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Synthesis and opioid activity of novel 6-substituted-6-demethoxy-ethenomorphinans

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Dedicated to Professor Sándor Makleit on the occasion of his 80th birthday

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ABSTRACT

A set of novel 6-substituted orvinols was synthesized and pharmacologically characterized in order to explore the effect of the polarity and steric effects of these new moieties on the opioid activity. It was revealed that longer 6-*O*-alkyl chains led to increased agonistic activities, while the lack of C6-etheral oxygen gave rise to an antagonistic profile at the opioid receptors in the mouse ileum.

1. Introduction

Orvinols are a group of opioids[1] which were designed by Bentley and co-workers[2–4] in the search for analgesics comparable in efficacy to morphine but lacking its well-known undesired side-effects, such as tolerance, dependence, and respiratory depression, to name just the most serious. Bentley hypothesized that more complex and rigid structures based on the morphine molecule could allow to eliminate the side-effects without compromising analgesia. The synthesis of pharmaceutically important orvinols, such as opioid agonist ethorphine (**1**),[5] antagonist diprenorphine (**2**),[5] and μ-agonist/κ-antagonist buprenorphine (**3**)[6] was reported in the middle of the past century (Fig. 1).

Buprenorphine was originally developed as an analgesic agent with lower abuse potential than traditional opioid analgesics such as morphine.[7] However, due to its partial agonism at the μ-opioid receptor, buprenorphine has unique pharmacological properties and was approved for the treatment of opioid dependence.[8–10]

Very high analgesic activity of several orvinols strongly suggested that receptor binding in these opioids must involve a stereoselective component that was missing in morphine and its derivatives. It was early recognized that exceptional in vivo potency of orvinols is associated with the presence of the C7 side-chain.[4]

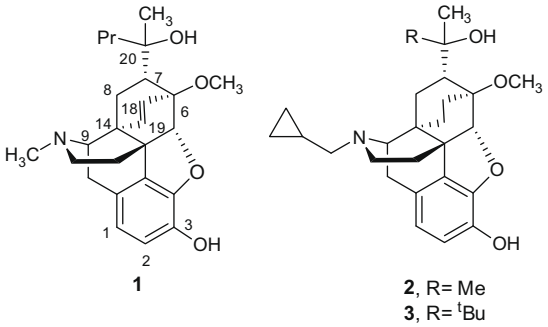

Figure 1. Structure of pharmacologically important orvinols.

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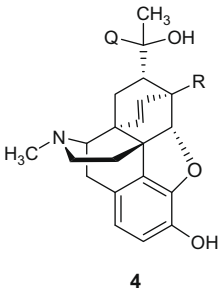


4

4	R	Q
a	H	*n*-Bu
b	CH_3	*n*-Bu
c	Cl	CH_3
d	Br	CH_3
e	F	CH_3

Figure 2. 6-Substituted-6-demethoxyorvinols.

However, the roles played by the C20 hydroxy and alkyl groups have not been clearly established. It was suggested[5] that the hydroxy group may form an intramolecular H-bond with the 6-methoxy group, thus extorting the appropriate conformation of the molecule for the binding with the receptor.

The pharmacological effect of the elimination of the intramolecular H-bonding between C6 and C20 substituents of the orvinol backbone was studied by Hutchins et al.[11] in a series of 6-substituted-6-demethoxyorvinols **4a–e** (Fig. 2). They concluded that not the formation of an intramolecular hydrogen bond was critical for the opioid agonist effects of the orvinols but the configuration of the C20. (*R*)-Configuration on this center was associated with much higher antinociceptive potency than (*S*)-configuration. Their observation was later confirmed by Crabbendam et al.[12]

In order to further study the effect of the elimination or modification of the intramolecular H-bonding between C6 and C20 substituents of the orvinol backbone on the pharmacological properties, several 6-substituted-6-demethoxy orvinols were prepared.

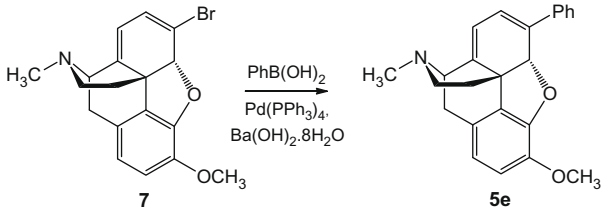
2. Results and discussion

2.1. Chemistry

The set of orvinols **10a–e** with substituents at C6 differing in steric bulk and electronegativity was synthesized. Starting morphinandienes **5a–d** were prepared as described by Seki,[13] treating codeinone (**6**) with *p*-toluenesulfonic acid (PTSA) and the corresponding alcohol in benzene (Scheme 1).

6-Phenyl-6-demetoxythebaine (**5e**) was prepared from 6-bromo-6-demethoxythebaine (**7**), applying the Suzuki–Miyaura cross-coupling[14] in a very high yield (91%) (Scheme 2). Compound **7** was obtained from natural alkaloid thebaine in a five step reaction sequence.[15]

Morphinans **5a–e** were next used in the synthesis of orvinols **10a–e**, applying a classical transformation sequence reported by Bentley and co-workers[2–4] (Scheme 3). The Diels–Alder reaction of the morphinans **5a–e** with methyl vinyl ketone (MVK) gave in each case complex mixtures of products, from which thevinones **8a–e** were separated using column chromatography.



7 5e

Scheme 2. Synthesis of 6-phenyl-6-demethoxythebaine **5e**.

In order to confirm the aimed configuration (i.e., 7α-acetyl-6β,14β-ethenomorphinan) of the obtained thevinones **8a–e**, 1D NOE experiments were performed for all five cycloadducts. The significant NOEs were identified on the basis of our previous experience with the structural elucidation of endoethenomorphinans[16] and were applied in the designation of the configuration as shown in the DFT optimized structure of **8b** (Fig. 3). To be able to estimate the H···H distances, we presented these data for the geometry optimized structure of **8b** in Table 1.

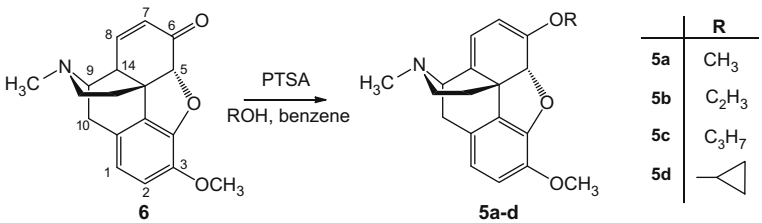
Grignard–Barbier reaction of thevinones **8a–e** with MeMgBr gave thevinols **9a–e**. MeMgBr was chosen as a Grignard reagent to avoid the formation of an additional stereogenic center at C20. It was considered a reasonable simplification, even though it is well-known from previous structure–activity relationships that compounds with propyl and butyl substituents at C20 possess significantly higher opioid and analgesic activity. Finally, target orvinols **10a–e** were prepared in the KOH-promoted *O*-demethylation of the thevinols **9a–e** in moderate yields.

The lack of C6-etheral function on the conformation of the C20 tertiary alcohol function was then studied. The geometry optimized structures and the corresponding formation energies undoubtedly confirmed for **10a** that the H-bonding between C20-OH and C6-O significantly contributed to the lowest energy conformation. However, for **10e** there was a clear energetic advantage of 13 KJ mol^{-1} in case of structure A over structure B due to intramolecular Van der Waals interactions between C20-Me and C6-Ph moieties (Fig. 5).

On the basis of these findings the synthesis and characterization of further derivatives are in progress and will be reported in due course.

2.2. Pharmacological results

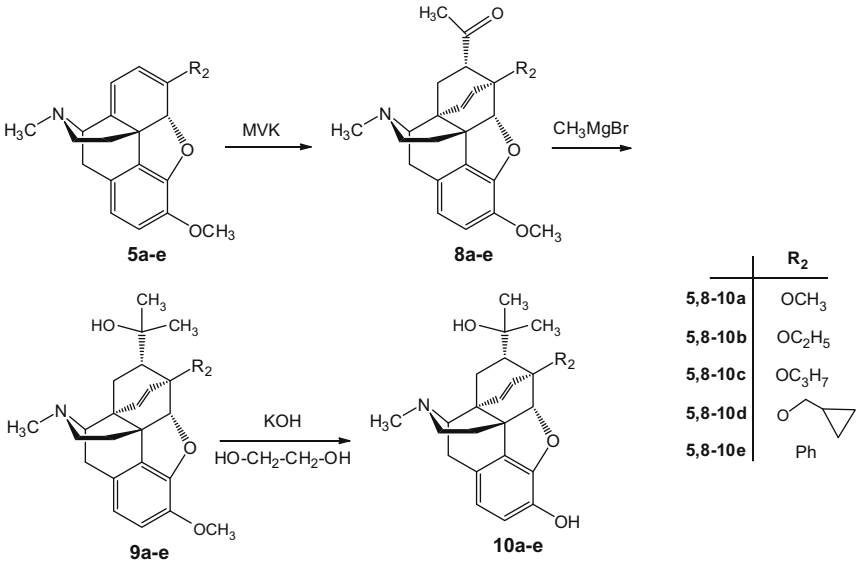
Affinity and selectivity of new analogs were evaluated by radioligand binding assays using rat brain membranes. IC_{50} values at μ- and δ-opioid receptors, determined against [^{3}H]DAMGO and [^{3}H]Ile^{5,6}deltorphin-2, respectively, are provided in Table 2. All new compounds had IC_{50} values in the nanomolar range. The μ-receptor affinities of compounds **10b–e** were quite similar and three to five-fold higher when compared with **10a** with methoxy substituent in position 6. The lack of the etheral oxygen in **10e** did not affect μ-affinity, but resulted in some enhancement of δ-affinity.



6 5a-d

	R
5a	CH_3
5b	C_2H_3
5c	C_3H_7
5d	

Scheme 1. Synthesis of 6-substituted-morphinandienes **5a–d**.



Scheme 3. Transformation of morphinandienes **5a–e** into orvinols **10a–e**.

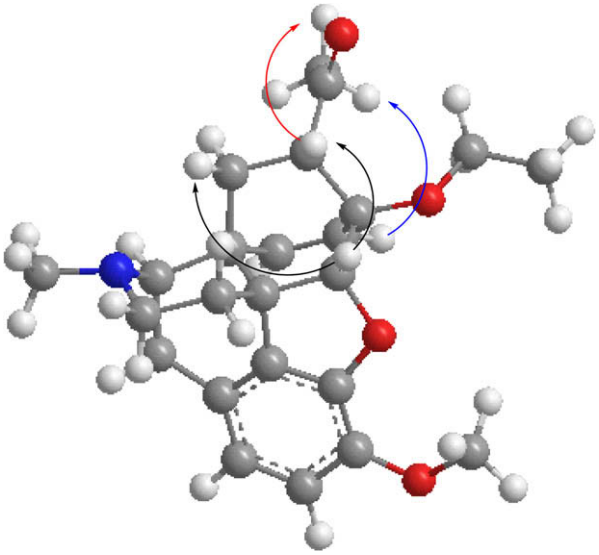


Figure 3. Significant NOEs in the geometry optimized structure of **8b** obtained at the B3LYP/6-31G(d,p) level of theory.

Table 1
H···H distances in the geometry optimized structure of **8b** obtained at the B3LYP/6-31G(d,p) level of theory

	H···H distances in **8b** (Å)					
	H7	H8a	H8b	H18	H19	H21
H5	2.306	3.539	4.403	4.190	4.872*	5.169*
H7	—	2.326	2.958	4.255	4.827*	3.893
H18	4.255	4.896*	4.074	—	2.504	2.738

* No NOE was observed.

We furthermore examined the effects of morphine and orvinols **10a–e** on electrically-stimulated contractions in the mouse ileum, to test the in vitro activity of these drugs in a tissue where opioid effects are well characterized. Electrical stimulation of ileal preparations results in activation of cholinergic neurons, which leads to twitch contractions of the smooth muscular tissue.[17] Morphine is known to block presynaptic neural release of acetylcholine and thus inhibits smooth muscular contractility.[18] The opioid-induced inhibition of electrically-stimulated twitch contractions provides a good functional assay for opioid activity.

Morphine and orvinols **10a–d** dose-dependently reduced the amplitude of electrically-induced twitch contractions (Fig. 4 A–D) and the EC_{50} values were in the nanomolar range (Table 3). Compound **10c** was the most potent agonist, with an EC_{50} of 1.99 ± 0.28 nM and the maximum effect of 41.31 ± 6.43%. The inhibitory effect of morphine and agonists **10a–d** on smooth muscle contractility was blocked by the opioid receptor antagonist naloxone (1 μM), indicating that the effects of the compounds **10a–d** were mediated by the opioid receptors.

Compound **10e** did not influence the smooth muscle contractions in mouse ileum tissue strips (Fig. 4E). Interestingly, at the high concentration of 1 μM, compound **10e** blocked the inhibitory effect of morphine. These data suggest that **10e** may act as an antagonist at the opioid receptors in the mouse ileum.

3. Conclusions

We hereby report on the formation of a new set of 6-substituted-6-demethoxyorvinols and the characterization of their opioid activities. On the basis of the presented data it could be concluded that length of the alkyl chain connected to the C6-etheral oxygen has a direct effect on the agonistic activity, while the lack of C6-etheral oxygen and the insertion of an aromatic ring in the proximity of position 6 cause an antagonistic profile at the opioid receptors in the mouse ileum.

4. Experimental

4.1. General details

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Thin layer chromatography was performed on pre-coated Merck 5554 Kieselgel 60 F254 foils using chloroform/methanol = 8:2 mobile phase. The spots were visualized with Dragendorff's reagent. ^1H and ^{13}C NMR spectra were recorded on a Bruker WP 200 SY or a Bruker AM 360 spectrometer, chemical shifts are reported in parts per million (δ) from internal TMS and coupling constants (J) are measured in hertz. NOESY experiments were performed on a Bruker AMX-400 spectrometer

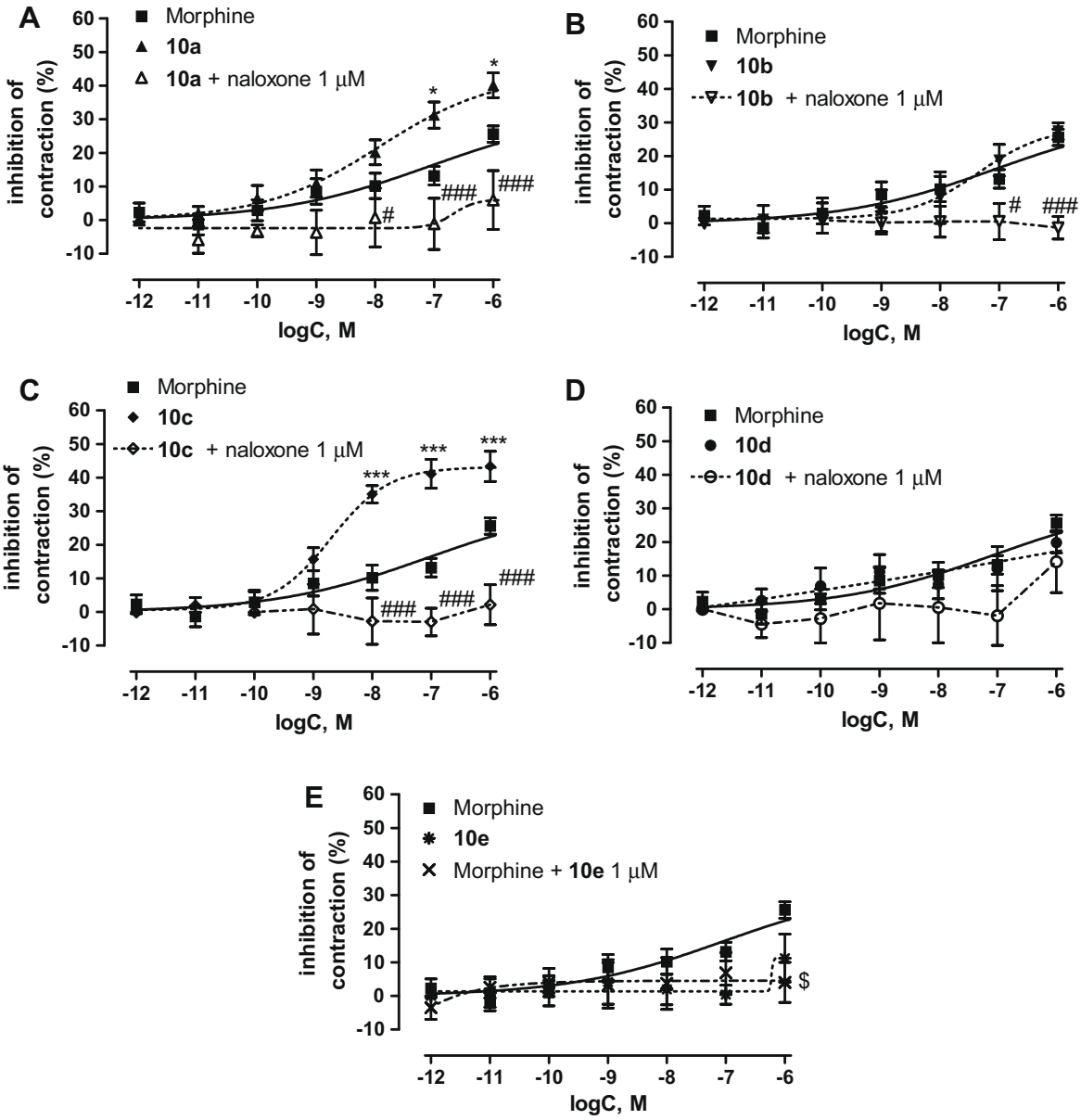


Figure 4. Concentration–response curves of inhibitory effects of compounds **10a** (A), **10b** (B), **10c** (C), **10d** (D), and **10e** (E) on longitudinal smooth muscle contractions in mouse ileum. Data represent mean ± SEM (n = 4–10). *p <0.05, ***p <0.001, as compared to morphine. #p <0.05, ###p <0.001 for orvinol versus naloxone + orvinol. $$p$ <0.05 for **10e** versus **10e** + morphine.

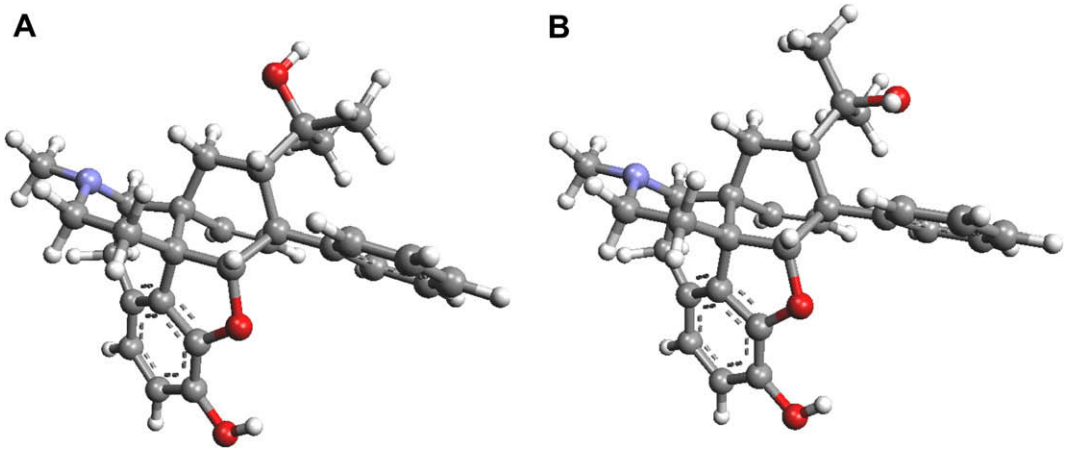


Figure 5. Geometry optimized structures for two conformers of **10e** obtained at the B3LYP/6-31G(d,p) level of theory.

Table 2
Opioid receptor binding affinities of 6-substituted-6-demethoxy-ethenomorphinans **10a–d**

Structure	IC_{50} ± S.E.M. (nM)		
	μ^b	δ^c	δ/μ
Morphine	5.64 ± 0.7	404 ± 50	71.6
10a	0.54 ± 0.04	1350 ± 150	2500
10b	0.18 ± 0.03	230 ± 30	1277
10c	0.13 ± 0.06	320 ± 28	2461
10d	0.14 ± 0.02	650 ± 70	4642
10e	0.11 ± 0.015	440 ± 50	4000

[a] All values are expressed as mean ± S.E.M. of three determinations performed in duplicate.
[b] Determined against [^{3}H]DAMGO.
[c] Determined against [^{3}H][Ile^{5,6}]deltorphin-2.

Table 3
Effect of morphine and novel orvinol derivatives, **10a–d**, on electrically-stimulated longitudinal smooth muscle contractions in mouse ileum. Data represent mean ± SEM (n = 4–10)

	EC_{50} (nM)	E_{max} (%)
Morphine	85.5 ± 12.1	24.41 ± 3.50
10a	11.9 ± 0.7	39.19 ± 5.23
10b	44.0 ± 5.3	25.58 ± 3.32
10c	1.99 ± 0.28	41.31 ± 6.43
10d	90.0 ± 7.5	18.97 ± 1.87

in $CDCl_3$. Mass spectra were obtained with a VG–TRIO–2 spectrometer. Optical rotation was determined with a Perkin–Elmer Model 241 polarimeter. IR spectra were recorded on Perkin–Elmer 283 B spectrometer. Elemental analyses (C, H, N) were obtained on a Carlo Erba 1106 analyzer.

4.1.1. Thebaine (5a)
Physical and spectral data were fully in accordance with authentic sample of the compound.

4.1.2. 6-Ethoxy-6-demethoxythebaine (5b)
Physical and spectral data are in agreement with previously published results.[9] δ_H (200 MHz CD_3Cl) 6.68–6.61 (2H, 2d, H1, H2, J_{1-2} 8.1), 5.71 (1H, d, H8, J_{7-8} 5.1), 4.92 (1H, d, H7, J_{7-8} 5.1), 4.45 (1H, s, H5), 4.12 (2H, q, C6-OC*H*$_2$, *J* 7.4), 3.83 (3H, s, OCH_3), 3.55 (1H, dd, H9, *J* 8.7, *J* 2.2), 2.92–2.26 (7H, m, $H10_a$, $H10_b$, $H16_a$, $H16_b$, NCH_3), 1.72–1.57 (2H, m, $H15_a$, $H15_b$), 1.12 (3H, t, C6-OCH_2–*C*H$_3$, *J* 7.8); δ_C (90.6 MHz CD_3Cl) 155.76 (C6), 144.79 (C4), 142.11 (C3), 132.43–111.43 (4 aromatic, C14, C8), 96.92 (C7), 92.04 (C5), 69.56 (C9), 63.32 (C6-OCH_2), 56.16 (OCH_3), 48.42 (C16), 44.10 (C13), 42.65 (NCH_3), 36.25 (C15), 29.67 (C10), 17.43 (C6-OCH_2–*C*H$_3$).

4.1.3. 6-Propoxy-6-demethoxythebaine (5c)
Physical and spectral data are in agreement with previously published results.[9] δ_H (200 MHz CD_3Cl) 6.70–6.64 (2H, 2d, H1, H2, J_{1-2} 8.0), 5.65 (1H, d, H8, J_{7-8} 6.0), 4.98 (1H, d, H7, J_{7-8} 6.0), 4.52 (1H, s, H5), 3.93 (2H, q, C6-OC*H*$_2$, *J* 8.2), 3.87 (3H, s, OCH_3), 3.51 (1H, dd, H9, *J* 8.0, *J* 2.6), 3.01–2.29 (7H, m, $H10_a$, $H10_b$, $H16_a$, $H16_b$, NCH_3), 1.83–1.51 (4H, m, $H15_a$, $H15_b$, C6-OCH_2–*C*H$_2$), 1.21 (3H, t, C6-OCH_2–CH_2–*C*H$_3$, *J* 7.8); δ_C (90.6 MHz CD_3Cl) 154.12 (C6), 144.27 (C4), 142.65 (C3), 130.95–112.19 (4 aromatic, C14, C8), 93.04 (C7), 91.52 (C5), 69.56–69.01 (C9, C6-OCH_2), 56.96 (OCH_3), 48.07 (C16), 43.61 (C13), 43.00 (NCH_3), 37.49 (C15), 29.33 (C10), 23.74 (C6-OCH_2–*C*H$_2$), 11.29 (C6-OCH_2–CH_2–*C*H$_3$).

4.1.4. 6-(Cyclopropylmethoxy)-6-demethoxythebaine (5d)
Morphinandiene **5d** was prepared in line with the method described in Ref. 9 starting from 1000 mg (3.37 mmol) codeinone (**6**). Off-white powder; mp: 144–146 °C; yield: 812 mg (67%); $[\alpha]_D^{25}$ −234 (*c* 0.1, chloroform); ν_{max}(KBr disc) 3420, 3370, 2960, 1350, 1240, 1160; calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99; found: C, 75.02; H, 7.32; N, 3.90; MS *m*/*z* (%) 351 (M^+, 100); δ_H (200 MHz CD_3Cl) 6.66–6.59 (2H, 2d, H1, H2, J_{1-2} 8.2), 5.81 (1H, d, H8, J_{7-8} 6.3), 4.85 (1H, d, H7, J_{7-8} 6.3), 4.65 (1H, s, H5), 4.19 (2H, d, C6-OC*H*$_2$, *J* 10.2), 3.82 (3H, s, OCH_3), 3.60 (1H, dd, H9, *J* 8.7, *J* 2.5), 2.83–2.18 (7H, m, $H10_a$, $H10_b$, $H16_a$, $H16_b$, NCH_3), 1.83–1.51 (2H, m, $H15_a$, $H15_b$), 0.51–0.11 (5H, m, C6-OCH_2–*CH*–*CH*$_2$–*CH*$_2$); δ_C (90.6 MHz CD_3Cl) 155.69 (C6), 144.41 (C4), 142.20 (C3), 133.08–112.62 (4 aromatic, C14, C8), 92.54 (C7), 90.87 (C5), 76.48 (C6-OCH_2), 69.06 (C9), 56.50 (OCH_3), 47.67 (C16), 45.16 (C13), 42.33 (NCH_3), 37.08 (C15), 28.92 (C10), 13.59 (C6-OCH_2–*C*H═), 4.29 (2C, C6-OCH_2–CH–CH_2–CH_2).

4.1.5. 6-Phenyl-6-demethoxythebaine (5e)
Physical and spectral data are in agreement with previously published results.[14]

4.2. General procedure for Diels–Alder addition
Diene (8 mmol) was heated with methyl vinyl ketone (2.5 g, 36 mmol) in the presence of a small amount of hydroquinone at 100 °C for 4 h. The excess of methyl vinyl ketone was removed under reduced pressure, and the dark viscous residue was dissolved in warm glacial acetic acid (4 mL). This solution was diluted with water (30 mL) and extracted with ether. The aqueous phase was freed from ether by boiling and basified (cc. ammonia solution), and the precipitate was collected, washed with water, and dried to give the crude product. The major component was isolated by flash chromatography (silica, chloroform/methanol = 1:1).

4.2.1. 7α-Acetyl-6,7,8,14-tetrahydro-6β,14β-endoethenothebaine (8a)
Physical and spectral data are in agreement with previously published results.[1,21]

4.2.2. 7α-Acetyl-6-ethoxy-6-demethoxy-6,7,8,14-tetrahydro-6β,14β-endoethenothebaine (8b)
Pale yellow prisms; mp: 127–129 °C; yield: 2275 mg (72%); $[\alpha]_D^{25}$ −172 (*c* 0.1, methanol); ν_{max}(KBr disc) 1712 (CO) cm^{-1}; calcd for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54; found: C, 72.65; H, 7.45; N, 3.47; MS *m*/*z* (%) 395 (M^+, 100); δ_H (200 MHz $CDCl_3$) 6.41–6.35 (2H, 2d, H1, H2, J_{8-9} 7.8), 5.59 (1H, d, H18, J_{18-19} 8.9), 5.45 (1H, d, H19, J_{18-19} 8.9), 4.38 (1H, s, H5), 3.88–3.81 (5H, m, OCH_3, C6-OCH_2) 3.09–2.19 (9H, m, $H7_b$, H9, $H10_a$, $H10_b$, $H16_a$, $H16_b$, NCH_3), 1.98 (3H, s, C20-CH_3), 1.88–1.51 (4H, m, $H8_a$, $H8_b$, $H15_a$, $H15_b$), 1.21 (3H, t, C6-O–CH_2–C*H*$_3$, *J* 7.6); δ_C (90.6 MHz $CDCl_3$) 209.54 (C20), 147.29 (C4), 143.45 (C3), 136.81–112.43 (6C, 4 aromatics, C18, C19), 96.11 (C5), 89.56 (C6), 69.99 (C9), 58.39 (C6-O–*C*H$_2$), 56.06 (OCH_3), 53.82 (C7), 49.62 (C14), 47.42 (C16), 46.30 (C13), 44.65 (NCH_3), 34.25 (C15), 31.96 (C20-*C*H$_3$), 28.82 (C8), 23.06 (C10), 16.25 (C6-O–CH_2–*C*H$_3$).

4.2.3. 7α-Acetyl-6-propoxy-6-demethoxy-6,7,8,14-tetrahydro-6β,14β-endoethenothebaine (8c)
Yellow prisms; mp: 123–125 °C; yield: 2323 mg (71%); $[\alpha]_D^{25}$ −172 (*c* 0.1, methanol); ν_{max}(KBr disc) 1720 (CO) cm^{-1}; calcd for $C_{25}H_{31}NO_4$: C, 73.32; H, 7.63; N, 3.42; found: C, 72.98; H, 7.52; N, 3.47; MS *m*/*z* (%) 409 (M^+, 100); δ_H (200 MHz $CDCl_3$) 6.65–6.52 (2H, 2d, H1, H2, J_{8-9} 8.1), 5.92 (1H, d, H18, J_{18-19} 8.7), 5.69 (1H, d, H19, J_{18-19} 8.8), 4.58 (1H, s, H5), 3.80–3.76 (5H, m, OCH_3, C6-OCH_2) 3.19–2.32 (9H, m, $H7_b$, H9, $H10_a$, $H10_b$, $H16_a$, $H16_b$, NCH_3), 2.09 (3H, s, C20-CH_3), 1.88–1.51 (6H, m, $H8_a$, $H8_b$, $H15_a$, $H15_b$, C6-OCH_2–C*H*$_2$), 1.19 (3H, t, C6-O–CH_2–*CH*$_2$, *J* 8.0); δ_C (90.6 MHz $CDCl_3$)

210.14 (C20), 146.31 (C4), 142.93 (C3), 137.28–116.59 (6C, 4 aromatics, C18, C19), 96.01 (C5), 90.06 (C6), 70.11 (C9), 59.49 (C6-O–CH_2), 56.34 (OCH_3), 53.38 (C7), 49.60 (C14), 47.42 (C16), 45.90 (C13), 44.25 (NCH_3), 35.26 (C15), 32.09 (C20-CH_3), 29.31 (C8), 22.98 (C10), 16.25 (C6-O–CH_2–CH_3), 13.02 (C6-OCH_2–CH_2–CH_3).

4.2.4. 7α-Acetyl-6-(cyclopropylmethoxy)-6-demethoxy-6,7,8,14-tetrahydro-6β,14β-endoethenothebaine (8d)

Off-white prisms; mp: 121–123 °C; yield: 1920 mg (57%); $[\alpha]_D^{25}$ −224 (*c* 0.68, methanol); ν_{max}(KBr disc) 1723 (CO) cm^{-1}; calcd for $C_{26}H_{31}NO_4$: C, 73.91; H, 7.39; N, 3.31; found: C, 73.68; H, 7.52; N, 3.19; MS *m*/*z* (%) 421 (M^+, 100); δ_H (200 MHz $CDCl_3$) 6.59–6.50 (2H, 2d, H1, H2, J_{8-9} 8.0), 5.75 (1H, d, H18, J_{18-19} 8.7), 5.59 (1H, d, H19, J_{18-19} 8.8), 4.48 (1H, s, H5), 3.83 (3H, s, OCH_3), 3.43 (2H, d, C6-OCH_2, *J* 10.1) 3.23–2.19 (9H, m, $H7_b$, H9, $H10_a$, $H10_b$, $H16_a$, $H16_b$, NCH_3), 2.01 (3H, s, C20-CH_3), 1.91–1.61 (4H, m, $H8_a$, $H8_b$, $H15_a$, $H15_b$), 0.51–0.11 (5H, m, C6-OCH_2–*CH*–CH_2–CH_2); δ_C (90.6 MHz $CDCl_3$) 208.66 (C20), 147.28 (C4), 142.47 (C3), 133.81–112.23 (6C, 4 aromatics, C18, C19), 96.12 (C5), 89.76 (C6), 78.45 (C6-O–CH_2), 68.11 (C9), 56.34 (OCH_3), 54.17 (C7), 49.79 (C14), 48.11 (C16), 46.45 (C13), 44.25 (NCH_3), 33.26 (C15), 31.30 (C20-CH_3), 28.25 (C8), 22.50 (C10), 13.59 (C6-OCH_2–CH═), 4.29 (2C, C6-OCH_2–*CH*–CH_2–CH_2).

4.2.5. 7α-Acetyl-6-phenyl-6-demethoxy-6,7,8,14-tetrahydro-6β,14β-endoethenothebaine (8e)

Light brown solid; mp: 111–113 °C; yield: 2289 mg (67%); $[\alpha]_D^{25}$ −201 (*c* 0.1, methanol); ν_{max}(KBr disc) 1730 (CO) cm^{-1}; calcd for $C_{28}H_{29}NO_3$: C, 78.66; H, 6.84; N, 3.28; found: C, 78.38; H, 6.91; N, 3.20; MS *m*/*z* (%) 427 (M^+, 100); δ_H (360 MHz $CDCl_3$) 7.37–7.23 (5H, m, C6-Ph), 6.65–6.52 (2H, 2d, H1, H2, J_{8-9} 8.1), 5.92 (1H, d, H18, J_{18-19} 8.6), 5.69 (1H, d, H19, J_{18-19} 8.6), 4.58 (1H, s, H5), 3.80 (3H, s, OCH_3) 3.19–2.32 (9H, m, $H7_b$, H9, $H10_a$, $H10_b$, $H16_a$, $H16_b$, NCH_3), 2.09 (3H, s, C20-CH_3), 1.88–1.51 (4H, m, $H8_a$, $H8_b$, $H15_a$, $H15_b$); δ_C (90.6 MHz $CDCl_3$) 209.54 (C20), 147.71 (C4), 142.51 (C3), 136.65–113.48 (12C, 10 aromatics, C18, C19), 87.01 (C5), 68.91 (C9), 56.25 (OCH_3), 51.16 (C7), 49.38 (C14), 48.42 (C16), 46.30 (C13), 44.55 (NCH_3), 41.06 (C6), 33.62 (C15), 31.31 (C20-CH_3), 30.09 (C8), 22.06 (C10).

4.3. General procedure for Grignard–Barbier reaction

Thevinones **8a–e** (2.5 mmol) in anhyd THF (5 mL) was added slowly to a solution of alkylmagnesium halide prepared from the methyl bromide (282 mg, 3 mmol) and magnesium (73 mg, 3 mmol) in diethyl ether (10 mL). Directly after the addition, TLC showed complete conversion. The excess of Grignard reagent was decomposed with a saturated solution of ammonium chloride (10 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (2 × 15 mL), the combined organic layers were washed with a saturated NaCl solution and dried (Na_2SO_4). Evaporating of the solvent in vacuo yielded the crude product.

4.3.1. 7α-(1-Hydroxy-1-methyl-ethyl)-6,7,8,14-tetrahydro-6β,14β-endoethenothebaine (9a)

Physical and spectral data are in agreement with previously published results.[1,21]

4.3.2. 7α-(1-Hydroxy-1-methyl-ethyl)-6-ethoxy-6-demethoxy-6,7,8,14-tetrahydro-6β,14β-endoethenothebaine (9b)

White prisms; mp: 118–120 °C; yield: 606 mg (59%); $[\alpha]_D^{25}$ −118 (*c* 0.4, methanol); ν_{max}(KBr disc) 3420 (OH); calcd for $C_{25}H_{33}NO_4$: C, 72.96; H, 8.08; N, 3.40; found: C, 72.67; H, 8.31; N, 3.19; MS *m*/*z* (%) 411 (M^+, 100); δ_H (200 MHz $CDCl_3$) 6.41–6.34 (2H, 2d, H1, H2, J_{1-2} 8.1), 5.63 (1H, d, H18, J_{18-19} 8.5), 5.58 (1H, d, H19, J_{18-19} 8.5), 4.36 (1H, s, H5), 3.83–3.72 (5H, m, OCH_3, C6-OCH_2) 3.03–2.26 (8H, m, H9, $H10_a$, $H10_b$, $H16_a$, $H16_b$, NCH_3), 1.91–1.24 [11H, m, $H7_b$, $H8_a$, $H8_b$, $H15_a$, $H15_b$, C20-$(CH_3)_2$], 1.14 (3H, t, C6-O–CH_2–CH_3, *J* 7.3); δ_C (90.6 MHz $CDCl_3$) 147.76 (C4), 142.29 (C3), 135.61–113.45 (6C, 4 aromatics, C18, C19), 101.23 (C5), 89.02 (C6), 75.93 (C20), 69.67 (C9), 58.43 (C6-O–CH_2), 56.56 (OCH_3), 52.42 (C14), 49.10 (C7), 48.11–47.66 (2C, C13, C16), 44.65 (NCH_3), 34.18 (C15), 29.67 (C8), 28.34 [2C, C20-$(CH_3)_2$], 22.45 (C10), 14.70 (C6-O–CH_2–CH_3).

4.3.3. 7α-(1-Hydroxy-1-methyl-ethyl)-6-propoxy-6-demethoxy-6,7,8,14-tetrahydro-6β,14β-endoethenothebaine (9c)

White prisms; mp: 135–137 °C; yield: 776 mg (73%); $[\alpha]_D^{25}$ −187 (*c* 0.5, chloroform); ν_{max}(KBr disc) 3400 (OH); calcd for $C_{26}H_{35}NO_4$: C, 73.38; H, 8.29; N, 3.29; found: C, 73.14; H, 8.23; N, 3.45; MS *m*/*z* (%) 425 (M^+, 100); δ_H (200 MHz $CDCl_3$) 6.49–6.41 (2H, 2d, H1, H2, J_{1-2} 8.0), 5.61 (1H, d, H18, J_{18-19} 8.4), 5.48 (1H, d, H19, J_{18-19} 8.5), 4.66 (1H, s, H5), 3.85–3.78 (5H, m, OCH_3, C6-OCH_2) 3.23–2.22 (8H, m, H9, $H10_a$, $H10_b$, $H16_a$, $H16_b$, NCH_3), 1.99–1.29 [13H, m, $H7_b$, $H8_a$, $H8_b$, $H15_a$, $H15_b$, C6-OCH_2CH–CH_2, C20-$(CH_3)_2$], 1.14 (3H, t, C6-O–CH_2CH–CH_3, *J* 8.3); δ_C (90.6 MHz $CDCl_3$) 147.26 (C4), 142.92 (C3), 136.15–115.48 (6C, 4 aromatics, C18, C19), 101.59 (C5), 89.51 (C6), 74.36 (C20), 71.43 (C6-O–CH_2), 69.51 (C9), 56.13 (OCH_3), 52.11 (C14), 49.39 (C7), 48.10–47.63 (2C, C13, C16), 44.22 (NCH_3), 33.68 (C15), 29.40 (C8), 28.31 [2C, C20-$(CH_3)_2$], 22.53 (C10), 21.25 (C6-O–CH_2CH–CH_3), 10.98 (C6-OCH_2–CH_2–CH_3).

4.3.4. 7α-(1-Hydroxy-1-methyl-ethyl)-6-(cyclopropylmethoxy)-6-demethoxy-6,7,8,14-tetrahydro-6β,14β-endoethenothebaine (9d)

Off-white needles; mp: 151–152 °C; yield: 821 mg (75%); $[\alpha]_D^{25}$ −204 (*c* 0.6, chloroform); ν_{max}(KBr disc) 3400 (OH); calcd for $C_{27}H_{35}NO_4$: C, 73.93; H, 8.04; N, 3.19; found: C, 73.69; H, 8.23; N, 3.09; MS *m*/*z* (%) 438 (M^+, 100); δ_H (200 MHz $CDCl_3$) 6.57–6.52 (2H, 2d, H1, H2, J_{1-2} 8.3), 5.74 (1H, d, H18, J_{18-19} 8.9), 5.56 (1H, d, H19, J_{18-19} 9.0), 4.59 (1H, s, H5), 3.83 (3H, s, OCH_3), 3.43 (2H, d, C6-OCH_2, *J* 10.7), 3.31–2.18 (9H, m, $H7_b$, H9, $H10_a$, $H10_b$, $H16_a$, $H16_b$, NCH_3), 2.02–1.41 [10H, m, $H8_a$, $H8_b$, $H15_a$, $H15_b$, C20-$(CH_3)_2$], 0.51–0.11 (5H, m, C6-OCH_2–*CH*–CH_2–CH_2); δ_C (90.6 MHz $CDCl_3$) 148.01 (C4), 143.16 (C3), 135.55-113.25 (6C, 4 aromatics, C18, C19), 101.59 (C5), 89.76 (C6), 78.45 (C6-O–CH_2), 74.67 (C20), 68.11 (C9), 56.34 (OCH_3), 52.79 (C14), 49.67 (C7), 48.11 (C16), 46.45 (C13), 44.25 (NCH_3), 33.26 (C15), 29.25 (C8), 28.30 [(2C, C20-$(CH_3)_2$], 22.56 (C10), 11.72 (C6-OCH_2–CH═), 3.19 (2C, C6-OCH_2–*CH*–CH_2–CH_2).

4.3.5. 7α-(1-Hydroxy-1-methyl-ethyl)-6-phenyl-6-demethoxy-6,7,8,14-tetrahydro-6β,14β-endoethenothebaine (9e)

White prisms; mp: 114–116 °C; yield: 753 mg (68%); $[\alpha]_D^{25}$ −167 (*c* 0.4, chloroform); ν_{max}(KBr disc) 3440 (OH); calcd for $C_{29}H_{33}NO_3$: C, 78.52; H, 7.50; N, 3.16; found: C, 78.34; H, 7.67; N, 3.01; MS *m*/*z* (%) 443 (M^+, 100); δ_H (360 MHz $CDCl_3$) 7.37–7.23 (5H, m, C6-Ph), 6.65–6.54 (2H, 2d, H1, H2, J_{1-2} 8.2), 5.97 (1H, d, H18, J_{18-19} 8.8), 5.61 (1H, d, H19, J_{18-19} 8.7), 4.59 (1H, s, H5), 3.81 (3H, s, OCH_3) 3.11–2.20 (8H, m, H9, $H10_a$, $H10_b$, $H16_a$, $H16_b$, NCH_3), 2.04–1.20 [11H, m, $H7_b$, $H8_a$, $H8_b$, $H15_a$, $H15_b$, C20-$(CH_3)_2$]; δ_C (90.6 MHz $CDCl_3$) 147.21 (C4), 142.33 (C3), 136.09–113.39 (12C, 10 aromatics, C18, C19), 88.25 (C5), 70.84 (C20), 69.51 (C9), 56.44 (OCH_3), 52.11 (C14), 49.89 (C7), 48.65–48.21 (2C, C13, C16), 44.65 (NCH_3), 39.51 (C6), 33.60 (C15), 28.31 [2C, C20-$(CH_3)_2$], 22.89–22.23 (2C, C8, C10).

4.4. General procedure for the 3-O-demethylation of thevinols 9a–e

The methyl ethers **9a–e** (1 mmol) and potassium hydroxide (350 mg, 6.2 mmol) were dissolved in a mixture of glycol (3 mL)

and water (0.6 mL) and refluxed for 8 h. After cooling to room temperature, the reaction mixture was diluted with water (10 mL) and adjusted to pH 8 with concentrated hydrochloric acid, ammonia, and acetic acid. This solution was extracted with chloroform (1×15 mL, 3×5 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo to dryness, giving the crude 3-O-demethylated adducts **10a–e**.

4.4.1. 7α-(1-Hydroxy-1-methyl-ethyl)-6,7,8,14-tetrahydro-6β,14β-endoethenooripavine (10a)

Physical and spectral data are in agreement with previously published results.[2,19]

4.4.2. 7α-(1-Hydroxy-1-methyl-ethyl)-6-ethoxy-6-demethoxy-6,7,8,14-tetrahydro-6β,14β-endoethenooripavine (10b)

White needles; mp: 257–260 °C; yield: 230 mg (57%); $[\alpha]_D^{25}$ −192 (*c* 0.26, methanol); ν_{max}(KBr disc) 3430 (OH), 3370 (OH); calcd for $C_{24}H_{31}NO_4$: C, 72.52; H, 7.86; N, 3.52; found: C, 72.19; H, 7.91; N, 3.34; MS *m*/*z* (%) 397 (M^+, 100); δ_H (200 MHz DMSO-d_6) 9.24 (1H, br s, C3-OH), 6.31–6.28 (2H, 2d, H1, H2, J_{1-2} 8.4), 5.58 (1H, d, H18, J_{18-19} 8.9), 5.51 (1H, d, H19, J_{18-19} 8.9), 4.87 (1H, br s, C20-OH), 4.36 (1H, s, H5), 3.88 (2H, q, C6-OCH_2, *J* 7.6), 3.04–2.19 (8H, m, H9, $H10_a$, $H10_b$, $H16_a$, $H16_b$, NCH_3), 1.85-1.27 [11H, m, $H7_b$, $H8_a$, $H8_b$, $H15_a$, $H15_b$, C20-$(CH_3)_2$], 1.14 (3H, t, C6-O–CH_2–CH_3, *J* 7.6); δ_C (90.6 MHz DMSO-d_6) 145.18 (C4), 138.98 (C3), 135.08-115.92 (6C, 4 aromatics, C18, C19), 101.49 (C5), 89.39 (C6), 74.18 (C20), 69.33 (C9), 57.41 (C6-O–CH_2), 52.19 (C14), 49.89 (C7), 48.01–47.86 (2C, C13, C16), 44.10 (NCH_3), 33.68 (C15), 29.99 (C8), 28.30 [2C, C20-$(CH_3)_2$], 22.53 (C10), 16.74 (C6-O–CH_2–CH_3).

4.4.3. 7α-(1-Hydroxy-1-methyl-ethyl)-6-propoxy-6-demethoxy-6,7,8,14-tetrahydro-6β,14β-endoethenooripavine (10c)

White needles; mp: 273–275 °C; yield: 267 mg (65%); $[\alpha]_D^{25}$ −218 (*c* 0.43, methanol); ν_{max}(KBr disc) 3430 (OH), 3370 (OH); calcd for $C_{25}H_{33}NO_4$: C, 72.96; H, 8.08; N, 3.40; found: C, 72.67; H, 8.31; N, 3.19; MS *m*/*z* (%) 411 (M^+, 100); δ_H (200 MHz DMSO-d_6) 9.12 (1H, br s, C3-OH), 6.41–6.34 (2H, 2d, H1, H2, J_{1-2} 8.1), 5.63 (1H, d, H18, J_{18-19} 8.7), 5.58 (1H, d, H19, J_{18-19} 8.7), 4.87 (1H, br s, C20-OH), 4.36 (1H, s, H5), 3.72 (2H, q, C6-OCH_2, *J* 7.5) 3.03-2.26 (8H, m, H9, $H10_a$, $H10_b$, $H16_a$, $H16_b$, NCH_3), 1.91-1.24 [13H, m, $H7_b$, $H8_a$, $H8_b$, $H15_a$, $H15_b$, C6-OCH_2–CH_2–CH_3, C20-$(CH_3)_2$], 1.14 (3H, t, C6-O–CH_2–CH_2–CH_3, *J* 7.7); δ_C (90.6 MHz DMSO-d_6) 145.28 (C4), 138.67 (C3), 134.21–114.47 (6C, 4 aromatics, C18, C19), 100.65 (C5), 89.82 (C6), 74.15 (C20), 70.23 (C6-O–CH_2), 69.51 (C9), 51.82 (C14), 49.43 (C7), 48.04–47.76 (2C, C13, C16), 44.12 (NCH_3), 33.68 (C15), 29.47 (C8), 28.89 [2C, C20-$(CH_3)_2$], 23.65 (C6-O–CH_2–CH_3), 22.75 (C10), 11.08 (C6-OCH_2–CH_2–CH_3).

4.4.4. 7α-(1-Hydroxy-1-methyl-ethyl)-6-(cyclopropylmethoxy)-6-demethoxy-6,7,8,14-tetrahydro-6β,14β-endoetheno-oripavine (10d)

Off-white needles; mp: 151–152 °C; yield: 258 mg (61%); $[\alpha]_D^{25}$ −187 (*c* 0.6, methanol); ν_{max}(KBr disc) 3430 (OH), 3370 (OH); calcd for $C_{26}H_{33}NO_4$: C, 73.54; H, 7.92; N, 3.23; found: C, 73.31; H, 7.94; N, 2.99; MS *m*/*z* (%) 423 (M^+, 100); δ_H (200 MHz DMSO-d_6) 9.02 (1H, br s, C3-OH), 6.68–6.61 (2H, 2d, H1, H2, J_{1-2} 8.0), 5.88 (1H, d, H18, J_{18-19} 8.9), 5.79 (1H, d, H19, J_{18-19} 8.9), 4.97 (1H, br s, C20-OH), 4.51 (1H, s, H5), 3.63 (2H, d, C6-OCH_2, *J* 11.0), 3.26-2.15 (9H, m, $H7_b$, H9, $H10_a$, $H10_b$, $H16_a$, $H16_b$, NCH_3), 1.89–1.40 [10H, m, $H8_a$, $H8_b$, $H15_a$, $H15_b$, C20-$(CH_3)_2$], 0.51–0.07 (5H, m, C6-O–CH_2–CH–CH_2–CH_2); δ_C (90.6 MHz DMSO-d_6) 145.07 (C4), 139.66 (C3), 134.83–112.12 (6C, 4 aromatics, C18, C19), 100.98 (C5), 89.16 (C6), 79.23 (C6-O–CH_2), 74.34 (C20), 69.51 (C9), 52.39 (C14), 49.31 (C7), 48.51 (C16), 47.59 (C13), 44.66 (NCH_3), 33.29 (C15), 29.11 (C8), 28.70 [(2C, C20-$(CH_3)_2$], 21.83 (C10), 12.22 (C6-OCH_2–CH═), 2.67 (2C, C6-OCH_2–CH–CH_2–CH_2).

4.4.5. 7α-(1-Hydroxy-1-methyl-ethyl)-6-phenyl-6-demethoxy-6,7,8,14-tetrahydro-6β,14β-endoethenooripavine (10e)

Off-white needles; mp: 248–252 °C; yield: 244 mg (57%); $[\alpha]_D^{25}$ −161 (*c* 0.4, methanol); ν_{max}(KBr disc) 3428 (OH), 3390 (OH); calcd for $C_{28}H_{31}NO_3$: C, 78.29; H, 7.27; N, 3.26; found: C, 78.34; H, 7.47; N, 3.01; MS *m*/*z* (%) 429 (M^+, 100); δ_H (360 MHz DMSO-d_6) 9.12 (1H, br s, C3-OH), 7.31–7.21 (5H, m, C6-Ph), 6.71–6.67 (2H, 2d, H1, H2, J_{1-2} 8.0), 5.87 (1H, d, H18, J_{18-19} 9.1), 5.77 (1H, d, H19, J_{18-19} 9.1), 4.87 (1H, br s, C20-OH), 4.48 (1H, s, H5), 3.20–2.13 (8H, m, H9, $H10_a$, $H10_b$, $H16_a$, $H16_b$, NCH_3), 2.09–1.21 [11H, m, $H7_b$, $H8_a$, $H8_b$, $H15_a$, $H15_b$, C20-$(CH_3)_2$]; δ_C (90.6 MHz DMSO-d_6) 145.78 (C4), 139.29 (C3), 133.11–113.82 (12C, 10 aromatics, C18, C19), 88.43 (C5), 70.84 (C20), 69.31 (C9), 52.51 (C14), 48.92–48.21 (3C, C7, C13, C16), 44.10 (NCH_3), 38.70 (C6), 33.65 (C15), 28.20 [2C, C20-$(CH_3)_2$], 23.12-22.93 (2C, C8, C10).

4.5. Computational procedure

We have carried out the geometry optimization at Becke's three parameter hybrid (B3LYP)[20] levels in the DFT with the basis set 6-31G(d,p) using GAUSSIAN 03.[21] The solvent effect was not considered. The model for a deoxygenated etorphine analogue[22] and for (−)-7α-acetyl-4,5α-epoxy-3-methoxy-*N*-methyl-6,14-ethenoisomorphinan,[23] two structurally analogous 6,14-bridged morphinans were obtained at the B3LYP/6-31G(d,p) level and compared to X-ray data in order to test the performance of this DFT method in the case of this group of morphinans.

4.6. Pharmacology

4.6.1. Radioligand binding assay

The opioid receptor binding assays were performed using rat brain membrane preparations, as reported in detail elsewhere.[24] Binding affinities for the μ- and δ-opioid receptors were determined by displacing [^{3}H]DAMGO and [^{3}H][Ile^{5,6}]deltorphin-2, respectively.

Briefly, crude membrane preparations, isolated from Wistar rat brains, were incubated at 25 °C for 120 min. with appropriate concentration of a tested peptide in the presence of 0.5 nM radioligand in a total volume of 0.5 mL of Tris–HCl (50 mM, pH 7.4), containing $MgCl_2$ (5 mM), EDTA (1 mM), NaCl (100 mM), and bacitracin (20 mg/l). Non-specific binding was determined in the presence of naloxone (1 μM). Incubations were terminated by rapid filtration through Whatman GF/B (Brentford, UK) glass fiber strips, which had been pre-soaked for 2 h in 0.5% polyethylamine, using Millipore Sampling Manifold (Billerica, USA). The filters were washed three times with 4 mL of ice-cold Tris buffer solution. The bound radioactivity was measured in Packard Tri-Carb 2100 TR liquid scintillation counter (Ramsey, MN, USA) after overnight extraction of the filters in 4 mL of Perkin–Elmer Ultima Gold scintillation fluid (Wellesley, MA, USA). Three independent experiments for each assay were carried out in duplicate.

4.7. Animals

Male Swiss albino mice (CD1, Charles River, Canada), weighing 20–26 g, were used throughout the studies. The animals were housed at a constant temperature (22 °C) and maintained under

a 12 h light/dark cycle in sawdust coated plastic cages with access to standard laboratory chow and tap water ad libitum.

Animal use for these studies was approved by the University of Calgary Animal Care Committee and the experiments were performed in accordance with institutional animal ethics committee guidelines that follow the guidelines established by the Canadian Council of Animal Care.

4.8. Isolated smooth muscle strips

Mice were killed by cervical dislocation. Segments of the distal ileum were removed and submerged in ice-cold oxygenated Krebs-Ringer Solution (mmol/L: NaCl 119, KCl 4.7, KH_2PO_4 1.2, $NaHCO_3$ 25, $MgSO_4$ 1.5, $CaCl_2$ 2.5, and glucose 11). Luminal contents were gently flushed. Up to four segments of full-thickness strips, 1.5 cm each, were used from each animal. All experiments lasted less than 3 h and each preparation was used for a single experiment only.

The preparations were mounted between two platinum electrodes, which were 1 cm apart and placed in eight separate organ baths (25 mL; 37 °C; oxygenated with 95% O_2/5% CO_2). Using a silk thread one end of the preparations was attached to the bottom of the organ bath, while the other end was connected to a FT03 force displacement transducer (Grass Technologies, West Warwick, RI, USA). Tension (0.5 g) was applied and the preparations were allowed to equilibrate for 30 min. Changes in tension were amplified by a P11T Compact Transducer Amplifier (Grass Technologies, West Warwick, RI, USA) and recorded on personal computer using the PolyView software (Polybytes Inc., Chedar Rapids, Iowa, USA).

Continuous electrical field stimulation (EFS; 4 Hz, 24 V, stimulus duration 0.5 ms, train duration 10 s) was applied by a S88X Dual Output Square Pulse Stimulator (Grass Technologies, West Warwick, RI, USA).

Compounds (10^{-12}–10^{-6} M) were added cumulatively into the organ baths and effects on the EFS induced contractions were recorded. Each concentration was allowed to incubate for 10 min.

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References and notes

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