b**, which was a white crystalline solid. (8.21g, 91.3%). ^{1}H NMR 300 MHz DMSOd_6 δ (ppm): 7.076 (d, 1H, H2, J = 8.0 Hz); 6.743 (d, 1H, H1, J = 8.0 Hz); 4.877 (bs, 1H, OH14); 4.611 (s, 1H, H5); 3.970 (m, 1H, O-CH2-CH2-O); 3.685 (m, 3H, O-CH2-CH2-O); 3.110 (d, 1H, J = Hz); 2.756 (d, 1H, J = Hz); 2.526 (m, 1H); 2.369 (m, 1H); 2.266 (s, 3H, N CH3); 2.208 (m, 1H); 1.915 (m, 2H); 1.340 (m, 3H); 1.123 (m, 1H). HRFABMS MNOBA matrix for C20H22NO7F3S: calculated 477.1069, observed 478.1132 [M+H]+.

17-Methyl-6,6-[2-(1,3-dioxolanyl)]-4,5-α-epoxy-3-carbomethoxy-14 dihydroxymorphinan. (4b)

In a 500ml round bottom flask was placed 6.00g (0.013 mol) of compound **3b**. The compound was dissolved in a mixture of DMSO and methanol (120ml:80ml). To this solution was added palladium acetate (0.1 eq), dppf (0.21 eq) and TEA (2.2 eq). The mixture was stirred at room temperature while carbon monoxide gas was bubbled through it for 10 minutes. The reaction vessel was then sealed under a carbon monoxide atmosphere and heated to 65˚C for 3 hours. The reaction mixture was cooled to room temperature and excess methanol was evaporated under reduced pressure. The resulting solution was poured into 1200ml of water and extracted (4 x 500ml) with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered and concentrated to a brown oil. This was placed on a silica gel column and the desired product was eluted with 94.5:5.0:0.5; C:M:A. The first compound eluted (**4b**) was isolated as a white solid (4.08g, 81.1%). ^{1}H NMR 300 MHz DMSOd_6 δ (ppm): 7.487 (d, 1H, H2, J = 8.0 Hz); 6.731 (d, 1H, H1, J = 8.0 Hz); 4.847 (bs, 1H, OH14); 4.496 (s, 1H, H5); 4.015 (m, 1H, O-CH2-CH2-O); 3.734 (s, 3H, OCH_3); 3.654 (m, 3H, O-CH2-CH2-O); 3.107 (m, 1H); 2.743 (m, 1H); 2.535 (m, 1H); 2.335 (m, 1H); 2.263 (s, 3H, N-CH3); 2.178 (m, 1H); 2.013 (m, 1H); 1.860 (m, 1H); 1.369 (m, 3H); 1.116 (m, 1H). IR KBr: 1712. HRFABMS MNOBA matrix for C21H25NO6: calculated 387.1682, observed 388.1786 [M+H]+.

17-Methyl-6,6-[2-(1,3-dioxolanyl)]-4,5-α-epoxy-3-hydrazide-14 dihydroxymorphinan. (5b)

Compound **4b** (3.00g, 7.7mmol) was added to 10 ml of hydrazine monohydrate which had been cooled to 0˚ C. This mixture was allowed to come to ambient temperature and was then heated to 50˚C for 4 hours to ensure complete transformation. It was cooled to room temperature and then poured into 200 ml of water and the product was extracted with dichloromethane (3 x 150ml). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated to afford the desired product as a white solid. (1.66g, 55.3%). ^{1}H NMR 300 MHz DMSOd_6 δ (ppm): 8.381(bs, 1H, CO$\underline{NH}NH_2$); 7.342 (d, 1H, H2, J = 8.0 Hz); 6.616 (d, 1H, H1, J = 8.0 Hz); 4.737 (bs, 1H, OH14); 4.444 (s, 1H, H5); 4.371 (bs, 2H, CONH$\underline{NH_2}$); 3.879 (m, 1H, O-CH2-CH2-O); 3.628 (m, 1H, O-CH2-CH2-O); 3.500 (m, 2H, O CH2-CH2-O); 2.976 (m, 1H); 2.618 (m, 1H); 2.400 (m, 1H); 2.214 (m, 1H); 2.138 (m, 3H); 2.061 (m, 1H); 1.866 (m, 1H); 1.725 (m, 1H); 1.235

(m, 3H); 1.033 (m, 1H). IR KBr: 1683, 1669, 1646, 1635. HRFABMS MNOBA matrix for C20H25N3O5: calculated 387.1794, observed 388.1869 [M+H]+.

17-Methyl-6,6-[2-(1,3-dioxolanyl)]-4,5-α-epoxy-3-acylazide-14 dihydroxymorphinan. (6b)

Compound **5b** (1.00g, 2.58 mmol) was dissolved in 20 ml of THF and cooled to 0˚C. To the stirring solution was added t-butyl nitrite (1.1 eq). Then 20 ml of a 1:1 v/v mixture of 2N-HCl/H2O was added to form nitric acid in situ. This solution stirred at 0˚C for 10 minutes. The reaction was quenched by the addition of 20 ml of TEA. The reaction solution was then added to a 500ml separatory funnel containing 100 ml of methylene chloride and 100 ml of water. The compound was extracted into the organic layer and dried over sodium sulfate. The solvent was then filtered and concentrated under reduced pressure at room temperature to afford the desired azide (**6b**) as an off-white solid which required no further purification (0.950g, 92.3%). IR KBr: 2135.

17-Methyl-6,6-[2-(1,3-dioxolanyl)]-4,5-α-epoxy-3-amino(benzyloxycarboxylate) 14-dihydroxymorphinan. (7b)

Compound **6b** (0.950g, 2.38 mmol) was dissolved in 5 ml of benzene containing 4 eq of triethylamine. This solution was allowed to reflux for 2 hours during which time azide underwent Curtius rearrangement. The solution was cooled below reflux and benzyl alcohol (0.94ml, 4.0 eq) was added. The solution was again heated to reflux and was held there for 24 hours. The solution was cooled to room temperature and washed with water (4 x 25ml), and the organic layer was dried over anhydrous potassium carbonate, filtered and concentrated under reduced pressure to a light brown oil. This was placed on a silica gel column and eluted with CMA (94.5:5.0:0.5). The desired compound (**7b**) was the first to elute and was isolated as a yellowish solid. (0.275g, 24.0%). ^{1}H NMR 300 MHz DMSOd_6 δ (ppm): 9.037 (bs, 1H, carbamate NH); 7.313 (m, 5H, Ar), 7.079 (m, 1H, Ar); 6.557 (m, 1H, Ar); 5.064 (bd, 2H, benzylic CH2); 4.805 (bs, 1H, OH14); 4.348 (s, 1H, H5); 3.954 (m, 1H); 3.706 (m, 2H); 3.597 (m, 1H); 2.701 (m, 1H); 2.328 (m, 1H); 2.263 (s, 3H); 2.137 (m, 1H); 1.948 (m, 2H); 1.337 (m, 3H); 1.107 (m, 1H). IR KBr: 1737. HRFABMS MNOBA matrix for C27H30N2O6: calculated 478.2104, observed 479.2177 [M+H]+.

17-Methyl-6,6-[2-(1,3-dioxolanyl)]-4,5-α-epoxy-3-amino-14 dihydroxymorphinan. (8b)

Compound **7b** (250mg, 0.52 mmol) was dissolved in 10 ml of methanol in a parr flask. To this was added 40mg of 10% palladium on charcoal. The flask was placed on the parr hydrogenator at 55 p.s.i. of hydrogen for 1 hour. Afterwhich time, 50 ml of dichloromethane was added and the solution was filtered through celite, and concentrated to a white foam. (177mg, 98.2%). ^{1}H NMR 300 MHz DMSOd_6 δ (ppm): 6.341 (bs, 2H, Ar); 4.774 (bs, 1H, 14OH); 4.394 (bs, 2H, ArNH_2); 4.255 (s, 1H, H5); 2.958 (m, 1H); 2.648 (m, 1H); 2.400 (m, 1H); 2.318 (m, 1H); 2.251 (s, 3H, N-CH_3); 2.109 (m, 1H); 1.976 (m, 2H); 1.335 (m, 3H); 1.147 (m, 1H). HRFABMS MNOBA matrix for C19H24N2O4: calculated 344.1736, observed 345.1830 [M+H]+.

17-Methyl-6,6-[2-(1,3-dioxolanyl)]-4,5-α-epoxy-3-methanesulfonamido-14 dihydroxymorphinan. (9b)

Compound **8b** (160mg, 0.465 mmol) was dissolved in 5 ml of methylene chloride containing 1.1 eq of TEA. This solution was cooled to 0˚C. Next, 1.1 eq of methanesulfonyl chloride was added. After 4 hours the reaction was quenched with 2 eq of TEA. The mixture was transfered to a separatory funnel and washed with water and then brine. The organic phase was dried over magnesium sulfate, filtered and concentrated to a white solid (98.0mg, 49.4%). ^{1}H NMR 300 MHz DMSOd_6 δ (ppm): 9.125 (bs, 1H, SO_2NH); 6.884 (d, 1H, H2, J = 8.0 Hz); 6.593 (d, 1H, H1, J = 8.0 Hz); 4.833 (bs, 1H, OH14); 4.413 (s, 1H, H5); 4.022 (m, 1H); 3.882 (m, 1H); 3.768 (m,1H); 3.657 (m, 1H); 3.052 (m, 1H); 2.954 (s, 3H, SO_2CH_3); 2.713 (m, 1H); 2.505 (m, 1H); 2.335 (m, 1H); 2.263 (s, 3H, N-CH_3); 2.163 (m, 1H); 1.923 (m, 2H); 1.362 (m, 3H); 1.110 (m, 1H).

17-Methyl-4,5-α-epoxy-3-methanesulfonamido-14-dihydroxymorphinan. (10b)

Compound **9b** (80mg, 0.189 mmol) was dissolved in 10 ml of absolute alcohol and the solution was made acidic with the addition of conc. HCl. This mixture was heated to reflux for 8 hours at which time the reaction was cooled to room temperature. The solvent evaporated and the solution dissolved in aqueous saturated sodium bicarbonate solution and extracted with ethyl acetate (3x25) to afford **10b** in the free base form as a white solid (50 mg, 70.0%). ^{1}H NMR 300 MHz DMSOd_6 δ (ppm): 9.263 (bs, 1H, SO_2NH); 6.870 (d, 1H, H2, J = 8.0 Hz); 6.690 (d, 1H, H1, J= 8.0 Hz); 5.093 (bs, 1H, OH14); 4.956 (s, 1H, H5); 3.125 (m, 1H); 3.040 (s, 3H, SO_2CH_3); 2.899 (m, 1H); 2.382 (m, 1H); 2.297 (s, 3H, N-CH_3); 2.066 (m, 1H); 1.884 (m, 1H); 1.748 (m, 1H); 1.426 (m, 1H); 1.206 (m, 2H); 1.048 (m, 1H). IR KBr: 1725. HRFABMS MNOBA matrix for $C_{18}H_{22}N_2O_5S$: calculated 378.1249, observed 379.1341 [M+H]+.