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Functionalization of the 6,14-bridge of the orvinols. Part 3: Preparation and pharmacological evaluation of 18- and 19-hydroxyl substituted orvinols☆

Huifang Wu,[a] Trudy A. Smith,[a] Hongyan Huang,[a] Jia Bei Wang,[a] Jeffrey R. Deschamps[b] and Andrew Coop[a,*]

[a]*Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, 20 Penn Street, Room 637, Baltimore, MD 21201, USA*
[b]*Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, DC 20375, USA*

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Abstract—The orvinols are a class of potent opioids which have been extensively studied, yet little is known about the effects of introducing substituents into the 18- and 19-positions. The etheno bridge of thevinone was hydroxylated to give both the 18- and 19-hydroxyl substituted thevinols. After 3-*O*-demethylation to the corresponding orvinols, binding and GTPγS functional assays indicated that hydroxyl substitution at the 18- and 19-positions differentially affects the μ opioid efficacy of orvinols.

The opioid analgesic buprenorphine (**1**) has recently garnered significant interest because of its approval as a treatment for opioid dependence,[2,3] but it was originally developed as an analgesic agent with lower abuse potential than traditional opioid analgesics such as morphine.[4] Buprenorphine owes its unique profile to its partial agonism at μ opioid receptors, and similar partial agonists may prove useful in replacing the currently used full μ agonist prescription analgesics which are increasingly abused.[5] The orvinols (such as buprenorphine) were initially described by Bentley in the 1960s and continue to be the subject of intense research.[4,6] They are prepared through Diels–Alder reactions of the opium alkaloid thebaine (**2**) with dienophiles, such as methyl vinyl ketone, to give the thevinones (**3**). The addition of Grignard reagents, followed by *O*-demethylation, gives rise to the orvinols, including the extremely potent etorphine (**4**) (Fig. 1).[6] The orvinols possess affinity for all three opioid receptors (μ, κ, δ), generally with little selectivity between the receptor types; their differing pharmacological profiles are due to their differing efficacies at the receptor types.[6] The nature of the

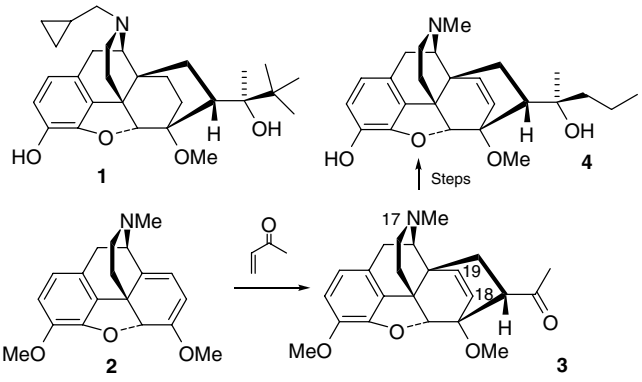

Figure 1. Buprenorphine and the synthesis of etorphine.

17-substituent almost universally determines efficacy at μ receptors: 17-methyl substituted orvinols, like etorphine (**4**), are full μ agonists,[6] whereas the 17-cyclopropylmethyl orvinols have lower μ efficacy. The fact that full κ agonism remains dominates the pharmacology, leading to κ agonism in vivo.[6] Buprenorphine (**1**) is the exception to this rule as it displays κ antagonism, leading to its in vivo profile of μ partial agonism.[6] The studies herein show that μ efficacy can be reduced through the introduction of hydroxyl groups into 17-methyl substituted orvinols.

Keywords: Analgesics; Partial agonism; Drug abuse.
☆ Ref. 1.
* Corresponding author. Tel.: +1 410 706 2029; fax: +1 410 706 5017; e-mail: acoop@rx.umaryland.edu

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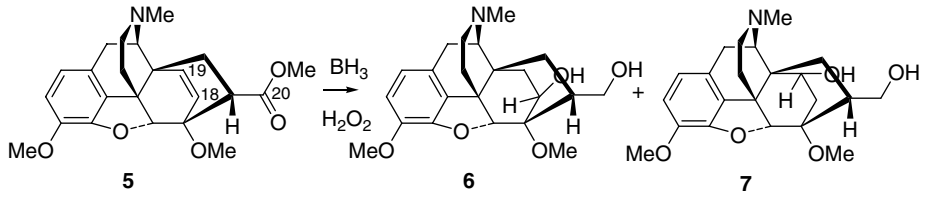
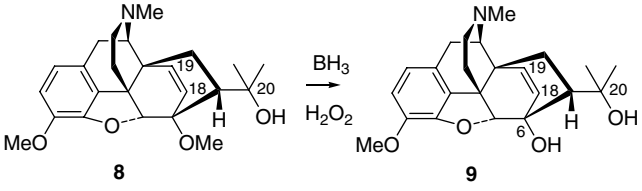


Figure 2. Previous synthesis of the 20-primary alcohols **6** and **7**.

We recently showed that the little studied 18- and 19-positions of the orvinols can be derivatized as alcohols through treatment of the methacrylate adduct (**5**) with BH_3 and H_2O_2, to give 20-primary alcohol orvinols (**6**, **7**) (Fig. 2).[1] These positions correspond to the 7- and 8-positions of the morphinans, where hydroxyl substitution significantly affects the pharmacology of morphinans.[7,8] In order to fully determine the effect of similar substitution in the orvinols, it was necessary to introduce 18- and 19-substituents into orvinols with secondary or tertiary alcohols at the 20-position, due to the fact that secondary and tertiary alcohols are optimal for high opioid antinociceptive activity. Herein, we report that hydroxyl groups can be introduced into both 18- and 19-positions of 20-secondary thevinols, and that the corresponding orvinols differ in their efficacy at μ receptors depending on the position of the hydroxyl group.

Results and discussion. The application of hydroboration to tertiary thevinol (**8**) led only to 6-demethylation (Scheme 1), a reaction which has been previously reported through the treatment of thevinols with metallic hydrides.[9] The lack of hydroxylation was attributed to hindrance of the etheno bridge by the two alkyl groups of the tertiary alcohol, and attention switched to the corresponding secondary alcohols which would be expected to suffer from less steric hindrance of the etheno bridge. As anticipated from previous studies, treatment of thevinone (**3**) with BH_3·THF at 55–60 °C for 5 h, followed by treatment with peroxide, led to four products which were isolated by preparative TLC and shown to be isomers with a mass of 18 above the corresponding secondary alcohols. Analysis of the ^1H NMR spectra proved complicated, and structural assignment of the four isomers was performed through single crystal X-ray analysis indicating the structures to be **10**–**13** (R = Me) (Scheme 2).

The hydroxyls on the bridge were oriented toward C-20, consistent with our previous findings[1] that BH_3 had approached from the least hindered direction. In contrast to the tertiary alcohol (**8**), no 6-demethylation was observed for the secondary alcohols, supporting the hypothesis the secondary and tertiary thevinols have different degrees of hindrance of the 18,19-double bond.

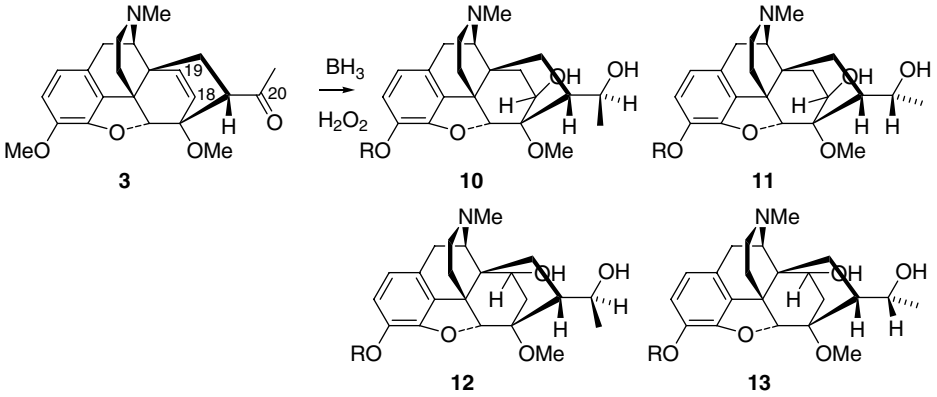


Scheme 1. 6-*O*-Demethylation through hydroboration of 20-methylthevinol (**8**).

Table 1. Binding data at μ, δ, and κ opioid receptors

	K_i (nM), ±SEM (n = 3)		
	μ	δ	κ
UMB94 (**11**, R = H)	20 ± 3.7	25 ± 4.6	26 ± 10
UMB95 (**10**, R = H)	13 ± 7.1	28 ± 4.7	64 ± 24
UMB96 (**12**, R = H)	34 ± 17	110 ± 17	170 ± 120
UMB97 (**13**, R = H)	4.3 ± 2.8	120 ± 16	230 ± 170
Thienorphine[13]	0.22 ± 0.07	0.69 ± 0.03	0.14 ± 0.06

Displacement of [^{3}H]DAMGO, [^{3}H]DPDPE or [^{3}H]U69,593 for μ, δ or κ from CHO cell membranes expressing cloned opioid receptors.



Scheme 2. Hydroboration of thevinone (**3**).

Table 2. GTPγS functional data at μ, δ, and κ opioid receptors ($n = 3$)

	μ		δ		κ	
	EC_{50} (nM)	RS	EC_{50} (nM)	RS	EC_{50} (nM)	RS
UMB94 (**11**, R = H)	43 ± 12	0.63 ± 0.14	88 ± 2.4	1.3 ± 0.08	240 ± 5	0.75 ± 0.24
UMB95 (**10**, R = H)	15 ± 1	0.51 ± 0.16	21 ± 5.1	1.2 ± 0.08	210 ± 67	0.55 ± 0.03
UMB96 (**12**, R = H)	89 ± 19	0.90 ± 0.11	210 ± 9.0	1.4 ± 0.60	520 ± 9	0.25 ± 0.03
UMB97 (**13**, R = H)	12 ± 1	0.97 ± 0.11	57 ± 18	1.4 ± 0.26	720 ± 8	0.47 ± 0.19
Thienorphine[13]	1.9 ± 0.4	0.19 ± 0.04	NA	0.02 ± 0.02	0.3 ± 0.2	0.75 ± 0.05

Standard agonists: DAMGO for μ; SNC80 for δ; dynorphin A for κ; stimulation % of standards was set as 1.0 in each experiment. RS: relative stimulation, % stimulation of compound divided by % stimulation of standard. Data expressed ±SEM.

3-*O*-Demethylation of the four isomeric products with NaPrS[10] gave rise to the corresponding target orvinols (**10**–**13**, R = H) in good yield, and were subjected to binding and GTPγS functional assays at the three cloned human opioid receptors (μ, κ, δ) using methods previously described.[11,12] The pharmacological results are shown in Tables 1 and 2.

All compounds showed reduced binding affinity and potency in GTPγS assays compared to thienorphine (under slightly modified conditions[13]), however UMB94 and 95 (with an 18-hydroxyl group) have similar affinity for all three sites, whereas the 19-hydroxyl isomers show a preference for μ over the other receptors. Indeed, UMB97 shows the highest affinity for μ receptors and approximately 30-fold selectivity over both δ and κ receptors. In functional assays, the 19-hydroxy isomers (UMB96 and UMB97) show full μ agonism, weaker full δ agonism, and low efficacy at κ receptors. The corresponding 18-hydroxyl isomers (UMB95 and UMB94) displayed partial μ agonism, a surprising finding for 17-methyl substituted orvinols, along with partial κ agonism.

In conclusion, the 18,19-double bond of the thevinones, but not tertiary 20-alcohols, can be functionalized through hydroboration, and the resulting orvinols have differing pharmacological profiles in vitro. The 18-alcohols are partial μ agonists, whereas the 19-alcohols are full μ agonists, demonstrating that the efficacy of orvinols at μ receptors can be reduced while retaining the 17-methyl group.

Supplementary data. Crystallographic data (excluding structure factors) for the structures in this paper (**10**–**13**, R = Me) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 626764, CCDC 626568, CCDC 626569, and CCDC 626570. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

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