The first synthesis of 3-deoxyoripavine and its utilization in the preparation of 10-deoxyaporphines and cyprodime

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This paper is dedicated to the memory of Prof. Sándor Makleit who passed away on 27.09.2012

Abstract - The synthesis of 3-deoxyoripavine (**7**) was realized as a novel and promising intermediate towards the synthesis of the important class of dopaminergic and/or serotonergic 10-deoxyaporphines and the special pharmacological tool μ opioid antagonist cyprodime. Generally, the preparation of these valuable biologically active compounds was achieved in remarkable yields.

The synthesis and neuropharmacological characterization of 10-deoxyapomorphine derivatives are a new and important direction in the development of potent and subtype selective dopaminergic and/or serotonergic ligands [1-6]. Currently all the synthetic methods towards deoxyapomorphines are based on the preparation of 3-*O*-(trifluoromethyl)sulfonyl-morphine (**2**) or -oripavine (**5**), the acid-catalyzed rearrangement of these morphinans into aporphinoids and further manipulations on the sensitive aporphine backbone. Earlier procedures involved the synthesis and transformation of 3-(1-phenyltetrazoyl)morphine (**3**) [7, 8], however the rearrangement of this compound gave rise to a mixture of aporphines and the hydrogenolytic removal of the (phenyltetrazolyl)oxy moiety from the aporphines was reported to be 'erratic and capricious' in both catalytic hydrogenolysis reactions and in catalytic hydrogen-transfer reactions [8, 9].

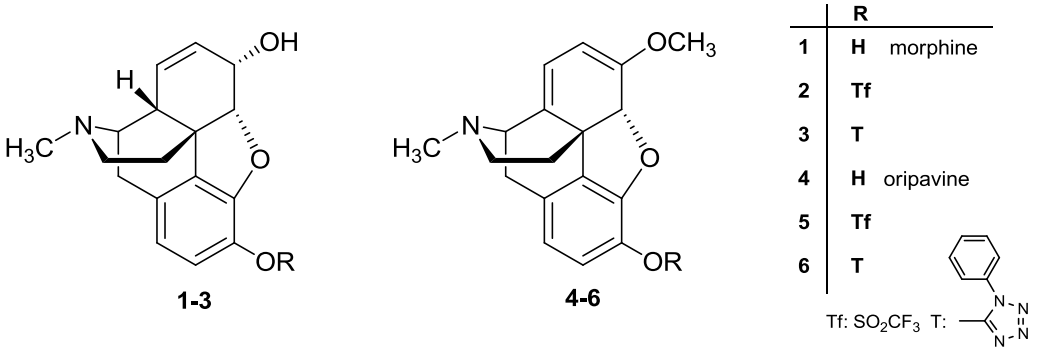

Figure 1. Structure of morphinans currently used for the synthesis of 10-deoxyapomorphines

Here we report a new, efficient and versatile route to 10-deoxyaporphines based on hitherto

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Keywords: oripavine, cyprodime, 10-deoxyaporphines, reduction, acid-catalyzed rearrangement.
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unknown 3-deoxyoripavine (**7**). The practical significance of this procedure is even higher due to the fact that the starting derivative of our procedure, oripavine (**4**), is one of the major industrial poppy alkaloids [10-12].
Towards the synthesis of 3-deoxyoripavine (**7**) we identified in view of literature two potential starting materials; either the 3-*O*-(trifluoromethyl)sulfonyl- **5** or 3-*O*-(1-phenyltetrazoyl)-derivatives **6** of the parent alkaloid **4**. The challenge in the preparation of the 3-deoxy derivative was to find an appropriate hydrogenolytic procedure active enough to remove the 3-etheral moiety but keep unaffected the conjugated diene system of ring C known to be especially sensitive to reductive and acidic conditions [11]. The phenyltetrazoyl ether **6** was prepared in excellent yields (94%) from oripavine (**4**) according to the protocol used for the synthesis of the similar morphine ether [7]. The procedure, in which the free base of **4** and 5-chloro-1-phenyl-*1H*-tetrazole was refluxed in acetone in the presence of K_2CO_3, resulted white crystals allowing us to perform X-ray analysis (Fig. 2, CCDC 860893) of the 3-etheral region of the molecule in view of a previous study [13]. The C3-O bond length is 1.413Å, and the C3-O-C bond angle was 116.6^o which are close the average values determined by Johnstone et al. [13] for a series of tetrazoyl ethers used for the removal of phenolic OH function.

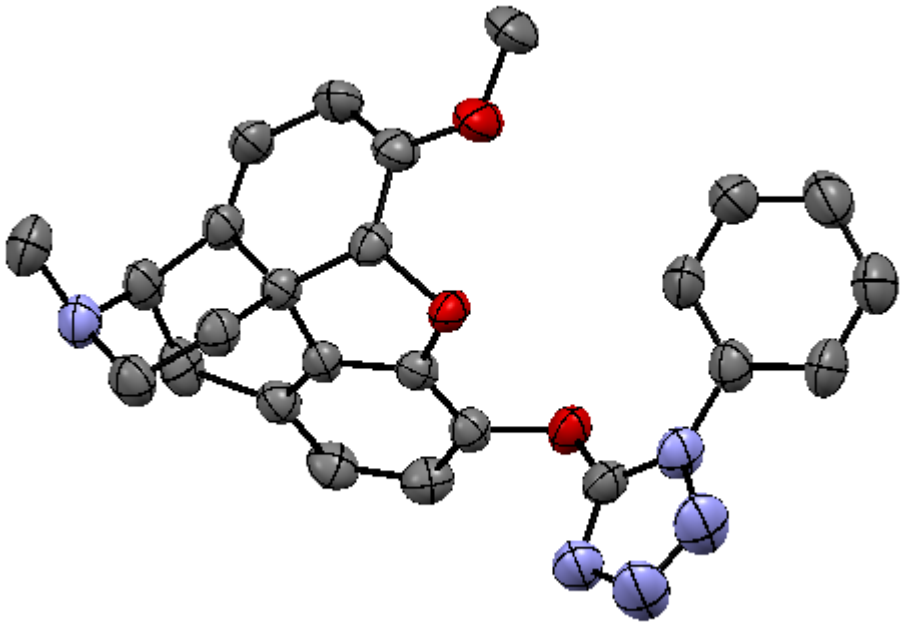
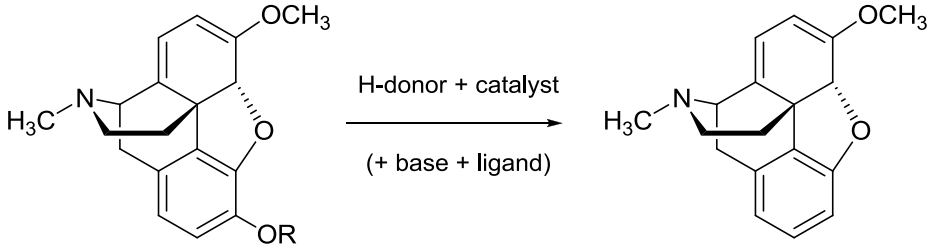


Figure 2. X-ray structure of compound **6**, showing 50% probability displacement ellipsoids (H atoms omitted for clarity)

This study confirmed that compound **6** is a promising starting derivative for the synthesis of 3-deoxyoripavine (**7**) on the basis of the determining parameters deduced of Johnstone's group [14-17]. The alternative starting compound of the aimed deoxygenated oripavine **7** was the 3-*O*-[(trifluoromethyl)sulfonyl]oripavine (**5)** prepared according to the literature procedure in 75% yield [2].
There were several potential hydrogenolytic conditions identified in the literature, however, as it was referred, finding the appropriate reductive capacity and acidity of the applied conditions was the real task of a complex optimization procedure. This procedure is summarized in Table 1 focusing on the most relevant steps.

Table 1. Results of the hydrogenolysis reactions aiming 3-deoxyoripavine (**7**)



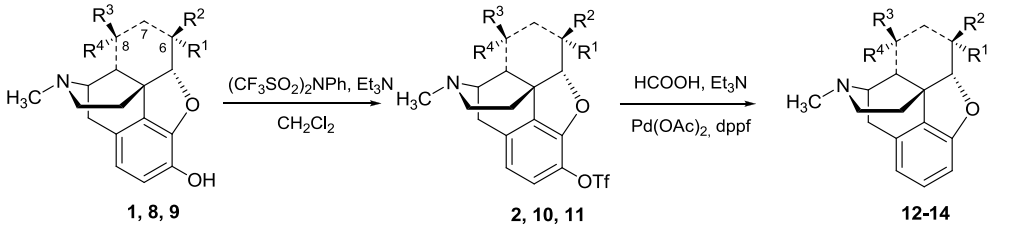
5 or **6** **7**

Reactions	Starting diene	H-donor	Catalyst	Base	Ligand	Isolated yield (%) of **7**	Reference to the procedure
1	**6**	$NH_2NH_2.H_2O$[a]	10% Pd/C	-	-	5	14, 15
2	**6**	NaH_2PO_2[b]	10% Pd/C	-	-	7	15
3	**6**	1,4-cyclohexadiene[c]	10% Pd/C	-	-	17	15
4	**5**	HCOOH[d]	$Pd(OAc)_2$	Et_3N	PPh_3	37	18
5	**5**	HCOOH[d]	$Pd(OAc)_2$	Et_3N	dppf	49	18
6	**5**	(MeOH)[e]	10% Pd/C - Mg	-	-	15	19
7	**5**	$HCOONH_4$, (MeOH)[e]	10% Pd/C - Mg	-	-	43	19
8	**5**	$HCOOH+Et_3N$[f]	$Pd(OAc)_2$	Et_3N	dppf	92	20

[a]Two-phase system of toluene:ethanol:water=7:3:2, r.t., 1.5 h, under argon. [b]0.4M aquoeous solution of NaH_2PO_2, toluene:ethanol=7:3, reflux (ca. 70°C) under argon, 1h. [c]Refluxing methanol under argon, 1.5 h; [d]0.2 eq. $Pd(OAc)_2$, 3 eq. Et_3N, 0.4 eq. phosphine [dppf=1,1'-bis(diphenylphosphino)-ferrocene], 2 eq. 99% HCOOH, DMF, 60°C, under argon, 1h. [e]1 eq. $HCOONH_4$, 1.2 eq. Mg in carefully deoxygeneted abs. MeOH under argon, r.t., 2h. [f]2.5 eq. HCOOH, 3.8 eq. Et_3N, 0.1 eq. $Pd(OAc)_2$, 0.15 eq. dppf, DMF under argon, 60°C, 12 h.

The hydrogenolysis of the tetrazoyl ethers is usually achieved by catalytic hydrogenation; however this route was ruled out as a potential method on the basis of literature reports [21]. The hydrogenolysis of morphine-3-tetrazoyl ether resulted 3-deoxydihydromorphine and it is well known that the reductive stability of morphine-type alkaloids is considerably higher than the same for oripavine-type diene structures. Therefore, several attempts were made for the selective transfer hydrogenation of tetrazoyl moiety with different hydrogen donors. As it can be concluded from Table 1, these methods gave rise to the expected compound in poor yields (Entries 1 &2). In case of hydrazine the crude reaction mixture contained fully and partially saturated morphinans without 3-OH function besides the aimed compound **7**. The application of sodium hypophosphite led to a very complex mixture with partially saturated morphinans. The most promising attempts were made with 1,4-cyclohexadiene as H-donor. Besides 17% of target 3-deoxyoripavine (**7**) the mixture of partially saturated morphinans with unprotected 3-OH functions were also obtained. Generally the procedures based on 3-*O*-[(trifluoromethyl)sulfonyl]oripavine (**5**) proved to be a promising starting compound in view of the Pd-catalyzed deoxygenating methods. The application of formic acid in the presence of $Pd(OAc)_2$, triethylamine and triphenylphosphine led to compound **7** in 37% yield (Entry 4), however the use of sterically more demanding dppf resulted higher yield (49%) probably due to a steric hindrance towards ring C of the skeleton. Palladium-on-charcoal with magnesium metal in methanol gave rise to low amount of product besides a mixture of saturated morphinans. It was suggested that the application of ionic additives could improve efficacy and required reaction time [19]. In the course of those experiments ammonium acetate was found to be the best; however in our hands the use of ammonium formate resulted the highest conversion into the desired compound. It is interesting to note that according to the plausible mechanism suggested by Mori et al. methanol is an indirect H-donor interacting with magnesium [19]. The most efficient procedure for the synthesis of targeted product **7** (92%,

Entry 8) was the one formic acid and an excess of triethylamine in the presence of $Pd(OAc)_2$ and dppf. In case of replacing dppf with PPh_3 gave rise to considerably lower yields.
In order to further investigate the performance and conformity of our best conditions with different electronic systems in ring C, we synthesized the corresponding triflates of morphine (**1**), γ-isomorphine (**8**) and neomorphine (**9**) according to the method described for the synthesis of (-)-3-*O*-[-(trifluoromethyl)sulfonylmorphine (**2**) [1]. On the basis of the difference in the substitution pattern and electronic structure of the ring C of γ-isomorphine (**8**) [22] and neomorphine (**9**) [23] these compounds considered as hydroxylated metabolites of morphine (**1**) itself [24]. The triflate formation of alkaloids **1**, **8** and **9** (Scheme **1**) was performed in excellent yields (84-91%).

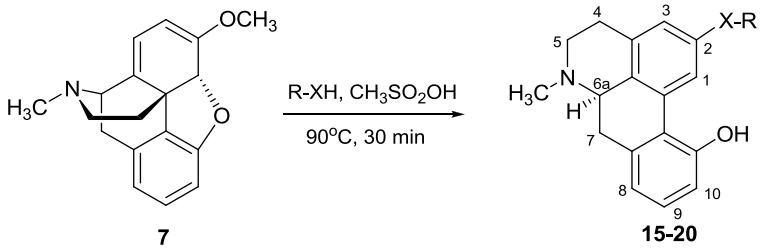


1, 8, 9 **2, 10, 11** **12-14**

	R^1	R^2	R^3	R^4	Position of C=C
1, 2, 12	OH	H	H	H	C7-C8
8, 10, 13	H	H	OH	H	C6-C7
9, 11, 14	OH	H	H	H	C8-C14

Scheme 1. Synthesis of 3-deoxymorphinans

The previously presented methodology (Table 1, Entry 8) for the hydrogenolysis of 3-*O*-triflate function was successfully applied for compounds **2**, **10**, **11** giving rise to the expected 3-deoxygenated morphinans **12-14** in 85-91% yields. The formation of products with saturated ring C of the morphinan skeleton was not observed. Therefore it can be stated that the substitution pattern and the position of the double bond in ring C are not limiting factors of the application of the 3-deoxygenation of morphinans.
As it was referred previously, one of the main areas for the utilization of new 3-deoxyoripavine (**7**) was the acid-catalyzed rearrangement into 10-deoxyaporphines exploiting all the accumulated knowledge regarding this procedure [25].



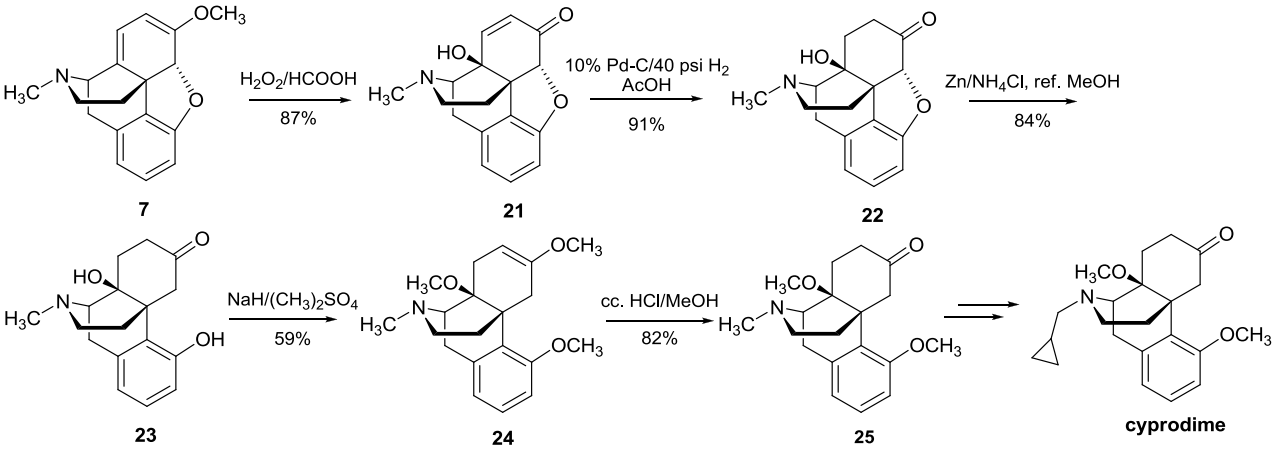
7 **15-20**

	R-X	Yield (%)	Ref.
15	OH	74	26, 27
16	OCH_3	89	3, 28
17	OCH_2CH_3	86	28
18	$O(CH_2)_2F$	78	6
19	SCH_2CH_3	91	-
20	$S(CH_2)_2CH_3$	84	-

Scheme 2. Synthesis of 2-substituted-11-hydroxyaporphines, the isolated yields for products **15-20** and the literature references for known compounds

The data summarized in Scheme 2 suggest that the acid-catalyzed rearrangement could be realized starting from deoxymorphinandiene **7** rather than from morphine (**1**) or oripavine (**4**) as in this new method no catechol system is involved. This catechol system often leads to the appearance of oxidized by-products [29]. These side-products make the work-up procedure difficult and contribute to the decrease of isolated yields. In these cases the average isolated yields of three runs were found to be good to excellent. Taking into consideration the high

yileding 3-*O*-triflation of oripavine and 3-deoxygenation of compound **5**, the overall yields for this series of 10-deoxyaporphines **15-20** were in the range of 51-62%.
Cyprodime [30] is a prototypical, selective μ opioid antagonist which is still the target of intense pharmacological research in part because of the availability of its tritium-labelled derivative [31]. The original synthesis of the cyprodime was based on the preparation of key intermediate **25** from oxymorphone, an expensive semi-synthetic major analgesic, in 6 steps [30, 32]. The structure of compound **7** offers the shortening of this procedure as it is presented in Scheme 3.



Scheme 3. New route to key intermediate **25** of the synthesis of cyprodime

All these standard synthetic steps were performed in accordance with a previous report on the alternative synthesis of cyprodime [33]. The overall yield for key intermediate **25** was 32% in the present 5-step study. Interestingly, it was possible to obtain the trimethoxymorphinan **24** in average yield (59%) under usual *O*-methylation conditions [31] in the presence of 5 equivalents of NaH and $(CH_3)_2SO_4$. The position of the double bond in ring C was established on the basis of the coupling constants of H7.

Conclusion

In conclusion, the preparation of 3-deoxyoripavine (**7**) was achieved starting from both 3-*O*-(5-phenyltetrazoil)ether and the 3-*O*-triflate of oripavine. The optimization of the hydrogenolitic conditions resulted in a highly efficient procedure yielding 92% of the desired compound **7**. The methodology was extended for morphine (**1**) and its isomers and found to be a useful route to 3-deoxymorphinans without change in the electronic system of ring C. It was recognized that 3-deoxyoripavine (**7**) was a valuable starting product towards the synthesis of the important class of dopaminergic and serotonerg 10-deoxyaporphines and the special pharmacological tool μ opioid antagonist cyprodime.

Experimental

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 dichloromethane:methanol = 8:2 mobile phase. The spots were visualized with Dragendorff's reagent. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer; chemical shifts are reported in parts per million (δ) from internal TMS and coupling constants (*J*) are measured in hertz. Mass spectral measurements were performed

with a Bruker micrOTOF-Q instrument in the ESI mode. Elemental analyses (C, H) were obtained on a Carlo Erba EA1108 analyzer.

Procedure for the formation of 3-*O*-[(trifluoromethyl)sulfonyl]morphinans
A suspension of the alkaloid (9.20 mmol) and Et_3N (1.92 mL, 13.8 mmol) in CH_2Cl_2 (150 mL) kept under nitrogen was stirred for 1 h at room temperature. *N*-Phenyl-trifluoromethanesulfonimide (3.94 g, 11.0 mmol) was added, and after being stirred for 48 h, the reaction mixture was extracted with 10% aqueous $NaHCO_3$. The organic layer was dried (K_2CO_3), filtered, and concentrated *in vacuo*. The oily residue was subjected to column chromatography.

3-*O*-[(Trifluoromethyl)sulfonyl]morhpine (2)
Physical and spectral data were fully in agreement with previously published data [1].

3-*O*-[(Trifluoromethyl)sulfonyl]oripavine (5)
Physical and spectral data were fully in agreement with previously published data [2].

γ-Isomorphine (8)
Physical data were fully in agreement with previously published data [22].
Calculated for free base $C_{17}H_{19}NO_3$: C, 71.56; H, 6.61; found: C, 71.49; H, 6.71; MS (ESI) m/z 285.1 ($M+H^+$), calculated for $C_{17}H_{20}NO_3^+$: 285.2; ^{1}H-NMR (DMSO-d_6) δ=9.33 (s, 1H, OH), 6.62 (dd, 2H, H1, H2, $J_{1\text{-}2}$=8.1), 5.88 (dd, 1H, H7, $J_{7\text{-}6,\ 7\text{-}8\alpha}$ =10.9, 1.8), 5.63 (dd, 1H, H6, $J_{6\text{-}7,\ 6\text{-}5\alpha}$ =10.9, 2.1), 5.09 (d, 1H, H5β, $J_{5\beta\text{-}6}$=2.4), 4.09 (m, 1H, H8α), 3.12 (dd, 1H, H10α, $J_{10\alpha\text{-}10\beta,\ 10\alpha\text{-}9}$=18.1, <2), 2.65-2.19 (m, 7H, H10β, H9, H16α, H16β, NCH_3), 1.98 (m, 2H, H15β, H14), 1.84 (ddd, 1H, H15α, J =5.2, <2, <2). ^{13}C-NMR (DMSO-d_6) δ=144.4, 140.1, 138.3, 129.4, 126.1, 125.4, 120.0, 118.2, 85.8, 63.5, 58.1, 47.5, 45.8, 45.1, 43.8, 32.8, 21.1.

Neomorphine (9)
Physical data were fully in agreement with previously published data [23].
Calculated for free base $C_{17}H_{19}NO_3$: C, 71.56; H, 6.61; found: C, 71.51; H, 6.79; MS (ESI) m/z 285.2 ($M+H^+$), calculated for $C_{17}H_{20}NO_3^+$: 285.2; ^{1}H-NMR (DMSO-d_6) δ=9.21 (s, 1H, phenolic OH), 6.69 (dd, 2H, H1, H2, $J_{1\text{-}2}$=7.8), 5.48 (dd, 1H, H8, $J_{7\alpha\text{-}8,\ 7\beta\text{-}8}$=3.4, 2.2), 4.64 (d, 1H, H5, $J_{5\beta\text{-}6\beta}$=5.3), 4.26 (dd, 1H, H6β, $J_{6\beta\text{-}5\beta,\ 7\beta\text{-}5\beta}$=5.1, <2), 3.69 (m, 1H, H9), 3.19-2.82 (m, 3H, H10α, H10β, H16α), 2.44-2.21 (m, 6H, H7α, H7β, H16β, NCH_3), 1.96 (ddd, 1H, H15β, J=5.2, >2, >2), 1.81 (ddd, 1H, H15α, J =5.2, >2, >2). ^{13}C-NMR (DMSO-d_6) δ=146.4, 142.1, 137.7, 131.2, 127.3, 124.7, 119.2, 113.4, 87.4, 66.8, 56.0, 49.1, 47.0, 43.4, 41.0, 35.4, 20.1.

6,7-Didehydro-8β-hydroxy-17-methyl-3-*O*-[(trifluoromethyl)sulfonyl]-4,5-epoxymorphinan (10)
Yield: 87%; colourless oil; calculated for free base $C_{18}H_{18}N_5F_3O_5S$: C, 51.80; H, 4.35; found: C, 51.61; H, 4.61; MS (ESI) m/z 418.1 ($M+H^+$), calculated for $C_{18}H_{19}N_5F_3O_5S^+$: 418.1; ^{1}H-NMR ($CDCl_3$) δ=6.75 (d, 1H, H1, $J_{1\text{-}2}$=8.1), 6.67 (d, 1H, H2, $J_{1\text{-}2}$=8.1), 5.79 (dd, 1H, H7, $J_{7\text{-}6,\ 7\text{-}8\alpha}$ =11.4, 2.0), 5.60 (dd, 1H, H6, $J_{6\text{-}7,\ 6\text{-}5\alpha}$ =11.4, 2.1), 5.12 (d, 1H, H5β, $J_{5\beta\text{-}6}$=2.2), 3.99 (m, 1H, H8α), 3.17 (dd, 1H, H10α, $J_{10\alpha\text{-}10\beta,\ 10\alpha\text{-}9}$=16.8, <2), 2.71-2.09 (m, 7H, H10β, H9, H16α, H16β, NCH_3), 1.91 (m, 2H, H15β, H14), 1.80 (ddd, 1H, H15α, J =5.2, <2, <2). ^{13}C-NMR ($CDCl_3$) δ=145.1, 140.1, 137.1, 128.6, 127.2, 125.1, 120.7, 119.4 (q, $J_{C\text{-}F}$=318 Hz), 113.5, 84.9, 63.3, 57.6, 47.1, 46.0, 45.2, 43.8, 32.6, 21.2.

8,14-Didehydro-6α-hydroxy-17-methyl-3-*O*-[(trifluoromethyl)sulfonyl]-4,5-epoxymorphinan (11)
Yield: 84%. white foam; calculated for free base $C_{18}H_{18}NO_5F_3S$: C, 51.80; H, 4.37; found: C, 51.66; H, 4.47; MS (ESI) m/z 417.1 ($M+H^+$), calculated for $C_{18}H_{19}NO_5F_3S^+$: 417.1; ^{1}H-NMR ($CDCl_3$) δ=7.01 (d, 1H, H2, $J_{1\text{-}2}$=7.9), 6.88 (d, 1H, H1, $J_{1\text{-}2}$=7.9), 5.43 (dd, 1H, H8, $J_{7\alpha\text{-}8,\ 7\beta\text{-}8}$=3.5, 2.0), 4.67 (d, 1H, H5, $J_{5\beta\text{-}6\beta}$=5.1), 4.26 (dd, 1H, H6β, $J_{6\beta\text{-}5\beta,\ 7\beta\text{-}5\beta}$=5.1, <2), 3.55 (m, 1H, H9), 3.13-2.80 (m, 3H, H10α, H10β, H16α), 2.51-2.17 (m, 6H, H7α, H7β, H16β, NCH_3), 1.92 (ddd, 1H, H15β, *J*=5.1, >2, >2), 1.80 (ddd, 1H, H15α, *J* =5.1, >2, >2). ^{13}C-NMR ($CDCl_3$) δ=147.2, 139.9, 137.7, 131.7, 127.3, 120.7, 119.7 (q, $J_{C\text{-}F}$=321 Hz), 114.2, 113.6, 88.0, 66.7, 58.1, 49.1, 46.5, 43.7, 41.0, 35.1, 23.1.

Procedure for the formation of 3-(*O*-1-phenyltetrazol-5-yl)morphinans
A suspension of the alkaloid (35.1 mmol) in 500 mL of acetone was allowed to reflux with 5-chlor-l-phenyl-1*H*-tetrazole (6 .33 g, 35.1 mmol) and K_2CO_3 (10.53 g, 76.3 mmol) for 24 h. The reaction mixture was cooled, diluted with H_2O (500 mL), and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over $MgSO_4$, and filtered. The filtrate, on evaporation to dryness and trituration with ether, gave the 3-*O*-protected alkaloid.

3-(*O*-1-Phenyltetrazol-5-yl)morphine (3)
Physical and spectral data were fully in agreement with previously published data [1].

3-(*O*-1-Phenyltetrazol-5-yl)oripavine (6)
Yield: 92%; white crystals; Mp.: 183-185^{o}C, calculated for free base $C_{25}H_{23}N_5O_3$: C, 68.01; H, 5.25; found: C, 68.10; H, 5.27; MS (ESI) m/z 442.2 ($M+H^+$), calculated for $C_{25}H_{24}N_5O_3^+$: 442.2; ^{1}H-NMR ($CDCl_3$) δ=7.67-7.42 (m, 5H, Ph), 6.62 (dd, 2H, H1-H2, $J_{1\text{-}2}$=8.2), 5.61 (d, 1H, H8, $J_{7\text{-}8}$=6.1), 5.40 (s, 1H, H5), 5.10 (d, 1H, H7, $J_{7\text{-}8}$=6.1), 3.67 (m, 1H, H9), 3.62 (s, 3H, OCH_3), 3.34 (1H, d, H10α, $J_{10\alpha\text{-}10\beta}$= 16.4), 2.84-2.52 (m, 3H, H10β, H16α, H16β), 2,47 (s, 3H, NCH_3), 2.23 (ddd, 1H, H15β, *J*=5.2, >2, >2), 1.76 (ddd, 1H, H15α *J*=5.2, >2, >2). ^{13}C-NMR ($CDCl_3$) δ=160.4, 154.7. 154.0, 152.4, 132.7, 131.2, 130.0, 128.7, 128.4, 127.8, 124.7, 123.4, 120.8, 119.2, 112.5, 96.4, 91.0, 69.8, 56.5, 48.1, 46.8, 42.4, 37.2, 29.1.

Optimized procedure for the hydrogenolysis of 3-*O*-[(trifluoromethyl)-sulfonyl]morphinans
1,1'-Bis(diphenylphosphino)-ferrocene (399 mg, 0.72 mmol) and palladium acetate (114 mg, 0.48 mmol) were added to a stirred mixture of the 3-*O*-[(trifluoromethyl)sulfonyl]morphinan (4.80 mmol), triethylamine (2.56 mL, 18.24 mmol), and formic acid (0.48 mL, 12.00 mmol) in DMF (8 mL) at 60 ^{o}C under argon for 12 h. After cooling to room temperature, the reaction mixture was poured onto 100 mL of water. After extraction with CH_2Cl_2 (4 x 15 mL), the combined organic layers were washed with water (3 x 25 mL), dried (sodium sulfate), filtered, and evaporated. Treatment with boiling ethanol provided the 3-deoxymorphinan.

3-Deoxyoripavine (7)
Yield: 92%; white powder; Mp.: 136-138^{o}C; calculated for free base $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; found: C, 76.88; H, 6.88; MS (ESI) m/z 282.2 ($M+H^+$), calculated for $C_{18}H_{20}NO_2^+$: 282.1; ^{1}H-NMR ($CDCl_3$) δ=7.06 (t, 1H, H2, $J_{1\text{-}2}$=7.3, $J_{2\text{-}3}$=7.3), 7.06 (t, 2H, H1, H3, $J_{1\text{-}2}$=7.3, $J_{2\text{-}3}$=7.3), 5.60 (d, 1H, H8, $J_{7\text{-}8}$=6.4), 5.60 (s, 1H, H5), 5.05 (d, 1H, H7, $J_{7\text{-}8}$=6.4), 3.68 (m, 1H, H9), 3.64 (s, 3H, OCH_3), 3.38 (1H, d, H10α, $J_{10\alpha\text{-}10\beta}$= 16.1) , 2.97-2.62 (m, 3H, H10β, H16α, H16β), 2.52 (s, 3H, NCH_3), 2.24 (ddd, 1H, H15β, *J*=5.2, >2, >2), 1.78 (ddd, 1H, H15α *J*=5.2, >2, >2). ^{13}C-NMR ($CDCl_3$) δ=157.7 (C4), 153.2 (C6), 136.2 (C11), 134.1 (C14), 132.2

(C12), 128.8 (C2), 119.3 (C1), 112.8 (C8), 107.8 (C3), 96.5 (C7), 89.0 (C5), 61.6 (C9), 55.7 (OCH_3), 46.6 (C16), 45.9 (C13), 42.8 (N-CH_3), 37.1 (C15), 31.1 (C10).

7,8-Didehydro-6α-hydroxy-17-methyl-4,5-epoxymorphinan (12)
Yield: 87%. Physical and spectral data were fully in agreement with previously published data [1].

6,7-Didehydro-8β-hydroxy-17-methyl-4,5-epoxymorphinan (13)
Yield: 85%; white powder; Mp.: 127-128°C; calculated for free base $C_{17}H_{19}NO_{22}$: C, 75.81; H, 7.11; found: C, 75.68; H, 7.20; MS (ESI) m/z 270.2 ($M+H^+$), calculated for $C_{17}H_{20}NO_2^+$: 270.1; ^{1}H-NMR ($CDCl_3$) δ=6.81 (t, 1H, H2, $J_{1\text{-}2}$=7.2, $J_{2\text{-}3}$=7.2), 6.59 (t, 1H, H3, $J_{2\text{-}3}$=7.2), 6.48 (t, 1H, H1, $J_{1\text{-}2}$=7.2), 5.84 (dd, 1H, H7, $J_{7\text{-}6,\ 7\text{-}8\alpha}$ =10.3, <2), 5.56 (dd, 1H, H6, $J_{6\text{-}7,\ 6\text{-}5\alpha}$ =10.4, 2.0), 5.10 (d, 1H, H5β, $J_{5\beta\text{-}6}$=2.7), 4.04 (m, 1H, H8α), 3.17 (dd, 1H, H10α, $J_{10\alpha\text{-}10\beta,\ 10\alpha\text{-}9}$=18.6, <2), 2.56-2.20 (m, 7H, H10β, H9, H16α, H16β, NCH_3), 1.93 (m, 2H, H15β, H14), 1.87 (ddd, 1H, H15α, J =5.4, <2, <2). ^{13}C-NMR ($CDCl_3$) δ=157.9, 134.3, 133.0, 131.4, 129.4, 126.1, 120.0, 109.2, 85.4, 63.5, 59.4, 47.3, 46.0, 45.3, 43.3, 32.9, 21.6.

8,14-Didehydro-6α-hydroxy-17-methyl-4,5-epoxymorphinan (14)
Yield: 91%; white powder; Mp.: 144-145°C; calculated for free base $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; found: C, 78.72; H, 7.29; MS (ESI) m/z 270.1 ($M+H^+$), calculated for $C_{17}H_{20}NO_2^+$: 270.1; ^{1}H-NMR ($CDCl_3$) δ=7.02 (t, 1H, H2, $J_{1\text{-}2}$=7.2, $J_{2\text{-}3}$=7.2), 7.06 (t, 2H, H1, H3, $J_{1\text{-}2}$=7.2, $J_{2\text{-}3}$=7.2), 5.46 (dd, 1H, H8, $J_{7\alpha\text{-}8,\ 7\beta\text{-}8}$=3.6, 2.3), 4.67 (d, 1H, H5, $J_{5\beta\text{-}6\beta}$=5.4), 4.19 (dd, 1H, H6β, $J_{6\beta\text{-}5\beta,\ 7\beta\text{-}5\beta}$=5.4, <2), 3.58 (m, 1H, H9), 3.21-2.69 (m, 3H, H10α, H10β, H16α), 2.39-2.15 (m, 6H, H7α, H7β, H16β, NCH_3), 1.91 (ddd, 1H, H15β, J=5.4, >2, >2), 1.81 (ddd, 1H, H15α, J =5.4, >2, >2). ^{13}C-NMR ($CDCl_3$) δ=159.8, 138.7, 134.5, 131.6, 127.3, 119.2, 113.4, 107.6, 87.2, 67.1, 57.5, 48.5, 47.1, 43.5, 41.0, 35.4, 20.1.

Acid-catalyzed rearrangement of 3-deoxyoripavine (7) in the presence of alcohols or thiols
A mixture of **7** (200 mg, 0.71 mmol), methanesulfonic acid (1 ml) and alcohol/thiol (200 µl) was stirred for 30 min at 90 °C. Then the reaction mixture was added dropwise, with stirring and external ice-cooling, to a solution of potassium hydrogen carbonate (2 g) in water (10 ml). After extraction with dichloromethane (3x15 ml), the combined extracts were washed with saturated brine, dried ($MgSO_4$), and concentrated under reducer pressure. The purification of 10-deoxyapomorphines was performed by means of column chromatography (Kieselgel 40, dichloromethane:methanol= 8:2).

The characterizations of the novel morphinans related to the synthesis of cyprodime and new aporphines are presented in the supplementary document.

Acknowledgement
The authors are indebted for the support of the Hungarian Science Fund (NKTH-OTKA K101372) and the Austrian Science Fund (15481 and TRP 19-B18). The research was supported by the EU and co-financed by the European Social Fund under the project ENVIKUT (TÁMOP-4.2.2.A-11/1/KONV-2012-0043).

Supplementary data
Supplementary data associated with this article can be found, in the online version, at xxxxxx. This file includes crystallographic and spectral information of new compounds.

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Graphical Abstract

The first synthesis of 3-deoxyoripavine and its utilization in the preparation of 10-deoxyaporphines and cyprodime

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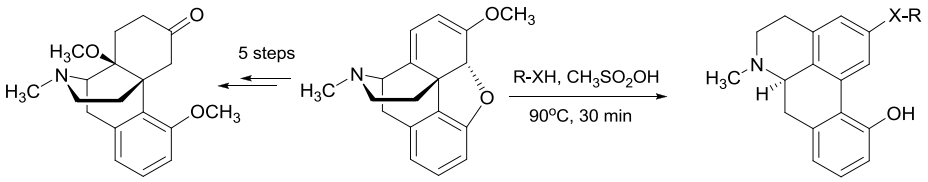

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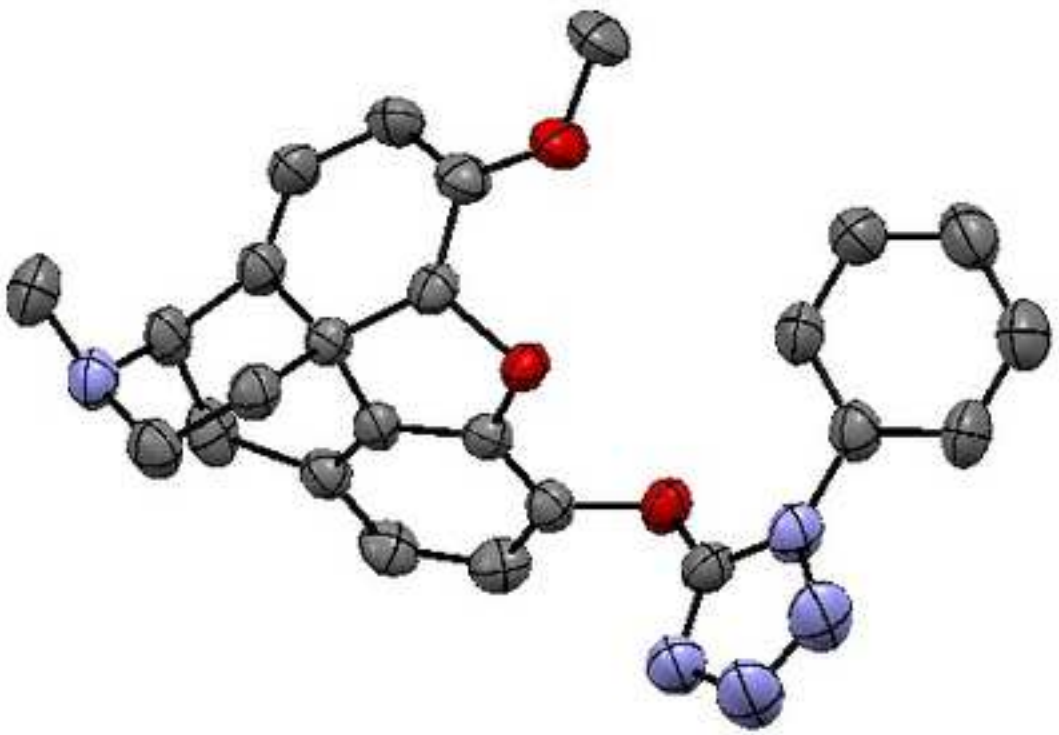

Supplementary material

The first synthesis of 3-deoxyoripavine and its utilization in the preparation of 10-deoxyaporphines and cyprodime

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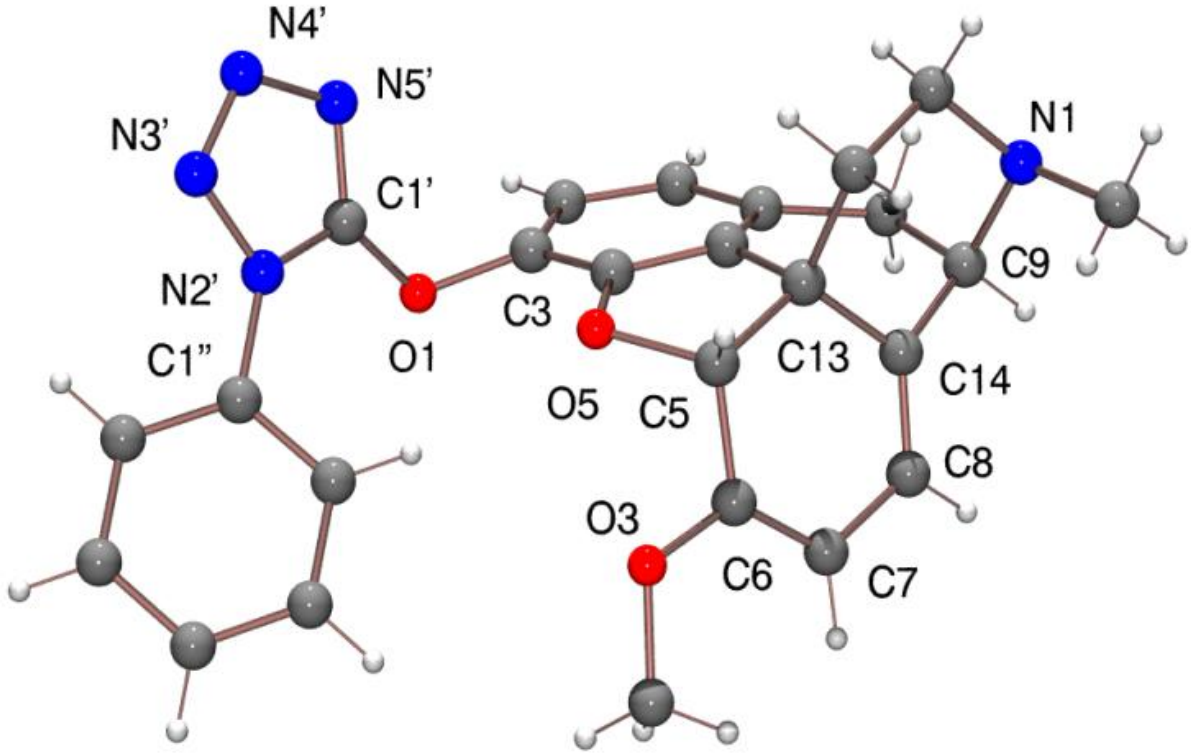
Details of the X-ray crystallographic analysis of compound **6**



Crystal data

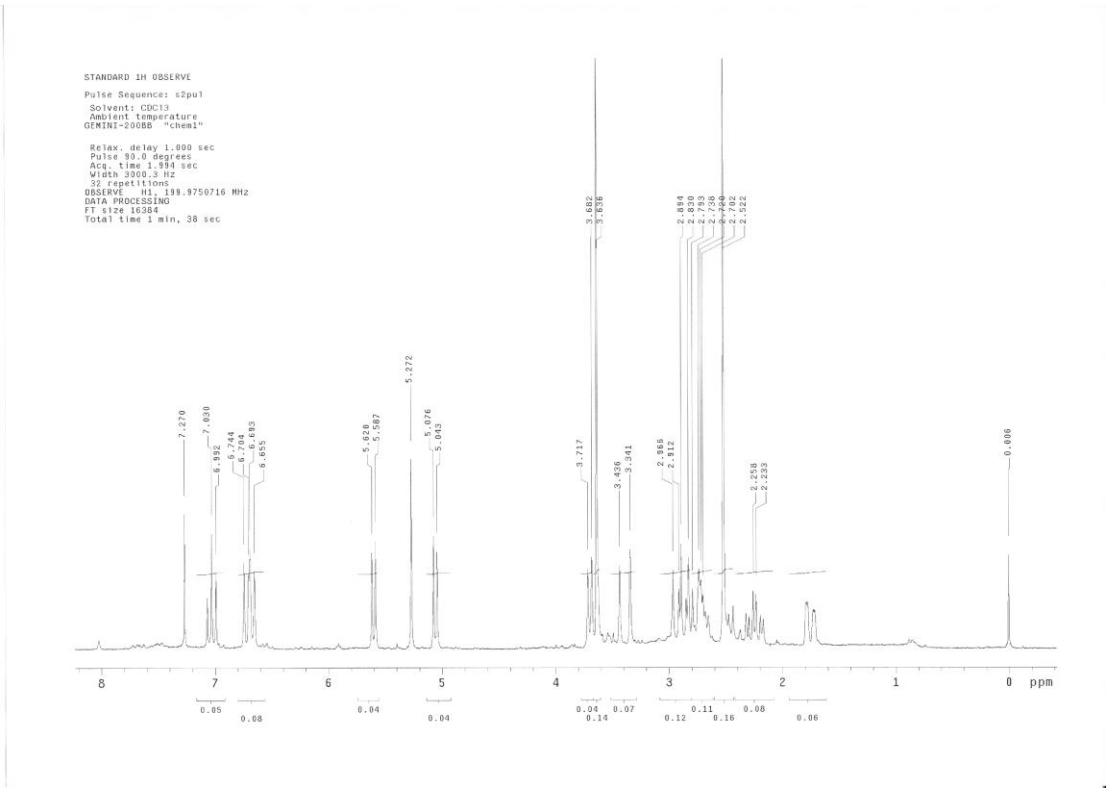
$C_{25}H_{23}N_5O_3$ V = 2157.5 (3) Å^3
Mr = 441.48 Z = 4
Orthorhombic, $P2_12_12_1$ Mo $K\alpha$ radiation, λ = 0.71073 Å
a = 8.226 (1) Å μ = 0.09 mm−1
b = 11.330 (1) Å T = 293 K
c = 23.149 (1) Å 0.54 × 0.32 × 0.2 mm
Data collection
Enraf Nonius MACH3
diffractometer 2007 reflections with $I > 2\sigma(I)$
Absorption correction: ψ scan

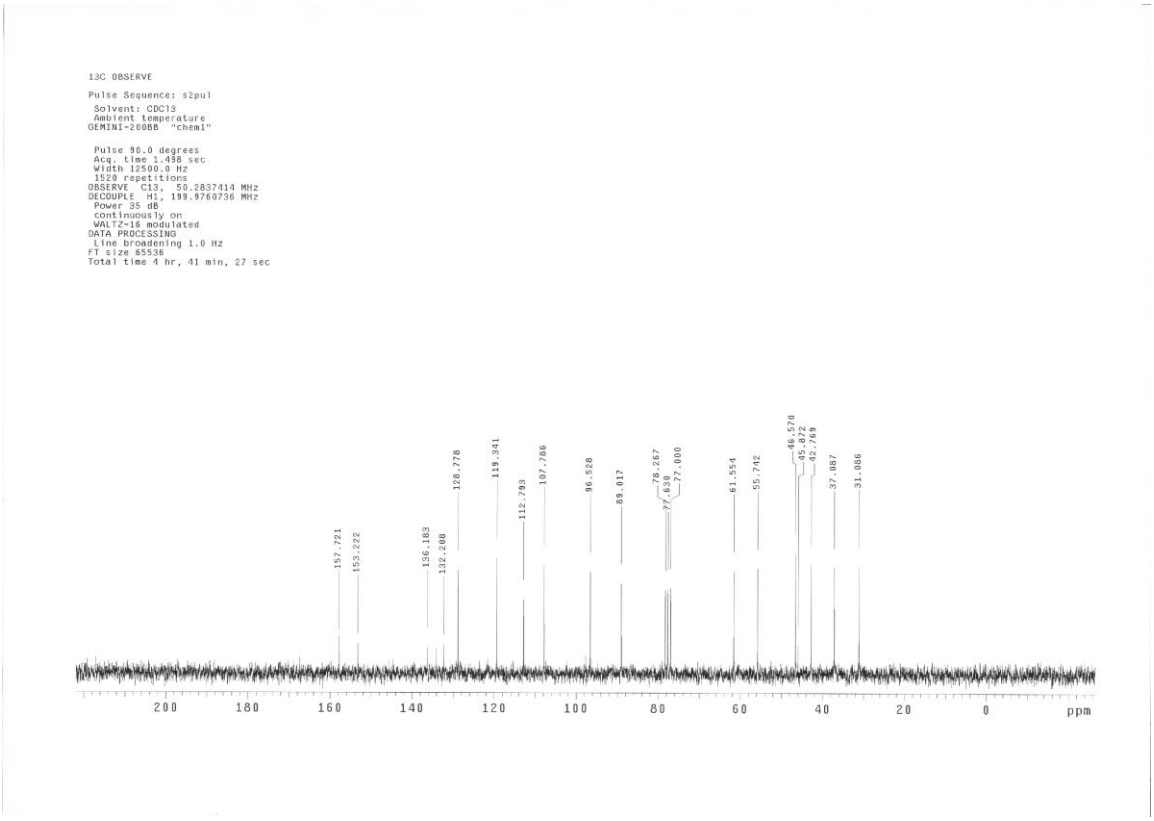
Selected geometric parameters (Å, º)

C1—C2	1.394 (7)	C8—C14	1.316 (6)
C1"—C2"	1.371 (7)	C9—N1	1.477 (7)
C1"—C6"	1.379 (8)	C9—C14	1.515 (6)
C1"—N2'	1.433 (7)	C9—C10	1.550 (8)
C1'—N5'	1.298 (6)	C1'—N2'	1.335 (6)
C10—C11	1.519 (7)	C1'—O1	1.347 (6)

C2"—C3"	1.375 (9)	C11—C12	1.375 (6)
C2—C3	1.380 (7)	C12—C13	1.491 (6)
C13—C14	1.518 (6)	C3"—C4"	1.379 (9)
C13—C15	1.528 (6)	C15—C16	1.514 (7)
C3—C4	1.367 (7)	C3—O1	1.416 (5)
C4"—C5"	1.372 (8)	C16—N1	1.490 (7)
C4—O5	1.359 (5)	C4—C12	1.387 (6)
C18—O3	1.424 (6)	C5—C6	1.483 (6)
C5—O5	1.489 (5)	C5—C13	1.552 (6)
C19—N1	1.464 (7)	C5"—C6"	1.378 (8)
C6—C7	1.342 (7)	N2'—N3'	1.361 (6)
C6—O3	1.358 (6)	N3'—N4'	1.292 (7)
C7—C8	1.458 (7)	N4'—N5'	1.377 (7)
C11—C1—C2	120.9 (5)	C2"—C1"—C6"	121.2 (5)
C2"—C1"—N2'	119.2 (5)	C12—C11—C1	116.3 (4)
C6"—C1"—N2'	119.5 (5)	C12—C11—C10	118.0 (4)
N5'—C1'—N2'	112.0 (5)	C1—C11—C10	125.3 (4)
N5'—C1'—O1	127.1 (5)	C11—C12—C4	123.3 (4)
N2'—C1'—O1	120.7 (4)	C11—C12—C13	126.9 (4)
C1"—C2"—C3"	119.4 (6)	C4—C12—C13	109.0 (4)
C12—C13—C14	103.6 (4)	C12—C13—C15	112.6 (4)
C3—C2—C1	120.5 (5)	C14—C13—C15	110.1 (4)
C12—C13—C5	101.6 (4)	C14—C13—C5	116.4 (4)
C2"—C3"—C4"	120.1 (6)	C15—C13—C5	111.9 (4)
C8—C14—C9	128.6 (4)	C8—C14—C13	121.2 (4)
C4—C3—C2	119.4 (4)	C9—C14—C13	109.3 (4)
C4—C3—O1	119.4 (4)	C16—C15—C13	112.1 (4)
C2—C3—O1	120.7 (5)	O5—C4—C3	127.0 (4)
C3—C4—C12	119.0 (4)	C6—C5—C13	115.4 (4)
C5"—C6"—C1"	118.9 (5)	C7—C6—O3	127.7 (5)
C7—C6—C5	122.4 (4)	C6—C7—C8	121.7 (5)
C19—N1—C9	112.5 (4)	C19—N1—C16	110.7 (5)
C14—C8—C7	122.4 (4)	C9—N1—C16	109.9 (4)
C1'—N2'—N3'	105.9 (4)	C1'—N2'—C1"	132.5 (4)
N1—C9—C14	111.8 (4)	N3'—N2'—C1"	121.5 (4)
N1—C9—C10	110.1 (4)	N4'—N3'—N2'	107.3 (5)
C14—C9—C10	111.8 (4)	N3'—N4'—N5'	110.7 (4)
N1—C9—H9	107.6	C1'—N5'—N4'	104.1 (5)
C1'—O1—C3	116.5 (4)	C6—O3—C18	117.5 (4)
C11—C10—C9	114.7 (4)	C4—O5—C5	106.6 (3)

^{1}H and ^{13}C spectra of compound **7** (200 MHz and 50 Mhz, respectively, in $CDCl_3$)





^{1}H (200 MHz in $CDCl_3$) and elemental analysis data of novel morphinans

Co.	Description and m.p. (^{o}C)	^{1}H NMR data (ppm, multiplicity and cupling constant in Hz)								Elemental analysis (%)	
		H1	H2	H3	H5	H7	H8	NCH_3	OCH_3	Calculated	Found
21	white foam	6.41-6.32 (m)	6.87-6.81 (m)	6.41-6.32 (m)	5.01 (s)	6.21 (d, 6.9)	6.87-6.81 (m)	2.28 (s)	-	C: 76.84 H: 6.81 N: 4.98	C: 76.79 H: 6.91 N: 5.01
22	In accordance with ref. 1										
23	In accordance with ref. 1										
24	off-white solid, 119-121	6.39-6.31 (m)	6.87 (t, 7.7)	6.39-6.31 (m)	2.44-2.31 (m)	4.66 (dd, 4.9, 1.2)	2.17-1.86 (m)	2.31 (s)	3.87 (s) 3.59 (s) 3.24 (s)	C: 72.92 H: 8.26 N: 4.25	C: 73.04 H: 8.33 N: 4.19
25	In accordance with ref. 2										

^{1}H (200 MHz in $CDCl_3$) and elemental analysis data of novel aporphines

Co.	Description and m.p. (^{o}C)	^{1}H NMR data (ppm, multiplicity and cupling constant in Hz)								Elemental analysis (%)	
		H1	H2	H3	H8	H9	H10	NCH_3	S-Alkyl	Calculated	Found
15	In accordance with ref. 3										
16	In accordance with ref. 4										
17	In accordance with ref. 4										
18	In accordance with ref. 5										
19	white solid, 142-145	7.41 (d, 2.1)	-	7.20-7.09 (m)	6.99 (dd, 6.4, 2.2)	7.20-7.09 (m)	6.77 (dd, 6.4, 2.2)	2.31(s)	3.21-2.66 (m) 1.27 (t, 7.2)	C: 73.27 H: 6.80 N: 4.50	C: 73.34 H: 6.68 N: 4.61
20	off-white solid, 127-129	7.31 (d, 2.3)	-	7.14-7.07 (m)	6.90 (dd, 6.1, 2.0)	7.14-7.07 (m)	6.69 (dd, 6.2, 2.0)	2.33 (s)	3.11-2.73 (m) 1.34-1.30 (m) 0.94 (t, 6.7)	C: 73.81 H: 7.12 N: 4.30	C: 73.61 H: 7.24 N: 4.41

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