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Functionalization of the 6,14-Bridge of the Orvinols. 2.[1] Preparation of 18- and 19-Hydroxyl-Substituted Thevinols and Their Treatment with Benzyl Bromide

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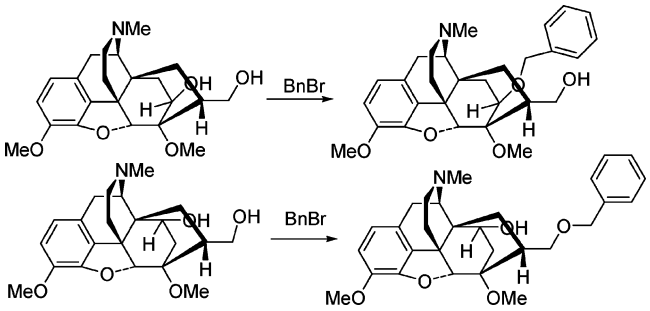

The etheno bridge of a thevinone was treated with BH_3 and H_2O_2 to give both the 18- and 19-hydroxyl- substituted thevinols. Selective benzylation of the primary 20-hydroxyl over the 19-hydroxyl was successful; however, benzylation of the 18-hydroxylated product led to a reaction at the more hindered alcohol. Thus, the 6,14-bridge of the Diels−Alder products of thebaine can be hydroxylated, which opens up these positions for further chemical manipulation.

The orvinols, such as buprenorphine and diprenorphine, comprise a class of extremely potent opioids.[2,3] They possess affinity for all three opioid receptors (μ, κ, δ), generally with little selectivity between the receptor types, with their pharmacological profiles being dominated through their differing efficacies at the receptor types.[4] 17-Methyl-substituted etorphine (**1**) (Figure 1) is a full μ agonist like all other 17-methyl orvinols, whereas the 17-cyclopropylmethyl orvinol buprenorphine (**2**) (Figure 1) is a μ partial agonist,[5] and the 17-cyclopropylmethyl-substituted diprenorphine (**3**) (Figure 1) is a μ antagonist.[4] Recent studies have focused on developing orvinols with differing efficacies at κ and δ receptors, and the orientation of the 20-alcohol has been shown to dramatically affect κ efficacy.[6,7] The orvinols are therefore attractive as a class from which to develop ligands with mixed profiles such as μ agonism and δ antagonism for potential analgesics with lower degrees of tolerance.[8]

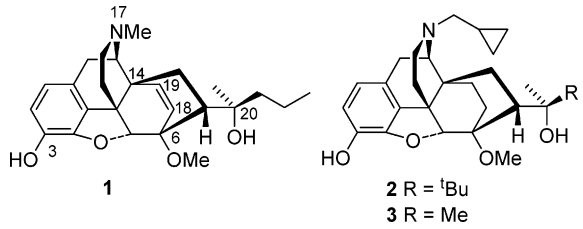

FIGURE 1. Etorphine (**1**), buprenorphine (**2**), and diprenorphine (**3**).

The orvinols are prepared through a Diels−Alder reaction of thebaine (**4**) with various dienophiles to give the 6,14-bridged thevinones, the prototypical being thevinone (**5**) (Figure 2).[2] Addition of Grignard reagents give the 20-hydroxyl derivatives termed the thevinols (such as **6**, Figure 2), which is followed by 3-*O*-demethylation to yield the 3-phenolic orvinols (such as **1**).[2] Numerous derivatives have been prepared primarily through chemical manipulation of substituents at positions 17 and 20.[9] The 6,14-bridge (namely the 18- and 19-positions) has received less attention, mainly due to the fact that it suffers from steric hindrance being positioned inside the concave opioid skeleton. Indeed, even the hydrogenation of the 18,19-double bond in **5** can require extended periods of time at 60 psi,[10] and the only orvinols previously prepared with functionality at the 18- or 19-positions were described by Matt, where a 7-chloro derivative of thebaine was prepared and employed as the starting diene yielding a 18-chlorinated thevinone.[11] In addition, we have recently shown that the 7-position of thebaine can be silylated with large silylating groups, and that a subsequent Diels−Alder reaction leads to an 18-silylated thevinone.[1] Early studies with the morphinan series showed that hydroxyl groups could be tolerated at the 7- and 8-positions of the morphine skeleton[2] which correspond to the 18- and 19-positions of the orvinols, respectively. We considered that the etheno function of the thevinones may serve as a useful handle for the introduction of hydroxyl groups to allow further func-

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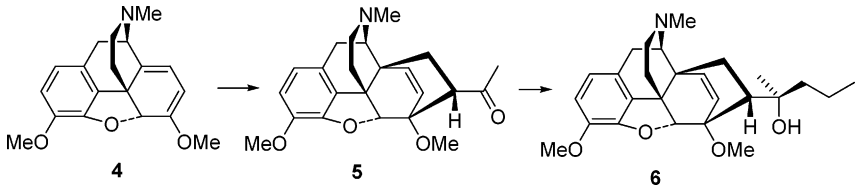
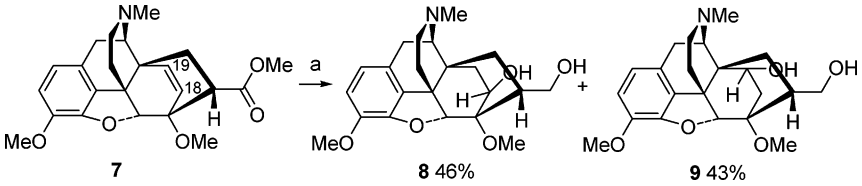


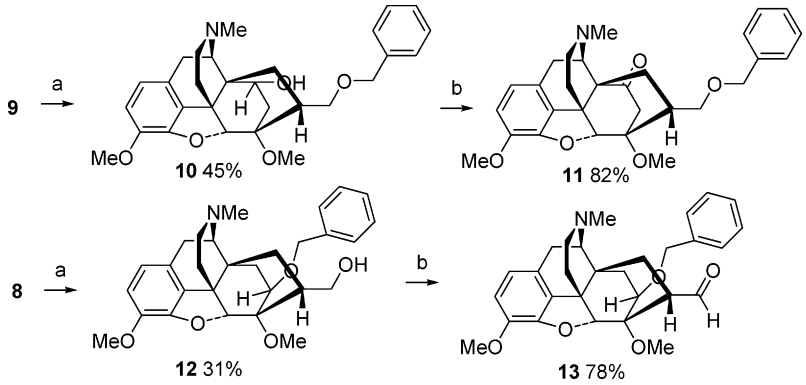
FIGURE 2. The preparation of thevinols from thebaine (**4**).

SCHEME 1[a]



[a] Reagents and conditions: (a) (i) $BH_3{\cdot}Me_2S$, THF, 65−70 °C; (ii) NaOH, 30% H_2O_2.

SCHEME 2[a]



[a] Reagents and Conditions: (a) NaH, $PhCH_2Br$, DMF; (b) DMP, wet CH_2Cl_2.

tionalization at these positions, and that these positions may affect efficacy differentially at the receptor types.

Results and Discussion. Treatment of the methyl acrylate adduct of thebaine (**7**)[12]with $BH_3{\cdot}Me_2S$ at 65−70 °C for 5 h, followed by treatment with basic hydrogen peroxide led to two products which were isolated by preparative TLC (Scheme 1). Mass spectral analysis of each product was consistent with reduction of the ester at C-20 to the primary alcohol, and mono-hydroxylation of the 6,14-bridge. Analysis of the ^{1}H NMR spectra proved complicated, but the loss of the vinylic protons in both products clearly indicated that a reaction had occurred at the 18,19 double bond, further implying that hydroxylation had occurred. Confirmation of the structure of **8** as the 18-hydroxyl isomer was performed through single-crystal X-ray analysis (see the Supporting Information), and compound **9** was therefore assigned as the corresponding 19-hydroxyl isomer (Scheme 1), as the first two thevinols with hydroxyl groups on the 6,14-bridge.

The generation of alcohols at both the 18- and 19-positions in approximately equal quantities (46% and 43% yield, respectively) was noteworthy as the literature suggests that C-19 is more sterically hindered than C-18.[2] Obviously, for the present hydroboration reaction, both positions appear to possess similar steric hindrance. The 18-hydroxyl in **8** was oriented toward C-20, consistent with the idea that attack by BH_3 had occurred from the least hindered direction, and a similar stereochemistry was confirmed for the 19-hydroxyl in **9** through the studies described below.

The fact that **8** and **9** contain two alcohols (one secondary on the 6,14-bridge and one primary at C-20) led to the consideration that further manipulation of these structures would require a method to differentiate between the alcohols. We therefore attempted to selectively protect the least hindered 20-hydroxyl, and oxidize the remaining secondary hydroxyl to the corresponding ketone. Benzylation of the 20-hydroxyl of **9** gave **10**, a structure confirmed by single-crystal X-ray analysis (see the Supporting Information), which also confirmed the assignment of structure **9** (Scheme 2). Treatment with the Dess−Martin[13] reagent gave the corresponding 19-ketone (**11**) in good yield, demonstrating the potential utility of **9** in the synthesis of novel orvinols.

Treatment of **8** under the same benzylating conditions was also expected to selectively protect the primary 20-hydroxyl. Mass spectral analysis was consistent with mono-benzylation, but treatment with the Dess−Martin reagent gave rise to an aldehyde as determined by ^{1}H NMR. The product was assigned structure **13**, which obviously arose from the oxidation of 18-benzyloxy **12** (Scheme 2). The origin of **12** was not initially clear, as

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12 may be forming in the initial benzylation reaction, or the benzyl group may be transferred between the 20- and 18-hydroxyls during treatment with the Dess−Martin reagent. No suitable crystal could be generated; however, COSY, TOCSY, and HMBC NMR analysis of the benzylation product confirmed that **12** is indeed the product formed from the treatment of **8** with benzyl bromide. A full analysis of the 2D NMR spectra is included in the Supporting Information.

The reason the apparently more hindered alcohol of **8** was selectively benzylated was not clear, although it was considered that initial benzylation of the 20-hydroxyl followed by an intramolecular benzyl group transfer to the 18-hydroxyl would account for **12**. Previous studies[14,15] have shown that such intramolecular transfers are disfavored, and this was also shown to be the case in the current studies through quantum mechanical determination of the transition state. Results, discussed in detail in the Supporting Information, revealed the barrier for transfer to be approximately 60 kcal/mol, and that the orientation of the groups is not consistent with an SN_2 process.

In conclusion, the 6,14-bridge of the thevinones can be hydroxylated to give both 18- and 19-hydroxylated products. The fact that benzylation of **8** leads to selective protection of the 18-hydroxyl, and benzylation of **9** leads to the selective protection of the 20-hydroxyl, provides a method to differentiate between the alcohols and facilitates the use of both **8** and **9** as intermediates in the synthesis of novel analogues of the orvinols.

Experimental Section

4,5α-Epoxy-18*R*-hydroxy-7α-hydroxymethyl-3-methoxy-17-methyl-6α,14α-*ethano*-isomorphinan (8) and 4,5α-Epoxy-19*S*-hydroxy-7α-hydroxymethyl-3-methoxy-17-methyl-6α,-14α-*ethano*-isomorphinan (9). BH_3·Me_2S (2M, THF, 35 mL, 70 mmol) was added dropwise with vigorous stirring to a solution of **7**[12] (1.80 g, 4.5 mmol) in THF (5 mL) at room temperature. After being stirred for 30 min at room temperature, the mixture was heated at 65−70 °C for 5 h. After cooling, water (3 mL) was added and the mixture was stirred at room temperature to 30 min to quench excess borane. Aqueous NaOH (15%, 30 mL) and hydrogen peroxide (30%, 40 mL) were added successively, and the mixture was stirred overnight, poured into an aqueous NaOH solution, and then extracted into $CHCl_3$ (3 × 50 mL). The organic extracts were washed successively with aqueous NaOH (100 mL) and brine (100 mL). After removal of the solvent, the two products were isolated by preparative TLC (Silica, CH_2Cl_2:MeOH:NH_4OH 96:4:0.1) after successive developments.

The higher running product was shown to be 18-hydroxyl isomer **8** (0.81 g, 46%). ^{1}H NMR δ 6.71 (1H, d, 8.5), 6.62 (1H, d, 8.5), 4.55 (1H, s), 4.06 (1H, s, br), 3.88 (1H, m), 3.86 (3H, s), 3.72 (1H, m), 3.49 (1H, m), 3.45 (3H, s), 3.12 (1H, d, 18.5), 2.92 (1H, s, br), 2.79−2.73 (2H, m), 2.46 (1H, dd, 5.5, 12.0), 1.2.34−2.29 (5H, m), 2.09 (1H, dt, 5.0, 13.0), 2.03 (1H, m), 1.80 (1H, dd, 7.0, 13.0), 1.70 (1H, d, 10.0), 1.30 (1H, m), 1.08 (1H, dd, 5.5, 13.5). ^{13}C NMR δ 146.5, 142.1, 132.4, 128.6, 119.8, 113.7, 91.2, 78.4 65.1, 61.2, 59.7, 56.7, 50.8, 45.6, 45.5, 43.7, 38.6, 26.5, 35.9, 35.3, 28.5, 22.1. MS (LCMS) *m/z* 388.3 (M + 1). (See the Supporting Information for X-ray crystal data.)

The lower running spot was shown to be the 19-hydroxyl isomer **9** (0.76 g, 43%). ^{1}H NMR δ 6.71 (1H, d, 8.5), 6.59 (1H, d, 8.5), 4.44 (1H, s), 3.87 (3H, s), 3.80 (2H, dd, 6.0, 14.0), 3.45 (3H, s), 3.13 (1H, d, 18.5), 3.90 (1H, m), 2.88 (1H, d, 14.5), 2.59 (1H, m), 2.49 (1H, m), 2.36 (3H, s), 2.13 (1H, dt, 5.5, 13.0), 2.30 (1H, m), 1.96 (1H, m), 1.68 (2H, m), 1.47 (1H, d, 14.5). ^{13}C NMR δ 146.7, 142.1, 135.5, 131.3, 119.6, 114.3, 93.6, 67.7, 62.9, 58.2, 56.9, 51.9, 45.8, 44.7, 43.7, 40.9, 37.0, 35.5, 30.6, 21.9, 21.7. MS (LCMS) *m/z* 388.4 (M + 1). The signal for C-6 was not present, and it is assumed to be masked by signals from $CHCl_3$.

7α-Benzyloxymethyl-4,5α-epoxy-19*S*-hydroxy-3-methoxy-17-methyl-6α,14α-*ethano*-isomorphinan (10). NaH (62 mg, 95%, 2.5 mmol) was added to a solution of **9** (0.43 g, 1.2 mmol) in DMF (8 mL) and the resulting mixture was stirred for 1 h at room temperature. After cooling to −78 °C, benzyl bromide (0.18 mL, 1.5 mmol) was added and the suspension was stirred for 10 min. The mixture was warmed to −60 °C and stirred for an additional 1 h. Saturated NH_4Cl (8 mL) was added and extracted with diethyl ether (4 × 15 mL). The ether extracts were washed with brine (2 × 5 mL) and dried (Na_2SO_4), and **10** was purified by preparative TLC (Silica, $CHCl_3$:MeOH, 97:3) after removal of the ether (0.24 g, 45%). ^{1}H NMR δ 7.34 (5H, m), 6.69 (1H, d, 8.5), 6.57 (1H, d, 8.54), 4.61 (1H, d, 10.0), 4.50 (1H, d, 10.0), 4.40 (1H, s), 3.94 (1H, dd, 2.0, 9.0), 3.86 (3H, s), 3.49 (1H, m), 3.40 (1H, m), 3.37 (3H, s), 3.11 (2h, m), 2.80 (1H, m), 2.60 (1H, m), 2.45 (1H, m), 2.37−2.31 (4H, m), 2.11 (1H, dt, 5.5, 12.5), 2.02 (1H, dd, 6.0, 14.0), 1.88 (1H, m), 1.68 (1H, m), 1.55 (1H, d, 15.1). ^{13}C NMR δ 146.7, 141.9, 137.4, 131.5, 129.1, 128.7, 128.3, 128.2, 119.5, 114.1, 92.5, 75.1, 74.0, 69.2, 67.9, 58.4, 56.8, 50.9, 45.8, 44.4, 43.7, 41.0, 35.7, 34.8, 31.7, 21.7, 21.6. MS (LCMS) *m/z* 478.3 (M + 1). (See the Supporting Information for X-ray crystal data.)

7α-Benzyloxymethyl-4,5α-epoxy-3-methoxy-17-methyl-19-oxo-6α,14α-*ethano*-isomorphinan (11). Dess−Martin salt (DMP, 0.1 g) was added to a solution of **10** (45 mg, 0.09 mmol) in CH_2Cl_2 (10 mL). To that solution was added wet CH_2Cl_2 (4 mL shake with 100 μL of water) dropwise over 1 h. The mixture was stirred for an additional 2 h as the solution became cloudy. A mixure of 10% $Na_2S_2O_3$ and saturated Na_2CO_3 (1:1, 4 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL) and the organic layers were combined and dried (Na_2SO_4). Removal of the solvent gave **11** (37 mg, 82%). ^{1}H NMR δ 7.34−7.24 (5H, m), 6.68 (1H, d, 8.2), 6.56 (1H, d, 8.2), 4.65 (1H, s), 4.49 (2H, s), 3.77 (3H, s), 3.56 (1H, dd, 3.9, 9.1), 3.43 (1H, dd, 7.4, 9.0), 3.36 (3H, s), 3.29 (1H, m), 2.98 (2H, m), 2.60 (1H, dd, 6.7, 18.1), 2.45 (1H, m), 2.35−2.23 (5H, m), 2.19 (1H, m), 2.07 (2H, m), 1.76 (1H, dd, 2.4, 13.0), 1.45 (1H, dd, 6.6, 14.6). MS (LCMS) *m/z* 476.5 (M + 1).

18*R*-Benzyloxy-4,5α-epoxy-7α-hydroxymethyl-3-methoxy-17-methyl-6α,14α-*ethano*-isomorphinan (12). 8 (110 mg, 0.3 mmol) was treated with NaH and benzyl bromide as for **9** above to yield the benzyl ether **12** (44 mg 31%) and recovered **8** (42 mg). ^{1}H NMR δ 7.29−7.16 (5H, m), 6.72 (1H, d, 8.1), 6.61 (1H, d, 8.1), 4.52/4.46 (s, 1H (2/1), 4.50/4.43 (1H, s, 2/1), 3.89 (1H, d, 11.5), 3.86 (s, 3H), 3.64 (2H, m), 3.49 (3H, s), 3.13 (1H, d, 18.5), 2.76 (2H, m), 2.46 (1H, dd, 5.1, 11.8), 2.31−2.24 (5H, m), 2.06 (1H, dt, 5.5, 12.8), 1.97 (1H, m), 1.69−1.63 (2H, m), 1,30−1.26 (1H, m), 1.15 (1H, dd, 4.8, 13.5). ^{13}C NMR δ 146.5, 142.0, 137.8, 132.4, 128.6, 128.4, 127.7, 127.7, 119.6, 114.2, 94.0, 79.1, 77.4, 77.2, 76.9, 72.7, 71.1, 61.0, 61.0, 56.8, 51.5, 45.3, 45.3, 43.6, 39.0, 37.8, 36.6, 35.1, 28.6, 22.0. MS (LCMS) *m/z* 478.3 (M + 1).

18*R*-Benzyloxy-7α-carboxaldehydo-4,5α-epoxy-3-methoxy-17-methyl-6α,14α-*ethano*-isomorphinan (13). 12 (47 mg, 0.1 mmol) was treated with DMP (0.1 g) following a similar procedure to **10** above to give aldehyde **13** (35 mg 78%). MS + 1^+, 476.4. The ^{1}H and ^{13}C NMR spectra indicated an aldehyde group exisiting as two rotamers, with chemical shifts at 10.18 (H), 205.8 (C) and 9.98 (H), 202 (C), respectively. See the Supporting Information for a copy of the NMR spectra.

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Supporting Information Available: ^{1}H NMR spectra of compounds **8**−**13**, ^{13}NMR spectrum of **13**, X-ray crystallographic data for compounds **8** and **10**, and modeling data concerning the proposed benzyl trafer reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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