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Chemistry of Opium Alkaloids. Part 44: Synthesis and Opioid Receptor Binding Profile of Substituted Ethenoisomorphinans and Ethenomorphinans*

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Abstract—7- And 8-substituted 6α,14α-ethenoisomorphinans were synthesized by reaction of properly substituted morphinan-6,8-dienes (analogues of thebaine) with methyl vinyl ketone or ethyl acrylate. Reaction with the appropriate Grignard reagent gave the 7- and 8-dialkylmethanols, respectively. Cleavage of the 3-methyl ether with KOH/glycol or boron tribromide afforded the 3-hydroxyl derivatives. In general, the compounds with the ethoxycarbonyl or dimethylmethanol substituent at the 8α-position showed lower affinity for the μ, κ, and δ opioid receptor subtypes than the corresponding 7α- and 7β-substituted compounds. Introduction of a chloro substituent in position 18 increased the potency significantly. The 7-substituent could be connected to the 18-position without loss of affinity. 5β-alkyl substitution of 6α,14α-ethenoisomorphinans led to a decrease in affinity for the three opioid receptor subtypes. In the 5β-methyl series the affinity for the μ and δ receptors increased from 7α-dimethylmethanol to 7α-methylhexylmethanol. In the 5β-alkyl series, the affinity for the μ-receptor could be increased by connecting the 5- and 7-substituents, yielding a compound with high μ-selectivity. The new 6β,14β-ethenomorphinans did not show affinity for any of the opioid receptors, in accordance with the inactivity earlier found in in vivo experiments.

Introduction

Pharmacological studies of morphinans are mostly restricted to a relatively small number of well-established compounds. Typical examples are morphine, codeine, dextromethorphan, and 6α,14α-ethenoisomorphinans¶ such as etorphine and buprenorphine.[1–3] The latter compounds are characterized by a 6α,14α-etheno bridge and a lipophilic substituent in position 7α of the C-ring. One reason for the structural limitation in this class of opioids is the direct availability of 7α-substituted 6α,14α-ethenoisomorphinans as the main product of the Diels–Alder reaction of thebaine with methyl vinyl ketone (but-3-en-2-one) or acrylates (propenoates). In contrast, the 7β- and 8-substituted 6α,14α-ethenoisomorphinans and the 6β,14β-ethenomorphinans[1] (Fig. 1) are usually minor products from the Diels–Alder reaction of thebaine and other morphinan-6,8-dienes if formed at all.[4–6]

Etorphine (**4**) and dihydroetorphine (**5**), two extremely potent analgesics (Fig. 2), were developed in the sixties and have found application in veterinary practice.[5] They appear to have a pharmacological profile[7,8] which is very different from that of e.g. morphine.

Since the beginning of the eighties, dihydroetorphine is in clinical practice in China.[9,10] Its use in detoxification has been studied in China,[10] and it has been recommended to the National Institute of Drug Abuse (NIDA) as a potential replacement of methadone for the treatment of opiate addicts.[11] Furthermore, the liability for abuse and physical dependence of etorphine and dihydroetorphine might be lower than originally anticipated.[12–16] It is known that **4** and **5** are aselective opioid ligands which bind to the opioid receptor subtypes μ, κ, and δ‖ with comparable affinity.[7] Introducing substituents in the morphinan skeleton may alter the binding profile and lead to more selective compounds as, for example, has been shown by Schmidhammer for 14-oxygenated morphinans.[17] Recent studies suggest that compounds with both high affinity and selectivity for μ receptors might be of clinical importance.[18] Furthermore, it has been

Key words: Alkaloids; analgesics; NMR; receptors; thebaine analogues; morphinan-6,8-dienes; Diels–Alder reactions.

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¶For an explanation on the use of the designations 6α,14α-ethenoisomorphinan and 6β,14β-ethenomorphinan, see Ref. 28, footnote 1.

‖Recently, Dhawan et al.[16] advocated the use of the designations OP_1, OP_2 and OP_3 for the δ, κ and μ receptor subtypes, respectively.

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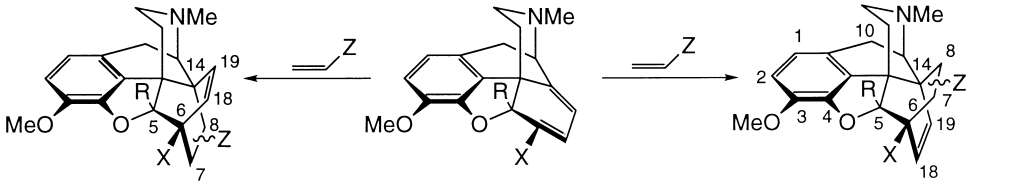


1 R = H, X = OMe, thebaine
2 R = X = H, 6-demethoxythebaine
3 R = Me, X = OMe, 5β-methylthebaine

Figure 1.

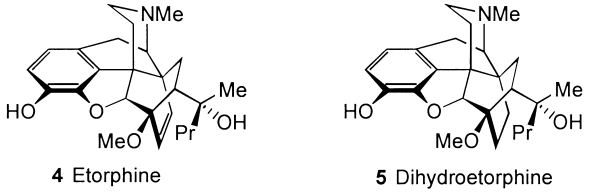


Figure 2.

shown that the presence of a functional μ-receptor is essential for the analgesic effect of morphine.[19]

Not until recently has there been renewed interest for the synthesis and pharmacology of differently substituted ethenoisomorphinans.[20–24] Several years ago, Rapoport and co-workers[25,26] and our group[27–34] showed that new ethenoisomorphinans and ethenomorphinans can be obtained by changing the substitution pattern on the morphinan-6,8-diene starting material. The 6-methoxy group in thebaine determines the regioselectivity of the Diels–Alder reaction. Replacing the 6-OMe by Me or H led to a change of regioselectivity affording also the 8-substituted morphinans in low but significant yield. Similarly, introduction of substituents in positions 5 and 7 of the morphinan-6,8-diene influenced both the regio and stereoselectivity.[31–33] Disconnecting the 4,5α-epoxy bridge resulted in a complete reversal of the course of the Diels–Alder reaction giving exclusively the 6β,14β-ethenomorphinans.[28,35]

In this paper we disclose the opioid receptor binding profiles of several substituted 6α,14α-ethenoisomorphinans and 6β,14β-ethenomorphinans, obtained from the Diels–Alder adducts of substituted morphinandienes which have been prepared in our laboratory. To our knowledge, there are no reports in which the binding affinities for the opioid receptor subtypes have been studied for a large number of structurally related etheno-bridged morphinans.

Chemistry

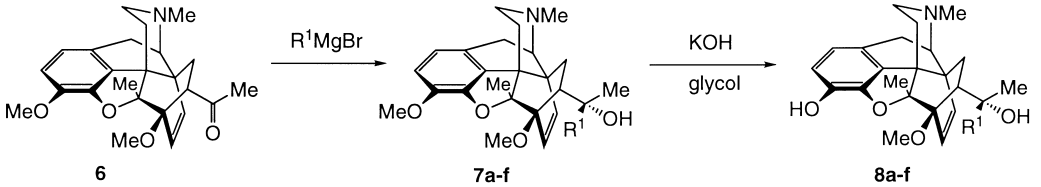
Reaction of 5β-methylthebaine (**3**)[36] with methyl vinyl ketone gave the 7α-acetyl ethenoisomorphinan **6**.[31] Reaction with an excess of Grignard reagent, followed by *O*-demethylation with KOH in glycol gave the phenolic carbinols **8a–f**. The stereochemistry of the carbinols was assigned as R in analogy with earlier published analogues[4,5] (Scheme 1).

In order to remove the oxygen atoms in the 7-substituent, the 7α- and 7β-ethoxycarbonyl derivatives **9**, **10a–b** were reduced with $LiAlH_4$ to give **11** and **13a–b**, respectively.

Treatment of **11** with KOH in glycol gave phenol **12**. Mesylation of the 7α-hydroxymethyl group in **13a–b**, followed by $LiAlH_4$ reduction of the mesylate gave the 7α-methyl derivatives **14a–b**, which were 3-*O*-demethylated with KOH/glycol to give **15a–b** (Scheme 2).

In order to prepare the 7α-ethyl analogue, the Diels–Alder adduct **16**[37] was treated with MeMgBr to give the secondary alcohol, which was converted into the mesylate. However, upon treatment with $LiAlH_4$, the 7-ethylidene **18** was obtained instead of the desired 7α-ethyl derivative (Scheme 3).

The configuration of the methyl group on the 7-ethylidene substituent was established by NOE experiments. A cross peak was observed between the 6-OMe group and the vinylic proton of the vinylidene group, which proves the E configuration of the methyl group. Also the absence of any NOE between the H-8 protons and



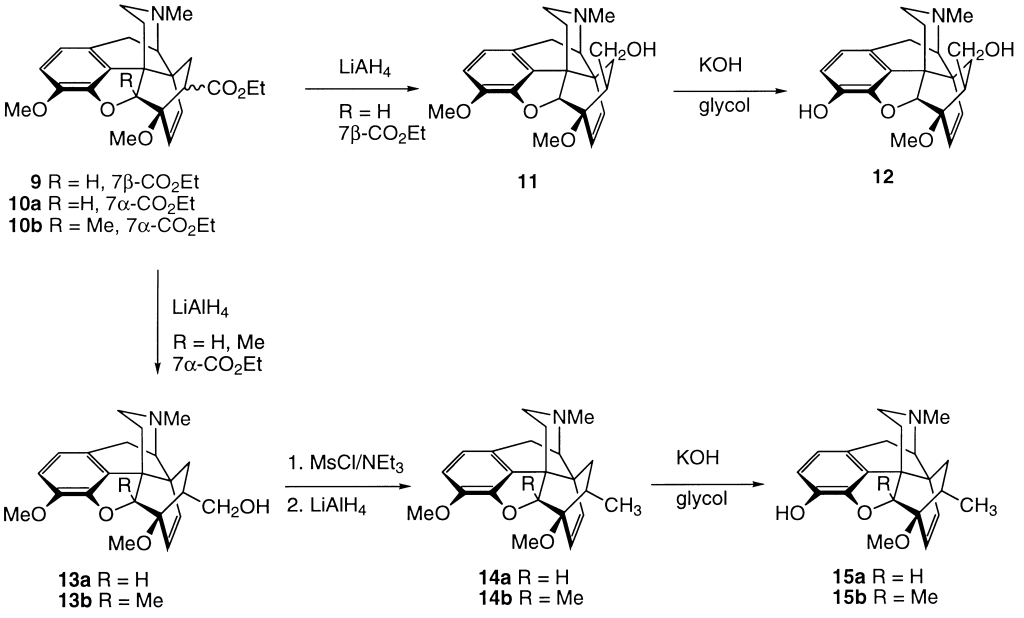
a $R^1 = CH_3$ d $R^1 = C_4H_9$
b $R^1 = C_2H_5$ e $R^1 = C_5H_{11}$
c $R^1 = C_3H_7$ f $R^1 = C_6H_{13}$

Scheme 1.

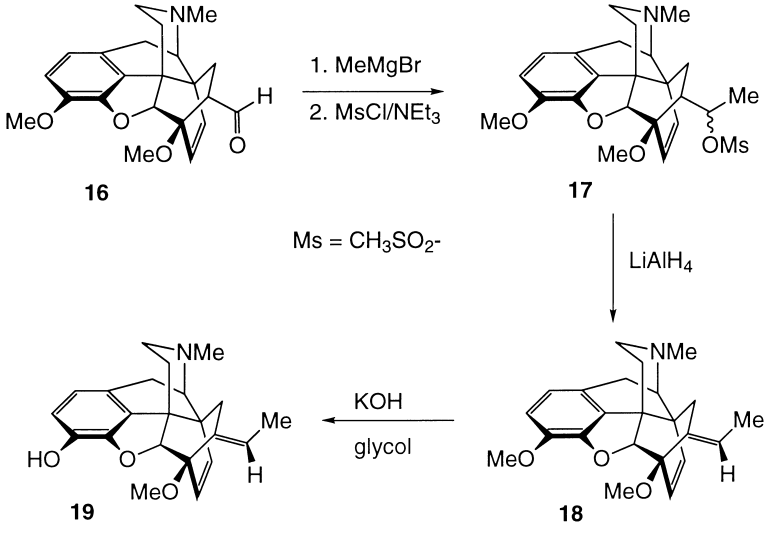
the vinylic proton of the vinylidene group confirms the E configuration.

Reaction of thebaine with methyl methacrylate (methyl 2-methylpropenoate)[38] gave the 7β-methyl-7α-ethoxycarbonyl compound **20**, which was converted into the dimethylmethanol **21** with methylmagnesium bromide. Treatment with KOH/glycol resulted in the desired 3-*O*-demethylation, but also in the addition of the 7α-hydroxyl onto the etheno bridge, affording **22** (Scheme 4).

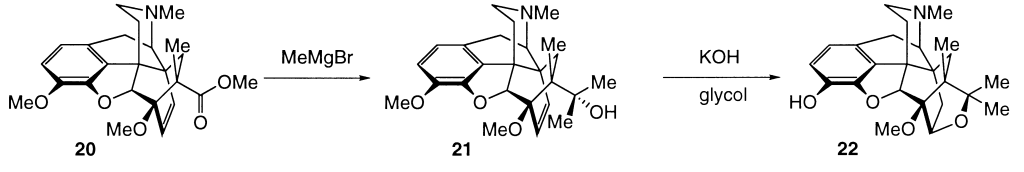
The 7- and 8-ethoxycarbonyl derivatives **23** and **24** (Fig. 3) were prepared according to known procedures by reaction of thebaine and analogues with ethyl acrylate,[27,33,39] followed by *O*-demethylation with BBr_3 or HBr/AcOH and re-esterification with ethanolic HCl.[39] The ester functions were converted into the corresponding dimethylmethanol group using an excess of methylmagnesium bromide. Subsequent 3-*O*-demethylation gave **25** and **26**. The 5,7-bridged ethenoisomorphinans **27a–d** were synthesized according to



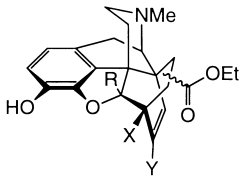
Scheme 2.



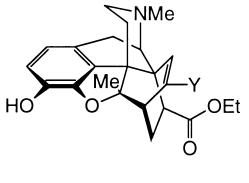
Scheme 3.



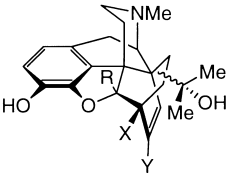
Scheme 4.



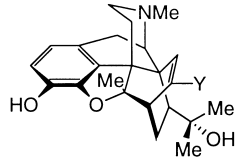
23a R =H, X = Y = H, 7α-CO_2Et
23b R =H, X = OH, Y = H, 7α-CO_2Et
23c R =H, X = OH, Y = H, 7β-CO_2Et
23d R =Me, X = OH, Y = H, 7α-CO_2Et
23e R =H, X = H, Y = Cl, 7α-CO_2Et
23f R =H, X = H, Y = Cl, 8α-CO_2Et



24 Y = Cl



25a R =H, X = Y = H, 7α-CMe_2OH
25b R =H, X = OMe, Y = H, 7α-CMe_2OH
25c R =H, X = H, Y = Cl, 7α-CMe_2OH
25d R =H, X = H, Y = Cl, 8α-CMe_2OH



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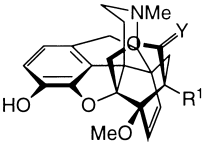
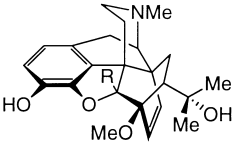


27a R^1 = H, Y = O
27b R^1 = Me, Y = O
27c R^1 = H, Y = H_2
27d R^1 = Me, Y = H_2



28a R = ethyl
28b R = hydroxymethyl
28c R = methyl, 10α-ethyl

Figure 3.

Woudenberg et al.[34] 5-Substituted adducts **28** were prepared according to Ref. 32.

Results and Discussion

Upon introduction of a 5β-methyl group, the in vivo activity of some reference compounds decreases (Table 1). The antinociceptive activity of 5β-methylmorphine is 5–10 times lower than that of morphine and comparable to that of codeine. 5β-Methyletorphine is only 60–80 times stronger than morphine, and 5β-methylbuprenorphine is inactive in the agonist preparations, in contrast to the unsubstituted 5β-H compound.

Table 1. In vivo antinociceptive activity (mg/kg) of some morphinans and their 5-methyl analogues

	Hot plate	Nilsen	Ref.
Morphine	0.98	1.3	36
5-Me-morphine	5.3	11.5	36
Codeine	6.8	7.4	36
5-Me-codeine	14.6	–	36
Etorphine	0.001	–	15b
5-Me-etorphine	0.015	0.016	40a
Buprenorphine	0.035	0.04	40b
5-Me-buprenorphine	Inactive	Inactive	40c

When the binding data for etorphine are compared to those of 5β-methyletorphine (**8c**, Table 2), some characteristic effects of the substitution in the 5β-position can be noted. The affinity for μ hardly changes but a significant decrease in affinity is observed for the δ and κ receptor subtypes. This suggests that some degree of receptor selectivity can be attained by introducing a 5β-methyl group.

In the dimethylmethanol series, increasing the size of the alkyl substituent in position 5 lowers the affinity for all receptor subtypes (Table 3). However, in the 5β-CH_2OH derivative **28b** the μ-affinity is almost restored, in contrast to the κ-affinity. This results in a more selective compound. Higher selectivity for μ is also obtained by ethyl substitution in position 10α (**28c**), which does not affect the affinity for μ or δ, but lowers the affinity for κ. A similar substitution at the 16-position in some etorphine analogues yielded compounds with strongly reduced analgesic potency.[6,41]

We found that in a series of 5β-methyl substituted ethenoisomorphinans with different (*R*)-alkylmethylmethanol substituents in position 7 (**8a**–**f**), the κ and δ affinities increase from methyl to pentyl, whereas the μ affinity is almost constant (Table 4). A similar correlation was found in the original 5-H series by Bentley, in

Table 2. In vitro binding data (nM) for some morphinans

	μ	κ_1	κ_2	κ_3	δ
Morphine	2.5	33.9	6834.0	13.9	58.0
Codeine	121.2	> 10,000	> 10,000	> 10,000	> 10,000
Etorphine	2.0	0.8	99.3	4.0	0.4
5-Me-etorphine (**8c**)	1.1	45.5	2670	12.7	7.9

which the analgesic potency (which is mainly determined by the μ-affinity)[19] increased from methyl to butyl or pentyl.[4–6] It is noteworthy that simple 5-unsubstituted ethenoisomorphinans with a 7α-methyl (**15a**,**b**) or 7-ethylidene group (**19**) also have quite high affinity for μ and κ, but less for δ. Earlier experiments by Bentley showed that even the 7-unsubstituted ethenoisomorphinan was still 40 times more active than morphine.[6]

Introduction of a chlorine atom on the etheno bridge has a profound effect on the binding affinity (Table 5), both in the ethyl ester (**23e**,**f**) and the dimethylmethanol series (**25c**,**d**). Indeed, **25c** has the highest affinity for the μ-receptor of all compounds that were studied in this series.

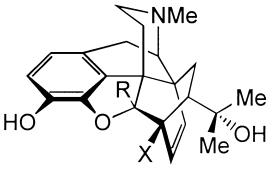
When in the dimethylmethanol series, the 5-substituent is conformationally restricted in a ring, as in **27a**–**d**, a surprisingly high affinity is observed for especially the μ-subtype (Table 6). Apparently, the substituent effects for the μ-receptor are additive. The affinity for δ increased with the introduction of a 7α-methyl group (**27b**,**d**). Connecting the 7α-dimethylmethanol group to the etheno bridge afforded compound **22**, which hardly changed the binding characteristics, as compared to the unrestricted compound **25b**. Connecting the 7β-hydroxymethyl to the 5β-methyl group (**27c**) lowered the μ affinity relative to **12**, but increased the μ/κ selectivity.

Earlier studies by Maurer and Rapoport[42] revealed that compounds in which the *N*-methyl was connected to the 8-position showed rather low activity. In contrast, restricting the 7α chain to the 6 position gave compounds with high analgesic activity.[43]

There are no significant differences between the binding affinities of the dimethyl methanols and the ethyl esters (Table 5). However, the latter compounds are probably hydrolyzed in vivo, making them less interesting for further in vivo profiling. Placing the substituent in position 8 (**23f**, **25d**) lowers the affinity for all subtypes, which is in agreement with the lower analgesic activity for 8-substituted etorphine analogues as reported by Rapoport et al.[25,26] Substituents in the 7β-position (**12**, **23c**) are very well tolerated and even increase binding affinity in some cases. This trend conforms to the results of in vivo studies by Bentley et al.[6]

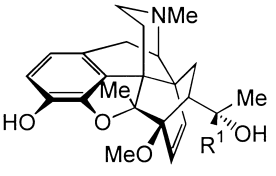
6β,14β-Ethenomorphinans (**24**, **26**) which have the etheno bridge at the opposite face of the C-ring compared to etorphine are devoid of binding affinity for any of the opioid receptor subtypes, in accordance with the inactivity of some analogues of these compounds in in vivo assays.[29] This inactivity is surprising in view of the fact that substitution of the etheno bridge in ethenoisomorphinans is allowed (see e.g. **23c** and **25**). Apparently,

Table 3. Binding affinities for 5β-substituted 6α,14α-ethenoisomorphinans



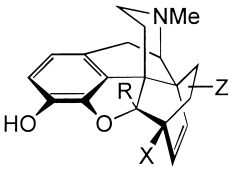
	X	R	Other	μ	κ_1	κ_2	κ_3	δ
25a	H	H		0.4	9.4	217	2.3	46.6
25b	OMe	H		0.6	2.4	169	0.9	18.8
8a	OMe	Me		6.6	560.2	> 10,000	36.7	98.7
28a	OMe	Et		419	1302.8	> 10,000	166.5	230.1
28b	OMe	CH_2OH		15.7	404.1	> 10,000	270	65.6
28c	OMe	Me	10α-ethyl	5.7	2293	> 10,000	24.7	63.7

Table 4. Binding affinities for 7α-substituted 5β-methyl-6α,14α-ethenoisomorphinans



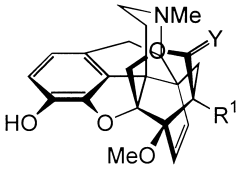
	R^1	μ	κ_1	κ_2	κ_3	δ
8a	Me	6.6	560.2	> 10,000	36.7	98.7
8b	Et	3.5	464.6	> 10,000	122.7	41.5
8c	Pr	1.1	45.5	2670	12.7	7.9
8d	Bu	0.6	6.1	384.5	3.6	3.4
8e	Pen	0.9	5.8	345	2.6	1.9
8f	Hex	2.6	11.5	400.5	7.6	8.7

Table 5. Binding affinities for various 7- and 8-substituted 6α,14α-ethenoisomorphinans and 6β,14β-ethenomorphinans

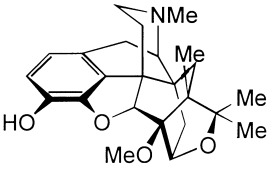


	R	X	Z	Other	μ	κ_1	κ_2	κ_3	δ
23a	H	H	7α-CO_2Et		0.2	3.1	674	10.1	10.1
23b	H	OH	7α-CO_2Et		0.5	7.5	791.5	2.3	19.7
23c	H	OH	7β-CO_2Et		0.3	1.7	578.3	1.2	23
23d	Me	OH	7α-CO_2Et		6.1	2093	> 10,000	53.6	290.7
23e	H	H	7α-CO_2Et	18-Cl	0.3	4	1792	3.2	1
23f	H	H	8α-CO_2Et	18-Cl	5.5	225.9	> 10,000	143.6	118.6
24	Me	H	8β-CO_2Et	18-Cl; 6β,14β-etheno	3963	> 10,000	> 1000	> 10,000	> 10,000
25a	H	H	7α-CMe_2OH		0.4	9.4	217	2.3	12.6
25b	H	OMe	7α-CMe_2OH		0.6	2.4	169	0.9	4.9
25c	H	H	7α-CMe_2OH	18-Cl	0.1	6.8	1963	1.3	2.3
25d	H	H	8α-CMe_2OH	18-Cl	0.7	54	8557.5	13.7	9.7
26	Me	H	8β-CMe_2OH	18-Cl; 6β,14β-etheno	> 10,000	> 10,000	> 1000	> 10,000	> 10,000
15a	H	OMe	7α-Me		0.3	3.9	1369	1.5	n.d.
19	H	OMe	7 = CHMe		1.1	3	454.4	2.1	18.4
15b	Me	OMe	7α-Me		3.8	49.9	> 10,000	12.5	110
12	H	OMe	7β-CH_2OH		0.5	2.5	1104.5	3.1	5.0

Table 6. Conformationally restricted 6α,14α-ethenoisomorphinans



27a-d



22

	Y	R^1	μ	κ_1	κ_2	κ_3	δ
27a	O	H	42.9	104.1	7900	162.2	34.6
27b	O	Me	11.2	22	2012	35.6	23.8
27c	H_2	H	3.9	177.4	6200	20.1	25.9
27d	H_2	Me	1	175.8	1524.5	10.8	13.4
22			0.4	4.4	460	5.1	3.1

there are very strict limits to size and position of these substituents.

The substituent at the 6-position (H, OMe, OH) has only a limited effect on the binding affinities, compare e.g. **25a**–**b** and **23a**–**b**. Rapoport and co-workers have shown[25,26] that the analgesic potency of etorphine analogues with 6-H and 6-Me is comparable to that of the parent etorphine (6-OMe). Recently, Berenyi et al. reported data on 6-halogen substituted compounds.[44] The 6-fluoro derivative was shown to be the most potent in vivo (mouse hot plate), but was only weakly active in the guinea pig ileum assay.

The 18-chloro compound **25c** which showed the highest affinity for the μ-receptor in the present series was further tested in vivo. Compound **25c** acted as a selective μ-agonist (27 nM) in the mouse vas deferens test. In the mouse hot plate and tail-flick test, it was active at 0.03 mg/kg (ED_{50}), 30–200 times more potent than morphine. In comparison, the 6-H analogue **25a** and 6-OMe analogue **25b** have been reported to be only 7 and 3 times more potent than morphine, respectively.[28,44] In monkeys, **25c** substituted completely for morphine with a potency of about 150 times that of morphine.[45,46]

Conclusions

7-Substituted 6α,14α-ethenoisomorphinans such as etorphine are very strong analgesic compounds that show high affinity for each of the μ, κ, and δ opioid receptors. In the 7α-dimethylmethanol series, 5β-alkyl substitution lowers the affinity for the three opioid receptors significantly. The affinity for the μ receptor can be restored by increasing the size of the 7-substituent. However, 5β-methyletorphine (**8c**) has been shown to be less potent than etorphine in in vivo assays

for antinociception, although their binding profiles are similar. Moving the substituent from position 7α to 7β or 8α decreases the affinity for κ and δ, the affinity for μ remaining constant. The isomeric 6β,14β-ethenomorphinans (**24**, **26**) only show very low affinity for the opioid receptors, and are without in vivo analgesic activity. Conformational restriction of the 7-substituent to position 5 or 18 (**27a**–**d**, **22**) decreases the affinity, especially for the κ receptor, affording compounds which are more selective for the μ receptor, compared to their unrestricted counterparts. Substituting a chlorine atom at the etheno bridge in 6α,14α-ethenoisomorphinans gives compounds with high affinity for the opioid receptors, and high in vivo activity. 18-Chloro derivative **25c**, which has a 7α-dimethylmethanol moiety (which should be considered as suboptimal for antinociceptive activity, compare etorphine and its dimethylmethanol analogue **25b**) is 30–200 times more potent than morphine. The results of this study clearly indicate that there are still ample possibilities to improve on the receptor selectivity and analgesic/antinociceptive activity of etorphine and its analogues.

Experimental

Chemistry

Mass spectra were determined using a VG 70-SE mass spectrometer. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ with TMS as reference, using a Varian VXR-400S spectrometer. IR spectra were obtained from KBr discs using a Beckman IR 4210 spectrophotometer. Unless otherwise stated optical rotations were measured on a Perkin–Elmer P141 polarimeter in chloroform/ethanol, 9/1. Melting points are uncorrected. Column chromatography was performed over silica with dichloromethane/methanol as eluent. Reactions were monitored by TLC on deactivated silica (0.25 mm, Merck F_{254}; eluent: dichloromethane/methanol/25% ammonia, 85/15/0.5). The compounds were detected with UV (254 nm) and iodine vapor.

General procedure A: Grignard reaction with (−)-7α-acetyl - 4,5α - epoxy - 3,6 - dimethoxy - 5β,17 - dimethyl - 6α,14α-ethenoisomorphinan (6). (−)-7α-Acetyl-4,5α-epoxy-3,6-dimethoxy-5β,17-dimethyl-6α,14α-ethenoisomorphinan (**6**) in anhyd THF (20 mL) was added slowly to a solution of alkylmagnesium halide prepared from the alkyl halide (30 mmol) and magnesium (0.73 g, 30 mmol) in diethyl ether (100 mL). Directly after the addition, TLC showed complete conversion. The excess of Grignard reagent was decomposed with a saturated solution of ammonium chloride (100 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (2×50 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.

(−)-(*R*)-2-(4,5α-Epoxy-3,6-dimethoxy-5β,17-dimethyl-6α,14α-ethenoisomorphinan-7α)-butan-2-ol (7b). Prepared from ethenoisomorphinan **6** (1.30 g, 3.29 mmol) and iodoethane, according to procedure A. Crystallization of the crude product from diethyl ether yielded **7b** (0.71 g, 1.67 mmol, 51%): mp 168–169 °C; $[\alpha]^{25}_{D}$ −140° (*c* 1.00); MS *m*/*z* 425 (M, 21); ^{1}H NMR δ 0.79 (dd, 1H, H-8α), 0.94 (t, 3H, CH_2CH_3), 0.94 (s, 3H, C-*Me*), 1.26–1.44 (m, 2H, CH_2CH_3), 1.68 (s, 3H, 5β-Me), 1.71 (ddd, 1H, H-15eq), 1.95 (m, 1H, H-15ax), 2.18 (dd, 1H, H-7β), 2.37 (s, 3H, *N*-Me), 2.38 (dd, 1H, H-10α), 2.38 (m, 1H, H-16ax), 2.55 (m, 1H, H-16eq), 2.80 (dd, 1H, H-8β), 3.06 (d, 1H, H-9), 3.24 (d, 1H, H-10β), 3.76 (s, 3H, 6-OMe), 3.80 (s, 3H, 3-OMe), 4.99 (s, 1H, 20-C–OH), 5.36 (d, 1H, H-19), 6.04 (d, 1H, H-18), 6.47 (d, 1H, H-1), 6.59 (d, 1H, H-2); ^{13}C NMR δ 147.56, 141.39, 135.54, 134.53, 128.70, 125.33, 118.67, 113.38, 100.60, 86.11, 74.99, 60.52, 56.70, 54.68, 48.22, 45.69, 45.46, 43.79, 43.48, 33.16, 30.24, 29.68, 23.96, 22.63, 16.51, 7.23; IR ν 3470 (OH) cm^{-1}.

(−)-(*R*)-2-(4,5α-Epoxy-3,6-dimethoxy-5β,17-dimethyl-6α,14α-ethenoisomorphinan-7α)-pentan-2-ol (7c). Prepared from ethenoisomorphinan **6** (1.50 g, 3.80 mmol) and 1-iodopropane, according to procedure A. Crystallization of the crude product from diethyl ether yielded pure **7c** (1.23 g, 2.80 mmol, 74%): mp 127–129 °C; $[\alpha]^{25}_{D}$ −128° (*c* 1.00); MS *m*/*z* 439 (M, 20); ^{1}H NMR δ 0.80 (dd, 1H, H-8α), 0.89 (t, 3H, $CH_2CH_2CH_3$), 0.95 (s, 3H, C-*Me*), 1.19–1.50 (m, 4H, $CH_2CH_2CH_3$), 1.65 (s, 3H, 5β-Me), 1.70 (ddd, 1H, H-15eq), 1.93 (m, 1H, H-15ax), 2.18 (dd, 1H, H-7β), 2.35 (dd, 1H, H-10α), 2.36 (s, 3H, *N*-Me), 2.40 (m, 1H, H-16ax), 2.54 (m, 1H, H-16eq), 2.77 (dd, 1H, H-8β), 3.05 (d, 1H, H-9), 3.24 (d, 1H, H-10β), 3.76 (s, 3H, 6-OMe), 3.80 (s, 3H, 3-OMe), 5.01 (s, 1H, 20-C-OH), 5.36 (d, 1H, H-19), 6.03 (d, 1H, H-18), 6.47 (d, 1H, H-1), 6.61 (d, 1H, H-2); ^{13}C NMR δ 147.52, 141.35, 135.59, 134.60, 128.80, 125.28, 118.64, 113.26, 100.61, 86.18, 75.12, 60.47, 56.67, 54.67, 48.24, 46.11, 45.66, 43.79, 43.51, 33.32, 30.45, 29.71, 24.05, 22.56, 16.51, 15.85, 14.75; IR ν 3450 (OH) cm^{-1}.

(−)-(*R*)-2-(4,5α-Epoxy-3,6-dimethoxy-5β,17-dimethyl-6α,14α-ethenoisomorphinan-7α)-hexan-2-ol (7d). Prepared from ethenoisomorphinan **6** (1.30 g, 3.29 mmol) and 1-iodobutane, according to procedure A. Crystallization from diethyl ether yielded pure **7d** (0.91 g, 2.01 mmol, 61%): mp 136–138 °C; $[\alpha]^{25}_{D}$ −119° (*c* 1.00); MS *m*/*z* 453 (M, 17); ^{1}H NMR δ 0.80 (dd, 1H, H-8α), 0.92 (t, 3H, $CH_2CH_2CH_2CH_3$), 0.95 (s, 3H, C-*Me*), 1.2–1.5 (m, 6H, $CH_2CH_2CH_2CH_3$), 1.67 (s, 3H, 5β-Me), 1.70 (ddd, 1H, H-15eq), 1.95 (m, 1H, H-15ax), 2.18 (dd, 1H, H-7β), 2.37 (dd, 1H, H-10α), 2.37 (s, 3H, N-Me), 2.38 (m, 1H, H-16ax), 2.55 (m, 1H, H-16eq), 2.77 (dd, 1H, H-8β), 3.05 (d, 1H, H-9), 3.24 (d, 1H, H-10β), 3.76 (s, 3H, 6-OMe), 3.80 (s, 3H, 3-OMe), 5.05 (s, 1H, 20-C-OH), 5.36 (d, 1H, H-19), 6.02 (d, 1H, H-18), 6.47 (d, 1H, H-1), 6.61 (d, 1H, H-2); ^{13}C NMR δ 147.56, 141.37, 135.62, 134.61, 128.82, 125.29, 118.66, 113.36, 100.62, 86.21, 75.12, 60.45, 56.70, 54.69, 48.25, 46.31, 45.67, 43.80, 43.50, 40.71, 30.43, 29.73, 24.79, 24.00, 23.43, 22.58, 16.53, 14.23; IR ν 3470 (OH) cm^{-1}.

(−)-(*R*)-2-(4,5α-Epoxy-3,6-dimethoxy-5β,17-dimethyl-6α,14α-ethenoisomorphinan-7α)-heptan-2-ol (7e). Prepared from ethenoisomorphinan **6** (1.53 g, 3.87 mmol)

and 1-bromopentane, according to procedure A. Crystallization from diethyl ether yielded pure **7e** (0.84 g, 1.80 mmol, 47%): mp 131–132 °C; $[\alpha]_D^{25}$ −118° (*c* 1.00); MS *m*/*z* 467 (M, 16); ^{1}H NMR δ 0.79 (dd, 1H, H-8α), 0.88 (t, 3H, $CH_2CH_2CH_2CH_2CH_3$), 0.95 (s, 3H, C-*Me*), 1.2–1.5 (m, 8H, $CH_2CH_2CH_2CH_2CH_3$), 1.67 (s, 3H, 5β-Me), 1.72 (ddd, 1H, H-15eq), 1.95 (m, 1H, H-15ax), 2.20 (dd, 1H, H-7β), 2.38 (dd, 1H, H-10α), 2.38 (s, 3H, *N*-Me), 2.38 (m, 1H, H-16ax), 2.56 (m, 1H, H-16eq), 2.78 (dd, 1H, H-8β), 3.05 (d, 1H, H-9), 3.24 (d, 1H, H-10β), 3.75 (s, 3H, 6-OMe), 3.80 (s, 3H, 3-OMe), 5.04 (s, 1H, 20-C-OH), 5.38 (d, 1H, H-19), 6.04 (d, 1H, H-18), 6.46 (d, 1H, H-1), 6.62 (d, 1H, H-2); ^{13}C NMR δ 147.51, 141.34, 135.58, 134.59, 128.78, 125.26, 118.63, 113.23, 100.60, 86.18, 75.11, 60.47, 56.66, 54.70, 48.23, 46.38, 45.65, 43.78, 43.47, 40.89, 32.59, 30.42, 29.71, 23.87, 22.76, 22.54, 22.24, 16.52, 14.17; IR ν 3460 (OH) cm^{-1}.

(−)-(*R*)-2-(4,5α-Epoxy-3,6-dimethoxy-5β,17-dimethyl-6α,14α-ethenoisomorphinan-7α)-octan-2-ol (7f). From ethenoisomorphinan **6** (1.96 g, 4.96 mmol) and 1-bromohexane, according to procedure A. Crystallization from diethyl ether yielded pure **7f** (0.71 g, 1.48 mmol, 30%). mp 117–118 °C; $[\alpha]_D^{25}$ −113° (*c* 1.00); MS *m*/*z* 481 (M, 11); ^{1}H NMR δ 0.80 (dd, 1H, H-8α), 0.90 (t, 3H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.94 (s, 3H, C-*Me*), 1.2–1.5 (m, 10H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.68 (s, 3H, 5β-Me), 1.68 (m, 1H, H-15eq), 1.94 (m, 1H, H-15ax), 2.20 (dd, 1H, H-7β), 2.37 (dd, 1H, H-10a), 2.37 (s, 3H, *N*-Me), 2.37 (m, 1H, H-16ax), 2.56 (m, 1H, H-16eq), 2.78 (dd, 1H, H-8β), 3.05 (d, 1H, H-9), 3.24 (d, 1H, H-10β), 3.75 (s, 3H, 6-OMe), 3.80 (s, 3H, 3-OMe), 5.04 (s, 1H, 20-C-OH), 5.38 (d, 1H, H-19), 6.02 (d, 1H, H-18), 6.45 (d, 1H, H-1), 6.60 (d, 1H, H-2); ^{13}C NMR δ 147.52, 141.35, 135.59, 134.58, 128.79, 125.27, 118.64, 113.27, 100.61, 86.12, 75.11, 60.47, 56.67, 54.68, 48.23, 46.37, 45.65, 43.80, 43.49, 40.93, 31.95, 30.43, 30.03, 29.71, 23.90, 22.74, 22.54, 22.51, 16.53, 14.13; IR ν 3480 (OH) cm^{-1}.

General procedure B: 3-*O*-demethylation

The methyl ethers **7b**–**f** and potassium hydroxide (3.5 g) were dissolved in a mixture of glycol (15 mL) and water (1 mL) and refluxed for 8 h. After cooling to room temperature, the reaction mixture was diluted with water (50 mL) and adjusted to pH 8 with concentrated hydrochloric acid, ammonia, and acetic acid. This solution was extracted with chloroform (1×100 mL, 3×50 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 **8b**–**f**.

(−)-4,5α-Epoxy-7α-[(*R*)-1-hydroxy-1-methylpropyl]-6-methoxy-5β,17-dimethyl-6α,14α-ethenoisomorphinan-3-ol (8b). Prepared from **7b** (1.00 g, 2.35 mmol) according to procedure B. The free base was crystallized from diethyl ether. Yield 0.166 g (0.40 mmol, 17%). An analytical sample was recrystallized from diethyl ether: mp 264–268 °C; calcd for $C_{25}H_{33}NO_4$ (411.55): C 72.96; H 8.08; N 3.40, found C 72.7; H 7.9; N 3.6; $[\alpha]_D^{25}$ −135° (*c* 1.00); MS *m*/*z* 411 (M, 35); ^{1}H NMR δ 0.78 (dd, 1H, H-8α), 0.92 (t, 3H, CH_2CH_3), 0.94 (s, 3H, C-*Me*), 1.26–1.40 (m, 2H, CH_2CH_3), 1.66 (s, 3H, 5β-Me), 1.71 (ddd, 1H, H-15eq), 1.93 (m, 1H, H-15ax), 2.18 (dd, 1H, H-7β), 2.34 (dd, 1H, H-10α), 2.36 (s, 3H, *N*-Me), 2.40 (m, 1H, H-16ax), 2.55 (m, 1H, H-16eq), 2.77 (dd, 1H, H-8β), 3.05 (d, 1H, H-9), 3.22 (d, 1H, H-10β), 3.73 (s, 3H, 6-OMe), 4.93 (bs, 1H, 3-OH), 5.01 (s, 1H, 20-C-OH), 5.36 (d, 1H, H-19), 6.00 (d, 1H, H-18), 6.43 (d, 1H, H-1), 6.59 (d, 1H, H-2); ^{13}C NMR δ 146.02, 136.92, 135.31, 134.78, 128.26, 124.94, 119.15, 115.68, 101.38, 86.17, 75.14, 60.48, 54.63, 48.69, 45.65, 45.69, 43.87, 43.48, 33.10, 30.30, 29.69, 23.88, 22.61, 16.52, 7.23; IR ν 3275, 3450 (OH) cm^{-1}.

(−)-4,5α-Epoxy-7α-[(*R*)-1-hydroxy-1-methylbutyl]-6-methoxy-5β,17-dimethyl-6α,14α-ethenoisomorphinan-3-ol (8c). Prepared from **7c** (1.00 g, 2.28 mmol) according to procedure B. The free base was crystallized from diethyl ether. Yield 0.109 g (0.26 mmol, 11%). An analytical sample was recrystallized from diethyl ether: mp 271–274 °C; calcd for $C_{26}H_{35}NO_4{\cdot}0.5H_2O$ (434.58): C 71.86; H 8.35; N 3.22, found C 71.8; H 8.1; N 3.4; $[\alpha]_D^{25}$ −121° (*c* 1.00); MS *m*/*z* 425 (M, 32); ^{1}H NMR δ 0.80 (dd, 1H, H-8α), 0.90 (t, 3H, $CH_2CH_2CH_3$), 0.95 (s, 3H, C-*Me*), 1.18–1.51 (m, 4H, $CH_2CH_2CH_3$), 1.65 (s, 3H, 5β-Me), 1.70 (ddd, 1H, H-15eq), 1.93 (m, 1H, H-15ax), 2.18 (dd, 1H, H-7β), 2.33 (dd, 1H, H-10α), 2.36 (s, 3H, *N*-Me), 2.40 (m, 1H, H-16ax), 2.55 (m, 1H, H-16eq), 2.77 (dd, 1H, H-8β), 3.05 (d, 1H, H-9), 3.24 (d, 1H, H-10β), 3.73 (s, 3H, 6-OMe), 4.89 (s, 1H, 20-C-OH), 5.03 (bs, 1H, 3-OH), 5.36 (d, 1H, H-19), 6.00 (d, 1H, H-18), 6.43 (d, 1H, H-1), 6.58 (d, 1H, H-2); ^{13}C NMR δ 146.00, 136.90, 135.32, 134.76, 128.26, 124.94, 119.15, 115.66, 101.36, 86.22, 75.26, 60.48, 54.64, 48.67, 46.38, 45.66, 43.86, 43.49, 43.24, 30.43, 29.70, 24.05, 22.61, 16.51, 15.84, 14.74; IR ν 3450, 3250 (OH) cm^{-1}.

(−)-4,5α-Epoxy-7α-[(*R*)-1-hydroxy-1-methylpentyl]-6-methoxy-5β,17-dimethyl-6α,14α-ethenoisomorphinan-3-ol (8d). Prepared from **7d** (1.00 g, 2.21 mmol) according to procedure B, the free base was crystallized from diethyl ether to yield 0.271 g (0.62 mmol, 27%). An analytical sample was recrystallized from diethyl ether: mp 185–187 °C; calcd for $C_{27}H_{37}NO_4{\cdot}0.5H_2O$ (448.61): C 72.29; H 8.54; N 3.12, found C 72.6; H 8.2; N 3.3; $[\alpha]_D^{25}$ −114° (*c* 1.00); MS *m*/*z* 439 (M, 29); ^{1}H NMR δ 0.79 (dd, 1H, H-8α), 0.90 (t, 3H, $CH_2CH_2CH_2CH_3$), 0.95 (s, 3H, C-*Me*), 1.18–1.51 (m, 6H, $CH_2CH_2CH_2CH_3$), 1.65 (s, 3H, 5β-Me), 1.93 (ddd, 1H, H-15eq), 1.96 (m, 1H, H-15ax), 2.17 (dd, 1H, H-7β), 2.33 (dd, 1H, H-10α), 2.36 (s, 3H, *N*-Me), 2.39 (m, 1H, H-16ax), 2.55 (m, 1H, H-16eq), 2.76 (dd, 1H, H-8β), 3.05 (d, 1H, H-9), 3.22 (d, 1H, H-10β), 3.73 (s, 3H, 6-OMe), 5.01 (s, 1H, 20-C-OH), 5.35 (d, 1H, H-19), 6.00 (d, 1H, H-18), 6.41 (d, 1H, H-1), 6.57 (d, 1H, H-2); ^{13}C NMR δ 146.05, 137.08, 135.31, 134.76, 128.09, 124.92, 119.14, 115.81, 101.19, 86.24, 75.35, 60.51, 54.66, 48.63, 46.24, 45.67, 43.86, 43.48, 40.60, 30.38, 29.68, 24.76, 23.99, 23.38, 22.62, 16.54, 14.21; IR ν 3450, 3200 (OH) cm^{-1}.

(−)-4,5α-Epoxy-7α-[(*R*)-1-hydroxy-1-methylhexyl]-6-methoxy-5β,17-dimethyl-6α,14α-ethenoisomorphinan-3-ol (8e). Prepared from **7e** (1.00 g, 2.14 mmol) according to procedure B, the free base was purified by column

chromatography (98:2) and crystallized as its hydrochloride salt from ethanol to yield 0.169 g (0.36 mmol, 17%): mp 272–276 °C (**8e**.HCl); calcd for $C_{28}H_{39}NO_4$·HCl (490.09): C 68.62; H 8.23; N 2.86, found C 69.0; H 8.2; N 3.0; $[\alpha]_D^{25}$ −89° (**8e**.HCl, H_2O, *c* 1.00); MS *m*/*z* 453 (M, 33); ^{1}H NMR δ 0.80 (dd, 1H, H-8α), 0.88 (t, 3H, $CH_2CH_2CH_2CH_2CH_3$), 0.95 (s, 3H, C-*Me*), 1.1–1.5 (m, 8H, $CH_2CH_2CH_2CH_2CH_3$), 1.64 (s, 3H, 5β-Me), 1.68 (ddd, 1H, H-15eq), 1.93 (m, 1H, H-15ax), 2.16 (dd, 1H, H-7β), 2.36 (s, 3H, *N*-Me), 2.36 (m, 1H, H-16ax), 2.38 (dd, 1H, H-10α), 2.56 (m, 1H, H-16eq), 2.78 (dd, 1H, H-8β), 3.04 (d, 1H, H-9), 3.23 (d, 1H, H-10β), 3.73 (s, 3H, 6-OMe), 5.08 (s, 1H, 20-C-OH), 5.38 (d, 1H, H-19), 6.00 (d, 1H, H-18), 6.42 (d, 1H, H-1), 6.59 (d, 1H, H-2); ^{13}C NMR δ 146.09, 137.12, 135.30, 134.81, 127.97, 124.94, 119.14, 115.85, 101.06, 86.24, 75.20, 60.47, 54.69, 48.61, 46.38, 45.68, 43.86, 43.55, 40.79, 32.59, 30.40, 29.70, 23.85, 22.77, 22.60, 22.24, 16.57, 14.67; IR ν 3480, 3225 (OH) cm^{-1}.

(−)-4,5α-Epoxy-7α-[(*R*)-1-hydroxy-1-methylheptyl]-6-methoxy-5β,17-dimethyl-6α,14α-ethenoisomorphinan-3-ol (8f). Prepared from **7f** (1.00 g, 2.08 mmol) according to procedure B, the crude product was purified by column chromatography (98:2) and crystallized as its hydrochloride salt from ethanol to yield 0.187 g (0.38 mmol, 18%): mp 266–269 °C (**8f**.HCl); calcd for $C_{29}H_{41}NO_4$·HCl (504.12): C 69.10; H 8.40; N 2.78, found C 69.0; H 8.3; N 2.9; $[\alpha]_D^{25}$ −89° (**8f**.HCl, H_2O, *c* 1.00); MS *m*/*z* 467 (M, 25); ^{1}H NMR δ 0.80 (dd, 1H, H-8α), 0.90 (t, 3H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.95 (s, 3H, C-*Me*), 1.1–1.5 (m, 10H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.65 (s, 3H, 5β-Me), 1.68 (ddd, 1H, H-15eq), 1.94 (m, 1H, H-15ax), 2.20 (dd, 1H, H-7β), 2.35 (s, 3H, *N*-Me), 2.35 (m, 1H, H-16ax), 2.36 (dd, 1H, H-10α), 2.55 (m, 1H, H-16eq), 2.75 (dd, 1H, H-8β), 3.05 (d, 1H, H-9), 3.24 (d, 1H, H-10β), 3.75 (s, 3H, 6-OMe), 5.04 (s, 1H, 20-C-OH), 5.38 (d, 1H, H-19), 6.02 (d, 1H, H-18), 6.42 (d, 1H, H-1), 6.58 (d, 1H, H-2); ^{13}C NMR δ 146.14, 137.23, 135.29, 134.76, 127.84, 124.92, 119.11, 115.92, 100.95, 86.24, 75.12, 60.52, 54.63, 48.59, 46.37, 45.67, 43.86, 43.49, 40.88, 31.94, 30.40, 30.03, 23.84, 22.74, 22.61, 22.50, 16.56, 14.12; IR ν 3400, 3150 (OH) cm^{-1}.

(−)-(4,5α-Epoxy-3,6-dimethoxy-17-methyl-6α,14α-ethenoisomorphinan-7β)-methanol (11). (−)-Ethyl 4,5α-epoxy-3,6-methoxy-17-methyl-6α,14α-ethenoisomorphinan-7β-carboxylate[39] (1.0 g, 2.4 mmol) was dissolved in 25 mL of anhydrous THF and lithium aluminum hydride (0.75 g) was added. After complete conversion, water (0.25 mL), 15% sodium hydroxide solution (0.25 mL), and 1.25 mL of water were added subsequently. The inorganic salts were filtered off and washed with THF (25 mL). The combined organic layers were dried over Na_2SO_4 and the solvent evaporated under reduced pressure. Yield 763 mg of alcohol **11** (2.1 mmol, 85%): mp 164–165 °C; $[\alpha]_D^{25}$ −195° (*c* 1.00); MS *m*/*z* 369 (M, 22); ^{1}H NMR δ 1.51 (dd, 1H, H-8α), 1.75 (m, 1H, H-15eq), 2.12 (m, 1H, H-15ax), 2.18–2.30 (m, 2H, H-7β, H-10α), 2.36 (s, 3H, *N*-Me), 2.35–2.46 (m, 2H, H-16ax, H-8β), 2.51 (dd, 1H, H-16eq), 3.14 (d, 1H, H-9), 3.21 (d, 1H, H-10β), 3.63 (s, 3H, 6-OMe), 3.72 (dd, 1H, 7β-CH_2OH), 3.83 (s, 3H, 3-OMe), 4.01 (dd, 1H, 7β-CH_2OH), 4.93 (d, 1H, H-5), 5.47 (d, 1H, H-19), 6.08 (d, 1H, H-18), 6.52 (d, 1H, H-1), 6.62 (d, 1H, H-2); ^{13}C NMR δ 147.77, 142.11, 136.20, 135.20, 128.45, 127.97, 119.28, 113.87, 94.23, 82.99, 64.12, 60.52, 56.85, 54.04, 46.99, 45.51, 43.60, 42.86, 42.10, 30.96, 27.89, 22.31; IR ν 3420 (OH) cm^{-1}.

(−)-(4,5α-Epoxy-3,6-dimethoxy-17-methyl-6α,14α-ethenoisomorphinan-7β)-methanol (12). Prepared from **11** (501 mg, 1.36 mmol) according to procedure B, the free base was purified by column chromatography over silica (eluent dichloromethane/methanol, 98/2) and crystallized from diethyl ether to yield 0.105 g (0.30 mmol, 22%): mp 95–97 °C; $[\alpha]_D^{25}$ −163° (*c* 1.00); MS *m*/*z* 355 (M, 100); ^{1}H NMR δ 1.51 (dd, 1H, H-8α), 1.73 (m, 1H, H-15eq), 2.14–2.32 (m, 3H, H-7β, H-10α, H-15ax), 2.36 (s, 3H, *N*-Me), 2.35–2.46 (m, 2H, H-16ax, H-8β), 2.52 (dd, 1H, H-16eq), 3.18 (d, 1H, H-9), 3.20 (d, 1H, H-10β), 3.59 (s, 3H, 6-OMe), 3.76 (dd, 1H, 7β-CH_2OH), 4.01 (dd, 1H, 7β-CH_2OH), 4.99 (d, 1H, H-5), 5.49 (d, 1H, H-19), 6.07 (d, 1H, H-18), 6.50 (d, 1H, H-1), 6.63 (d, 1H, H-2); ^{13}C NMR δ 146.19, 138.11, 136.59, 134.76, 127.66, 126.95, 119.91, 116.57, 93.91, 82.96, 63.95, 60.52, 53.36, 47.19, 45.54, 43.55, 42.89, 40.70, 30.85, 27.76, 22.42; IR ν 3250, 3400 (OH) cm^{-1}.

(−)-(4,5α-Epoxy-3,6-dimethoxy-17-methyl-6α,14α-ethenoisomorphinan-7α)-methanol (13a). 10a[39](5.00 g, 13.6 mmol) was dissolved in 90 mL of anhyd THF and lithium aluminum hydride (3.5 g) was added. After complete conversion, water (1 mL), 15% sodium hydroxide solution (1 mL), and 5 mL of water were added subsequently. The inorganic salts were filtered off and washed with THF (2×25 mL). The combined organic layers were dried over Na_2SO_4 and the solvent evaporated under reduced pressure. Yield 3.89 g of alcohol **13a** (10.6 mmol, 77%): $[\alpha]_D^{25}$ −179° (*c* 1.00); MS *m*/*z* 369 (M, 98); ^{1}H NMR δ 0.49 (dd, 1 H, H-8α), 1.82 (ddd, 1 H, H-15eq), 1.99 (ddd, 1 H, H-15ax), 2.06 (m, 1 H, H-7β), 2.36 (s, 3 H, *N*-Me), 2.40 (m, 2 H, H-10α, H-16ax), 2.51 (dd, 1 H, H-16eq), 2.89 (dd, 1 H, H-8β), 3.11 (d, 1 H, H-9), 3.22 (m, 2 H, H-10α, 7-CH_2OH), 3.48 (t, 1 H, 7-CH_2OH), 3.71 (s, 3 H, 6-OMe), 3.83 (s, 3 H, 3-OMe), 4.57 (d, 1 H, H-5), 5.50 (d, 1 H, H-19), 5.92 (d, 1 H, H-18), 6.52 (d, 1 H, H-1), 6.63 (d, 1 H, H-2); ^{13}C NMR δ 147.91, 141.84, 136.59, 134.29, 128.24, 125.22, 119.28, 113.73, 97.05, 84.05, 65.44, 59.90, 56.77, 54.42, 46.94, 45.52, 43.51, 42.81, 39.64, 33.20, 29.21, 22.27; IR ν 3450 (OH) cm^{-1}.

(−)-4,5a-Epoxy-3,6-dimethoxy-7α,17-dimethyl-6α,14α-ethenoisomorphinan (14a). 13a (1.50 g, 4.09 mmol) and triethylamine (0.6 mL, 8.6 mmol) were dissolved in chloroform (50 mL). Methanesulfonyl chloride (0.73 mL, 8.6 mmol) was added dropwise. Water (25 mL) was added after completion of the reaction. The water layer was basified by concd ammonia and extracted with chloroform (25 mL). The organic layers were combined, washed with water (2×50 mL) and brine (25 mL). Removal of the solvent under reduced pressure gave 1.61 g of mesylate (3.69 mmol, 90%). The crude mesylate (1.20 g, 2.75 mmol) and lithium aluminum hydride (1.963 g) were dissolved in 50 mL of THF. The

reaction mixture was heated under reflux for 8 h. After cooling, water (0.75 mL), 15% sodium hydroxide solution (0.75 mL), and water (4 mL) were added subsequently. The inorganic salts were filtered off, and the salts were washed with THF (15 mL). The organic layers were combined, dried over Na_2SO_4, and the solvent evaporated under reduced pressure. The product was recrystallized as its hydrochloride salt from absolute ethanol. Yield 0.854 g (2.25 mmol, 82%) of **14a**: mp 197–199 °C; $[\alpha]_D^{25}$ −156° (*c* 0.99, H_2O); MS *m*/*z* 353 (M, 100); ^{1}H NMR δ 0.72 (dd, 1 H, H-8α), 0.81 (d, 3 H, 7-CH_3), 1.82 (ddd, 1 H, H-15eq), 1.99 (m, 2 H, H-15ax, H-7β), 2.36 (s, 3 H, *N*-Me), 2.40 (m, 2 H, H-10α, H-16ax), 2.51 (ddd, 1 H, H-16eq), 2.98 (dd, 1 H, H-8α), 3.11 (d, 1 H, H-9), 3.20 (d, 1 H, H-10α), 3.51 (s, 3 H, 6-OMe), 3.82 (s, 3 H, 3-OMe), 4.60 (d, 1 H, H-5), 5.43 (d, 1 H, H-19), 5.67 (d, 1 H, H-18), 6.52 (d, 1 H, H-1), 6.62 (d, 1 H, H-2); ^{13}C NMR δ 148.21, 141.89, 135.08, 134.61, 128.15, 127.47, 119.05, 113.11, 93.56, 81.64, 60.22, 56.48, 51.15, 46.99, 45.71, 43.57, 42.68, 34.31, 33.44, 30.06, 22.26, 16.83.

(−)-4,5α-Epoxy-6-methoxy-7α,17-dimethyl-6α,14α-ethenoisomorphinan-3-ol (15a). 14a (750 mg, 1.98 mmol) and 7.5 g of potassium hydroxide were dissolved in 18 mL of glycol. After refluxing the reaction mixture for 6 h, the reaction was stopped by cooling to room temperature, and the pH adjusted to 7. Extraction of the aqueous layer with chloroform (4×25 mL), drying over Na_2SO_4, and evaporation of the solvent gave the crude product. The product was purified by column chromatography (eluent: dichloromethane/methanol, 98/2) and crystallized as its hydrochloride salt from absolute ethanol. Yield 102 mg (0.27 mmol, 14%) of **15a**: mp >250 °C dec; $[\alpha]_D^{25}$ −175° (**15a**.HCl, H_2O, *c* 0.99); MS *m*/*z* 339 (M, 65); ^{1}H NMR δ 0.73 (dd, 1H, H-8α), 0.81 (d, 3H, 7α-Me), 1.80 (ddd, 1H, H-15eq), 1.95–2.05 (m, 2H, H-7α, H-15ax), 2.37 (s, 3H, *N*-Me), 2.35–2.44 (m, 2H, H-16ax, H-10α), 2.52 (dd, 1H, H-16eq), 3.00 (dd, 1H, H-8β), 3.15 (d, 1H, H-9), 3.21 (d, 1H, H-10β), 3.49 (s, 3H, 6-OMe), 4.62 (d, 1H, H-5), 5.41 (d, 1H, H-19), 5.62 (d, 1H, H-18), 6.47 (d, 1H, H-1), 6.60 (d, 1H, H-2); ^{13}C NMR δ 146.74, 137.62, 135.21, 134.35, 127.52, 127.16, 119.64, 116.31, 93.18, 81.77, 60.18, 50.71, 47.23, 45.73, 43.50, 42.78, 34.21, 33.23, 29.72, 22.39, 16.73; IR ν 3400, 3345 (OH) cm^{-1}. An analytical sample for elemental analysis was obtained as the free base. Calcd for $C_{21}H_{25}NO_3$ (339.42): C 74.31; H 7.42; N 4.13, found C 74.2; H 7.3; N 4.2.

(−)-(4,5α-Epoxy-3,6-dimethoxy-5β,17-dimethyl-6α,14α-ethenoisomorphinan-7α)-methanol (13b). 10b (2.014 g, 4.72 mmol) was dissolved in 28 mL of anhydrous THF and lithium aluminum hydride (765 mg) was added. After complete conversion, water (0.25 mL), 15% sodium hydroxide solution (0.25 mL), and 1.3 mL of water were added subsequently. The inorganic salts were filtered off, and washed with THF (2×10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent evaporated under reduced pressure. Yield 1.647 g of alcohol **13b** (4.30 mmol, 91%): mp 160–162 °C; $[\alpha]_D^{25}$ −139° (*c* 0.99); MS *m*/*z* 383 (M, 100); ^{1}H NMR δ 0.41 (dd, 1 H, H-8α), 1.64 (s, 3 H, 5-CH_3), 1.66 (m, 1 H, H-15eq), 2.02 (ddd, 1 H, H-15ax), 2.16 (m, 1 H, H-7β), 2.34 (s, 3 H, *N*-Me), 2.38 (m, 2 H, H-16ax, H-10α), 2.54 (m, 1 H, H-16eq), 2.81 (dd, 1 H, H-8β), 3.04 (d, 1 H, H-9), 3.11 (t, 1 H, CH_2OH), 3.22 (d, 1 H, H-10β), 3.46 (d, 1 H, CH_2OH), 3.73 (s, 3 H, 3-OCH_3), 3.76 (m, 1 H, CH_2OH), 3.80 (s, 3 H, 6-OCH_3), 5.45 (d, 1 H, H-19), 6.05 (d, 1 H, H-18), 6.48 (d, 1 H, H-1), 6.61 (d, 1 H, H-2); ^{13}C NMR δ 147.14, 141.50, 136.12, 135.68, 128.55, 125.02, 118.80, 113.26, 100.12, 86.50, 66.39, 60.54, 56.64, 54.72, 47.85, 45.57, 43.91, 43.46, 40.64, 28.93, 28.65, 22.56, 16.42; IR ν 3450 (OH) cm^{-1}.

(−)-4,5α-Epoxy-3,6-dimethoxy-5β,7α,17-trimethyl-6α,14α-ethenoisomorphinan (14b). 13b (1.647 g, 4.30 mmol) and triethylamine (0.6 mL, 8.6 mmol) were dissolved in chloroform (50 mL). Methanesulfonyl chloride (0.73 mL, 8.6 mmol) was added dropwise. Water (25 mL) was added after completion of the reaction. The water layer was basified with concd ammonia and extracted with chloroform (25 mL). The organic layers were combined, washed with water (2×50 mL) and brine (25 mL). Removal of the solvent under reduced pressure gave 1.905 g of the mesylate (3.97 mmol, 92%). The crude mesylate and lithium aluminum hydride (1.963 g) were dissolved in 50 mL of THF. The reaction mixture was heated under reflux for 8 h. After cooling, water (0.75 mL), 15% sodium hydroxide solution (0.75 mL), and water (4 mL) were subsequently added. The inorganic salts were filtered off, and the salts were washed with THF (15 mL). The organic layers were combined, dried over Na_2SO_4, and the solvent evaporated under reduced pressure. The product was recrystallized from absolute ethanol. Yield 0.891 g of **14b** (2.43 mmol, 96%): mp 160–162 °C; $[\alpha]_D^{25}$ −131° (*c* 0.99); MS *m*/*z* 367 (M, 30); ^{1}H NMR δ 0.67 (dd, 1 H, H-8α), 0.78 (d, 3 H, 7-CH_3), 1.58 (s, 3 H, 5-CH_3), 1.64 (m, 1 H, H-15eq), 1.94 (m, 1 H, H-7β), 2.04 (ddd, 1 H, H-15ax), 2.35 (s, 3 H, *N*-Me), 2.38 (m, 2 H, H-10α, H-16ax), 2.53 (m, 1 H, H-16eq), 2.85 (dd, 1 H, H-8β), 3.05 (d, 1 H, H-9), 3.22 (dd, 1 H, H-10β), 3.68 (s, 3 H, 3-OCH_3), 3.80 (s, 3 H, 6-OCH_3), 5.43 (d, 1 H, H-19), 5.97 (d, 1 H, H-18), 6.47 (t, 1 H, H-1), 6.61 (d, 1 H, H-2); ^{13}C NMR δ 147.33, 141.45, 136.22, 134.95, 128.62, 125.52, 118.50, 113.21, 100.92, 83.69, 60.82, 56.68, 54.84, 48.00, 45.68, 43.79, 43.52, 34.03, 33.63, 28.81, 22.52, 18.34, 16.31.

(−)-4,5α-Epoxy-6-methoxy-5β,7α,17-trimethyl-6α,14α-ethenoisomorphinan-3-ol (15b). 14b (646 mg, 1.76 mmol) and 7.5 g of potassium hydroxide were dissolved in 18 mL of glycol. After refluxing the reaction mixture for 22 h, the reaction was stopped by cooling to room temperature, and the pH adjusted to 7. Extraction of the aq layer with chloroform (4×50 mL), drying over Na_2SO_4, and evaporation of the solvent gave the crude product. The product was purified by column chromatography (eluent: dichloromethane/methanol, 98/2) and crystallized as its hydrochloride salt from absolute ethanol. Yield 44 mg (0.11 mmol, 6.3%) of **15b**: mp 266–269 °C (**15b**.HCl); $[\alpha]_D^{25}$ −89° (**15b**.HCl, H_2O, *c* 1.00); MS *m*/*z* 353 (M, 25); ^{1}H NMR (free base) δ 0.66 (dd, 1 H, H-8α), 0.78 (d, 3 H, 7-CH_3), 1.58 (s, 3 H, 5-CH_3), 1.63 (m, 1 H, H-15eq), 1.92 (m, 1 H, H-7β), 2.03 (ddd, 1 H, H-15ax), 2.35 (s, 3 H, *N*-Me), 2.39 (m, 2 H, H-10α, H-

16ax), 2.53 (m, 1 H, H-16eq), 2.84 (dd, 1 H, H-8β), 3.07 (d, 1 H, H-9), 3.20 (d, 1 H, H-10β), 3.64 (s, 3 H, 6-OCH_3), 5.41 (d, 1 H, H-19), 5.94 (d, 1 H, H-18), 6.42 (d, 1 H, H-1), 6.58 (d, 1 H, H-2); ^{13}C NMR (free base) δ 145.81, 137.02, 135.93, 135.07, 128.09, 125.13, 119.07, 115.55, 101.80, 83.72, 60.82, 54.82, 48.14, 45.70, 43.85, 43.50, 34.08, 33.24, 29.70, 28.71, 22.62, 18.34, 16.31; IR ν 3400, 3150 (OH) cm^{-1}.

(−)-1-(4,5α-Epoxy-3,6-dimethoxy-17-methyl-6α,14α-ethenoisomorphinan-7α)-ethyl methanesulfonate (17). The Diels–Alder adduct of thebaine with acrolein (**16**)[37] (1.378 g, 3.75 mmol) was dissolved in THF and added dropwise to methylmagnesium bromide (10 mmol) in 25 mL of THF. After 25 min, the reaction was worked up by the addition of water (3 mL) and saturated ammonium chloride (3 mL). The aqueous layer was extracted with chloroform (10 mL). After drying over Na_2SO_4, the solvents were removed under reduced pressure. Yield 1.298 g (3.399 mmol, 91%): mp 64–68 °C; $[\alpha]_D^{25}$ −109° (*c* 0.98); IR ν 3470 (OH) cm^{-1}. The crude alcohol (1.073 g, 2.81 mmol) and triethylamine (0.6 mL) were dissolved in dichloromethane (25 mL). Methanesulfonyl chloride (0.3 mL) was added and the reaction stirred for 1 h. Water (25 mL) was added and the aq layer basified by concd ammonia. After separation of the organic layer, the aqueous layer was extracted with dichloromethane (25 mL). The combined organic layers were washed with water (50 mL) and brine (25 mL). After drying over Na_2SO_4, the solvent was removed under reduced pressure. Yield of mesylate **17**: 1.016 g (2.21 mmol, 79%).

(−)-4,5α-Epoxy-3,6-dimethoxy-17-methyl-7-propylidene-6α,14α-ethenoisomorphinan (18). Mesylate **17** (3.00 g, 6.5 mmol) and lithium aluminum hydride (1.5 g, 40 mmol) were dissolved in 75 mL of anhyd THF. After refluxing for 8 h, the reaction was cooled and the excess of lithium aluminum hydride decomposed by subsequent addition of water (3 mL), 15% sodium hydroxide (3 mL), and water (10 mL). The salts were filtered off and washed with THF (2×25 mL). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated. Crude yield 2.321 g (6.34 mmol, 97%). Repeated crystallization from absolute ethanol gave **18**: mp 200–203 °C; $[\alpha]_D^{25}$ −217° (*c* 0.99); MS *m*/*z* 365 (M, 100); ^1H NMR δ 1.69 (dq, 3 H, CH_3), 1.74 (m, 1 H, H-8α), 1.82 (m, 1 H, H-15eq), 1.90 (ddd, 1 H, H-15ax), 2.40 (s, 3 H, *N*-Me), 2.42 (m, 2 H, H-10α, H-16ax), 2.52 (dd, 1 H, H-16eq), 3.23 (s, 1 H, H-9), 3.26 (dd, 1 H, H-10β), 3.30 (d, 1 H, H-8β), 4.36 (d, 1 H, H-5), 5.54 (d, 1 H, H-19), 5.75 (m, 1 H, =C*H*CH_3), 5.97 (dd, 1 H, H-18), 6.52 (d, 1 H, H-1), 6.62 (d, 1 H, H-2); ^{13}C NMR δ 148.38, 141.87, 136.57, 134.64, 134.11, 128.22, 126.03, 119.04, 118.79, 113.54, 96.19, 83.19, 60.09, 56.70, 53.39, 47.19, 45.71, 43.95, 43.66, 32.64, 30.71, 22.20, 14.09.

(−)-4,5α-Epoxy-6-methoxy-17-methyl-7-propylidene-6α,14α-ethenoisomorphinan-3-ol (19). Propylidene **18** (764 mg, 2.09 mmol) and potassium hydroxide (7.5 g) were dissolved in 20 mL of glycol. After 8 h refluxing, the reaction mixture was cooled, and the pH adjusted to 7 using hydrochloric acid and acetic acid. The aqueous layer was extracted with chloroform (4×25 mL) and the combined organic layers were dried over Na_2SO_4. After evaporation of the solvent, the product was recrystallized twice from absolute ethanol to yield 189 mg (0.54 mmol, 26%) of **19**: mp 232–235 °C; calcd for $C_{22}H_{35}NO_3$ (351.45): C 75.19; H 7.17; N 3.99, found C 75.5; H 7.1; N 4.2; $[\alpha]_D^{25}$ −256° (*c* 1.01); MS *m*/*z* 351 (M, 100); ^1H NMR δ 1.67 (dq, 3 H, CH_3), 1.74 (dq, 1 H, H-8α), 1.81 (dh, 1 H, H-15eq), 1.90 (ddd, 1 H, H-15ax), 2.40 (s, 3 H, *N*-Me), 2.41 (m, 2 H, H-10α, H-16ax), 2.53 (m, 1 H, H-16eq), 3.24 (d, 1 H, H-10β), 3.27 (d, 1 H, H-9), 3.32 (m, 1 H, H-8β), 3.49 (s, 3 H, 6-OCH_3), 4.32 (d, 1 H, H-5), 5.56 (d, 1 H, H-19), 5.72 (m, 1 H, =C*H*CH_3), 5.95 (m, 1 H, H-18), 6.49 (dt, 1 H, H-1), 6.61 (d, 1 H, H-2); ^{13}C NMR δ 146.68, 137.60, 137.08, 134.23, 133.60, 127.45, 124.86, 119.64, 119.00, 116.19, 96.45, 83.75, 60.02, 53.09, 47.54, 45.72, 44.17, 43.57, 32.50, 30.69, 22.31, 14.06; IR ν 3495 (OH) cm^{-1}.

(−)-2-(4,5α-Epoxy-3,6-dimethoxy-7β,17-dimethyl-6α,14α-ethenoisomorphinan-7α)-propan-2-ol (21). Thebaine (5 g, 16 mmol) was dissolved in 100 mL of freshly distilled methyl methacrylate. The reaction solution was heated for two weeks at 100 °C. After distilling off the excess of acrylate, HPLC analysis of the residue demonstrated a 50% conversion of thebaine into the Diels–Alder adduct. The residue was purified by column chromatography over silica gel (eluent dichloromethane). The Diels–Alder adduct (1.2 g, 2.9 mmol) was dissolved in 50 mL of anhyd diethyl ether. Methylmagnesium bromide (5.0 mL, 2 M in diethyl ether) was added dropwise at 0 °C. The reaction mixture was stirred for 15 min after the addition and then a saturated ammonium chloride solution (75 mL) was carefully added. The two layers were separated and the water layer extracted with 25 mL of diethyl ether. The combined organic layers were dried (Na_2SO_4) and the solvent evaporated. Crude yield 1.06 g (2.6 mmol, 88%). Repeated crystallization from absolute methanol gave **21**: mp 195–196 °C; $[\alpha]_D^{25}$ −190° (*c* 0.99); MS *m*/*z* 411 (M, 5); ^1H NMR δ 1.07 (s, 3H, 7α-C*Me*MeOH), 1.08 (s, 3H, 7α-C*Me*MeOH), 1.19 (d, 1H, H-8α), 1.46 (s, 3H, 7β-Me), 1.76 (ddd, 1H, H-15eq), 2.33–2.55 (m, 5H, H-8β, H-10α, H-15ax, H-16ax, H16-eq), 2.37 (s, 3H, *N*-Me), 3.09 (d, 1H, H-9), 3.22 (d, 1H, H-10β), 3.75 (s, 3H, 6-OMe), 3.82 (s, 3H, 3-OMe), 4.10 (m, 1H, 7α-CMeMe*OH*), 5.15 (d, 1H, H-5), 5.29 (d, 1H, H-19), 6.05 (d, 1H, H-18), 6.50 (d, 1H, H-1), 6.62 (d, 1H, H-2); ^{13}C NMR δ 148.03, 141.90, 135.79, 133.44, 128.33, 127.64, 119.15, 113.89, 95.26, 86.36, 60.66, 56.96, 55.27, 48.75, 47.05, 45.56, 43.70, 43.54, 37.41, 31.25, 31.17, 26.16, 22.48, 18.92; IR ν 3440 (OH) cm^{-1}.

(−)-4,5α-Epoxy-7α,18-(epoxymethano)-6-methoxy-7β,17,21,21-tetramethyl-6α,14α-ethenoisomorphinan-3-ol (22). Compound **21** (411 mg, 1.0 mmol) and potassium hydroxide (7.5 g) were dissolved in 20 mL of glycol. After 7 h refluxing, the reaction mixture was cooled and the pH adjusted to 7 using hydrochloric acid and acetic acid. The aqueous layer was extracted with chloroform (4×25 mL) and the combined organic layers were dried over Na_2SO_4. After evaporation of the solvent, the product was purified by column chromatography over

silica gel (eluent: dichloromethane/methanol, 98/2) and recrystallized from methanol to yield 132 mg (0.33 mmol, 33%) of **22**: mp 230–232 °C; $[\alpha]_D^{25}$ −129° (*c* 0.65); MS *m*/*z* 397 (M, 42); ^{1}H NMR δ 1.01 (ddd, 1H, H-19α), 1.10 (s, 3H, 7β-Me), 1.26 (s, 3H, 7α-C*Me*-MeOH), 1.31 (s, 3H, 7α-C*Me*MeOH), 1.65 (m, 1H, H-15eq), 2.13–2.37 (m, 5H, H-8α, H-8β, H-10α, H-15ax, H-16ax), 2.33 (s, 3H, *N*-Me), 2.52 (m, 1H, H16-eq), 2.69 (d, 1H, H-9), 3.11 (d, 1H, H-10β), 3.50 (s, 3H, 6-OMe), 4.05 (d, 1H, H-18α), 4.74 (s, 1H, H-5), 6.53 (dt, 1H, H-1), 6.69 (d, 1H, H-2); ^{13}C NMR δ 144.59, 138.12, 132.60, 127.49, 119.85, 116.72, 95.20, 85.11, 84.78, 69.40, 62.06, 52.65, 50.85, 48.17, 45.37, 44.50, 43.57, 39.77, 36.94, 34.18, 29.02, 27.44, 22.14, 18.46; IR ν 3490 (OH) cm^{-1}.

(−)-Ethyl 4,5α-epoxy-3-hydroxy-17-methyl-6α,14α-ethenoisomorphinan-7α-carboxylate (23a). (−)-Ethyl 4,5α-epoxy-3-methoxy-17-methyl-6α,14α-ethenoisomorphinan-7α-carboxylate[28] (1.5 g, 3.9 mmol) was dissolved in chloroform (50 mL) and cooled to 0 °C. Boron tribromide (1.5 g) was added dropwise and after the addition the reaction mixture was stirred for 30 min. The excess of boron tribromide was decomposed by slowly adding absolute ethanol (50 mL, exothermic reaction) and the solvents were removed in vacuo. The residue was dissolved in 50 mL of absolute ethanol and the solvent was removed in vacuo. This procedure was repeated in total three times. Finally, the residue was purified by two recrystallizations from absolute ethanol. Yield of **23a**. HBr 756 mg (1.7 mmol, 43%). An analytical sample was converted into its HCl-salt and recrystallized from ethanol: mp >260 °C dec (**23a**.HCl); calcd for $C_{22}H_{25}NO_4$·HCl (403.91): C 65.42; H 6.49; N 3.47, found C 65.7; H 6.4; N 3.7; $[\alpha]_D^{25}$ −118° (*c* 1.00 in H_2O); MS *m*/*z* 367 (M, 20); ^{1}H NMR (free base) δ 1.22 (t, 3 H, CH_2CH_3), 1.45 (dd, 1 H, H-8α), 1.81 (m, 1 H, H-15eq), 1.95 (ddd, 1 H, H-15ax), 2.38 (s, 3 H, *N*-Me), 2.39 (m, 1 H, H-10α), 2.45 (m, 1 H, H-16ax), 2.56 (dd, 1 H, H-16eq), 2.62 (m, 1 H, H-7β), 2.88 (dd, 1 H, H-8β), 3.19 (d, 1 H, H-9), 3.23 (d, 1 H, H-10), 3.26 (m, 1 H, OH), 4.10 (dq, 2 H, CH_2CH_3), 4.53 (d, 1 H, H-5β), 5.55 (d, 1 H, H-19), 5.73 (dd, 1 H, H-18), 6.47 (d, 1 H, H-1), 6.58 (dd, 1 H, H-2); ^{13}C NMR (free base) δ 174.17, 146.76, 138.38, 137.46, 134.42, 127.84, 124.35, 119.72, 116.12, 94.21, 60.78, 60.40, 45.75, 45.61, 43.57, 43.23, 39.23, 38.47, 33.00, 27.58, 22.53, 14.96; IR ν 3100 (OH), 1725 (C=O) cm^{-1}.

Receptor assays

Receptor binding studies were conducted on Hartley guinea pig membranes using standard procedures at SRI. Guinea pigs were decapitated and the brains quickly removed and weighed, then homogenized in 50 mM Tris HCl pH 7.5, using a Polytron homogenizer. The homogenate was centrifuged at 40,000 *g* for 15 min, rehomogenized and centrifuged once more. The final pellet was resuspended in Tris HCl, pH 7.5, at a final concentration of 6.67 mg original wet weight per mL. This crude membrane preparation was used for determination of binding to each receptor site. Assays were conducted using [^{3}H]DAMGO (μ), [^{3}H]Cl-DPDPE (δ), [^{3}H]69,593 (κ_1), and [^{3}H]NalbzOH (κ_3).[47] The affinity for κ_2 was determined by displacement of [^{3}H]bremazocine in the presence of 100 nM DAMGO, DPDPE and U69,593 to block μ, δ, and κ receptors, respectively. Brain membranes (1.8 mL of homogenate) were incubated with 0.1 mL of the test compounds at concentrations ranging from 10^{-5} to 10^{-10} nM for 1 h at 25 °C. After incubation, samples were filtered through glass fibres on 48-well Brandell cell harvester. Filters were left overnight in plastic scintillation vials, containing 5 mL of scintillation fluid, before the radioactivity levels were determined. Nonspecific binding was determined by using 1.0 μM of the unlabelled counterpart of each radioligand. Full characterization of compounds included two full inhibition curves and analysis for IC_{50} values and Hill coefficients by using the program ALLFIT.

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References and Notes

1. (a) Casy, A.; Parfitt, R. T. *Opioid Analgesics*; Plenum Press: New York, 1986. (b) Lenz, G. R.; Evans, S. M.; Walters, D. E.; Hopfinger, A. J. *Opiates*; Academic Press: Orlando, 1986.
2. Cherny, N. I. *Drugs* **1996**, *51*, 713.
3. Meert, T. F. *Pharm. World & Sci.* **1996**, *18*, 1.
4. Bentley, K. W.; Hardy, D. G. *J. Am. Chem. Soc.* **1967**, *89*, 3267.
5. Bentley, K. W. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1975; pp 75–125.
6. Lewis, J. W.; Bentley, K. W.; Cowan, A. *Ann. Rev. Pharmacol.* **1971**, *11*, 241 and references cited therein.
7. Katsumata, S.; Minami, M.; Nakagawa, T.; Iwamura, T.; Satoh, M. *Eur. J. Pharmacol.* **1995**, *291*, 367.
8. (a) Shen, K-F.; Crain, S. M. *Brain Res.* **1994**, *636*, 286. (b) Shen, K-F.; Crain, S. M. *Brain Res.* **1997**, *757*, 176.
9. Qin, B-Y. *New Drugs and Clin. Remedies* **1993**, *12*, 119.
10. (a) Huang, M.; Wang, D. X.; Qin, B-Y. *Regul. Pept.* **1994**, Suppl. 1, S81. (b) Qin, B-Y.; Wang, D. X.; Huang, M. *Regul. Pept.* **1994**, Suppl. 1, S293. (c) Qin, B-Y.; Huang, M.; Zhang, Y. C.; Miao, H. *Regul. Pept.* **1994**, *54*, 237.
11. Jacobson, A. E. Personal communication.
12. WHO Expert Committee on Dependence-producing Drugs, 15th Report, *World Health Organization Technical Report* **1966**, *343*, pp 1–18.
13. Niwa, M.; al-Essa, L. Y.; Ohta, S.; Kohno, K.; Nozaki, M.; Tsurumi, K.; Iwamura, T.; Kataoka, T. *Life Sci.* **1995**, *56*, PL 395.

14. (a) Tokuyama, S.; Takahashi, M.; Kaneto, H. *Biol. Pharm. Bull.* **1993**, *16*, 774. (b) Tokuyama, S.; Nakamura, F.; Takahashi, M.; Kaneto, H. *Biol. Pharm. Bull.* **1994**, *17*, 1056.
15. (a) Martin, T. J.; Kim, S. A.; Harris, L. S.; Smith, J. E. *Eur. J. Pharmacol.* **1997**, *324*, 141. (b) Aceto, M. D.; Harris, L. S.; Bowman, E. R. *Eur. J. Pharmacol.* **1997**, *338*, 215.
16. Dhawan, B. N.; Cesselin, F.; Raghubir, R.; Reisine, T.; Bradley, P. B.; Portoghese, P. S.; Hamon, M. *Pharmacol. Rev.* **1996**, *48*, 567.
17. Schmidhammer, H.; Schratz, A.; Schmidt, C.; Patel, D.; Traynor, J. R. *Helv. Chim. Acta.* **1993**, *76*, 476, and references cited therein.
18. Freye, E.; Neruda, B.; Smith, O. W. *Arzneim-Forschung/ Drug Res.* **1997**, *47*, 6.
19. Childers, S. R. *Curr. Biol.* **1997**, *7*, R 695, and references cited therein.
20. Barton, J. W.; Coop, A.; Lewis, J. W. *Tetrahedron Lett.* **1993**, *34*, 6777.
21. Coop, A.; Grivas, K.; Husbands, S.; Lewis, J. W.; Porter, *J. Tetrahedron Lett.* **1995**, *36*, 1689.
22. Coop, A.; Grivas, K.; Husbands, S.; Lewis, J. W. *Tetrahedron* **1995**, *51*, 9681.
23. Marton, J.; Hosztafi, S.; Berenyi, S.; Simon, C.; Makleit, S. *Monatsh. Chem.* **1994**, *125*, 1229.
24. (a) Marton, J.; Miklos, S.; Hosztafi, A.; Makleit, S. *Synth. Commun.* **1995**, *25*, 829. (b) Marton, J.; Simon, C.; Hosztafi, S.; Szabo, Z.; Marki, A.; Borsodi, A.; Makleit, S. *Bioorg. Med. Chem.* **1997**, *5*, 369.
25. Hutchins, C. W.; Cooper, G. K.; Purro, S.; Rapoport, H. *J. Med. Chem.* **1981**, *24*, 773.
26. Knipmeyer, L. L.; Rapoport, H. *J. Med. Chem.* **1985**, *28*, 461.
27. Crabbendam, P. R.; Maat, L.; Beyerman, H. C. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 293.
28. Crabbendam, P. R.; Lie, T. S.; Linders, J. T. M.; Maat, L. *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 296.
29. Linders, J. T. M.; Kokje, J. P.; Overhand, M.; Lie, T. S.; Maat, L. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 449.
30. Linders, J. T. M.; Briel, P.; Fog, E.; Lie, T. S.; Maat, L. *Recl. Trav. Chim. Pays-Bas* **1989**, *108*, 268.
31. Woudenberg, R. H.; Lie, T. S.; Maat, L. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 353.
32. Woudenberg, R. H.; Oosterhoff, B. E.; Lie, T. S.; Maat, L. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 119.
33. Woudenberg, R. H.; Maat, L. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 113.
34. Woudenberg, R. H.; Lie, T. S.; Maat, L. *J. Org. Chem.* **1993**, *58*, 6139.
35. Gosh, A. C.; Portlock, D. E.; Dalzell, H. C.; Malmberg, C.; Herlihy, P.; Razdan, R. K.; Duax, W. L.; Smith, G. D. *J. Org. Chem.* **1983**, *48*, 4137.
36. Gates, M.; Boden, R. M.; Sundararaman, P. *J. Org. Chem.* **1989**, *54*, 972.
37. Kopcho, J. J.; Schaeffer, J. C. *J. Org. Chem.* **1986**, *51*, 1620.
38. Lewis, J. W.; Readhead, M. J.; Selby, I. A.; Smith, A. C. B.; Young, C. A. *J. Chem. Soc. C* **1971**, 1158.
39. Beyerman, H. C.; Lie, T. S.; Maat, L.; Noordam-Weisdorf, M. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 455.
40. (a) Jacobson, A. E. Personal communication. (b) Jacobson, A. E. Personal communication. (c) Aceto, M. D.; Harris, L. S.; May, E. L. In *Problems of Drug Dependence 1983, NIDA Research Monograph 49*; Harris, L. S., Ed.; Washington, D. C., 1984; pp 368–420.
41. Lewis, J. W.; Mayor, P. A.; Haddlesey, D. I. *J. Med. Chem.* **1973**, *16*, 12.
42. Maurer, P. J.; Rapoport, H. *J. Med. Chem.* **1987**, *30*, 2016.
43. Hutchins, C. W.; Rapoport, H. *J. Med. Chem.* **1984**, *27*, 521.
44. Berenyi, S.; Toth, A.; Sepsi, A.; Zekany, A.; Gyulai, S.; Makleit, S. *Med. Chem. Res.* **1995**, *5*, 26.
45. Aceto, M. D.; Bowman, E. R.; Harris, L. S.; May, E. L. In *Problems of Drug Dependence 1995, NIDA Research Monograph 162*; Harris, L. S., Ed.; Washington, D. C., 1996; pp 408–468.
46. Woods, J. H.; Medzihradsky, F.; Smith, C. B.; Butelman, E. R.; Winger, G. D. *Problems of Drug Dependence 1995, NIDA Research Monograph 162*; Harris, L. S., Ed.; Washington, D. C., 1996; pp 377–407.
47. Clark, J. A.; Liu, L.; Price, M.; Hersh, B.; Edelson, M.; Pasternak, G. V. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 461.