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Benzylation of morphinandienes and new aspects of their acid-catalyzed rearrangement to new aporphines

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ABSTRACT

The benzylation of thebaine and 6-demethoxythebaine resulted in different product mixtures. Explanations were given for both the observed differences in the ratio of 5β- versus 7-benzyl products and the deviation of the electronic structure of ring C of 7-benzyl products. The acid-catalyzed rearrangement of morphinan-5,8-dienes, 5,6- and 6,7-disubstituted morphinan-6,8-dienes was achieved and mechanistic interpretations for the formation of new, potentially dopamine-active aporphines were provided.

1. Introduction

Thebaine (**1**) is the pharmaceutically most important, naturally occurring morphinan-6,8-diene, as it is used in the synthesis of a variety of opioid receptor agonist and antagonist compounds utilized as major alternatives in the treatment of severe pain and the management of drug dependence.[1] Besides this application, **1** is also an excellent starting compound to potent dopamine agonists such as *N*-propyl-2-fluoronorapomorphine via its acid-catalyzed rearrangement and further transformation.[2] The structure of thebaine (**1**) is frequently referred to as morphinandiene, as the chemically most interesting ring C of the morphinan backbone contains a conjugated diene motif, disregarding the fact that there is not only one type of morphinandiene. Maat et al. first reported the successful isolation and characterization of morphinan-5,8-diene structure.[3] It was the 7-methyl congener **2** that was formed in the 5-methylation reaction of 6-demethoxythebaine (**3**) under classic conditions elaborated by Gates and his colleagues (Fig. 1).[4]

The methanesulfonic acid-mediated rearrangement of morphinan-6,8-dienes into apocodeines was investigated by Neumeyer's and Berényi's groups (Scheme 1).[5]

The 5β-substitution has remained one of the frequently applied and well-studied subjects of morphinan chemistry; recent application of 5β-substituted derivatives was reported for the preparation of δ-selective opioid agonists.[6] Coop and his co-workers[7] investigated the relationship between the spatial size of the electrophile partner and the change in the ratio of conventional 5β-substituted versus 7-substituted products. On the basis of their previous observations regarding the formation of 5β-trimethylsilylthebaine with the conventional procedure, they applied alkylarylsilyl chlorides with gradually increasing steric size to test the

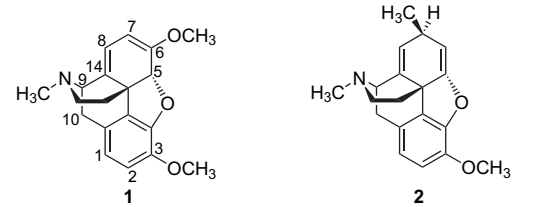
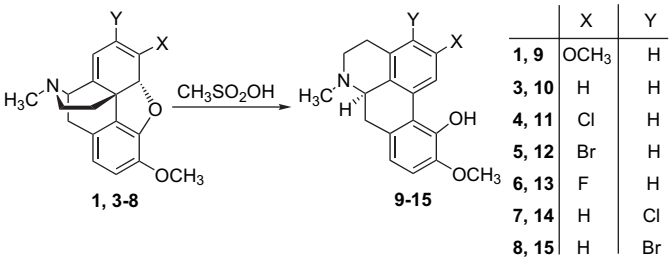


Figure 1. The structure of morphinandienes.



Scheme 1. Acid-catalyzed rearrangement of morphinan-6,8-dienes.

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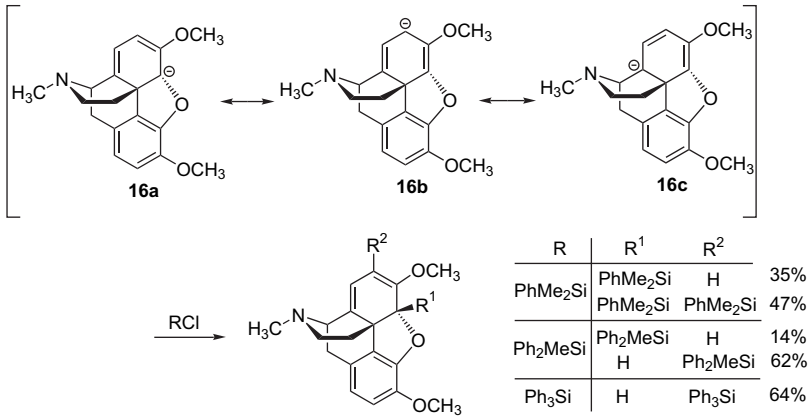


R	R^1	R^2	
$PhMe_2Si$	$PhMe_2Si$	H	35%
	$PhMe_2Si$	$PhMe_2Si$	47%
Ph_2MeSi	Ph_2MeSi	H	14%
	H	Ph_2MeSi	62%
Ph_3Si	H	Ph_3Si	64%

Scheme 2. The effect of the size of electrophile partner on the ratio of products.

effect of the steric bulk. It was confirmed that the 7-position was favoured at the expense of the formation of the original 5-substituted derivatives in the case of reactions of sterically large electrophiles with thebaine anion **16** (Scheme 2).

2. Results and discussion

We aimed to carry out the syntheses, full structural characterization and ab initio evaluation of the formation of benzyl congeners of thebaine (**1**) and 6-demethoxythebaine (**3**) in order to explore the fundamental reasons for the difference in the electronic structure of ring C of the resulting morphinan skeletons. Furthermore, the acid-catalyzed rearrangement of the benzyl derivatives of morphinan-5,8-dienes and 6,7-disubstituted morphinan-6,8-dienes was also achieved forming novel benzylapocodeines.

2.1. Benzylation of morphinandienes

On the basis of our preliminary studies, Gates' procedure[4] for the generation of thebaine anion **16** was modified in order to increase the amount of the resulting 7-substituted morphinandienes in the product mixture (Scheme 3). After dissolving morphinandiene **1** or **3** in dry THF, it was cooled to −78 °C and treated with 1.2 equiv of *tert*-BuLi. We reduced the amount of the anion-forming agent from 1.5 to 2.0 equiv[4,7] and applied a more reactive one. The benzylation of **16** was carried out with a variety of benzyl chlorides. The amount of benzyl chloride was also reduced from 1.5 to 1.2 equiv. The modification involved the extension of the mixing time after the 2 h-long warm-up period from −78 °C to room temperature, however, as it was concluded henceforth, it had a beneficial effect on the work-up of the crude products than a favourable thermal influence on the reaction itself.

The isolated yields of 5β- and 7-benzylthebaines **17a–e** and **18a–e** are collected in Table 1.

In an attempt to rationalize our observations, DFT calculations were performed to determine the electrophilic character of the benzyl carbon atoms primarily relevant to the reaction. The calculated net NBO (natural bond orbital) atomic charges of the benzyl carbon atoms are collected in Table 2. The above-presented results were found to be in good agreement with our expectations regarding the correlation between the electrophilic power of the applied benzyl chlorides and the ratio of 5- and 7-substituted products. The reactions of more reactive benzyl chlorides led to a dominance of kinetic control, i.e., the reaction at the less sterically hindered centre of the C ring.

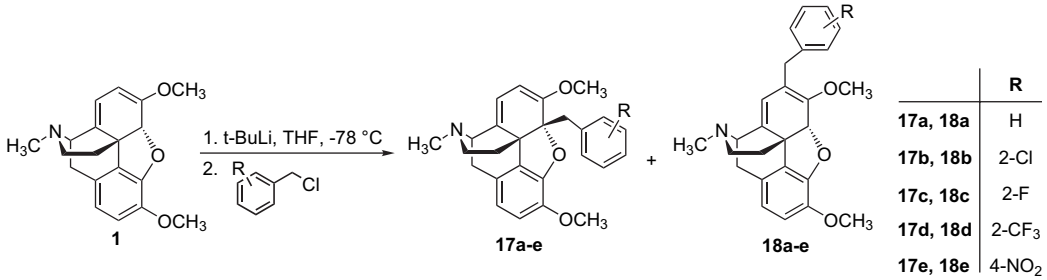
Table 1
Yields in benzylations of thebaine (**1**)

Product	Isolated yield[a] (%)	Product ratio (**17**:**18**)
17a	42	1.5:1
18a	28	
17b	47	2.35:1
18b	20	
17c	48	2:1
18c	24	
17d	40	1.38:1
18d	29	
17e	42	1.4:1
18e	30	

[a] Average of three reactions.

Table 2
Net NBO atomic charges for benzyl carbon atoms as obtained from B3LYP/6-31G* calculations

R	Atomic charge (*e*)	Difference (%)
H	0.0341	0
2-Cl	0.0314	−7.9
2-F	0.0338	−0.9
2-CF_3	0.0442	29.6
4-NO_2	0.0465	36.4



	R
17a, 18a	H
17b, 18b	2-Cl
17c, 18c	2-F
17d, 18d	2-CF_3
17e, 18e	4-NO_2

Scheme 3. Formation of 5β- and 7-benzylthebaines **17a–e** and **18a–e**.

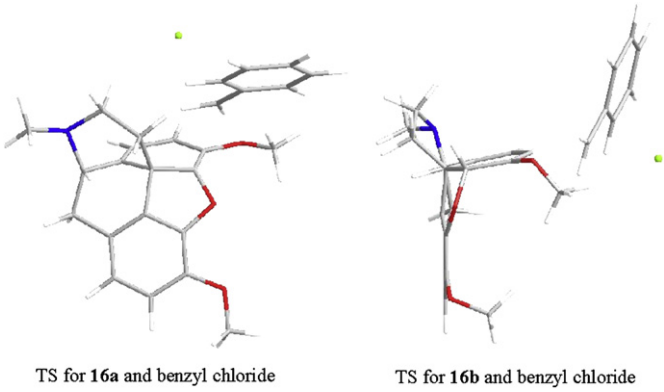
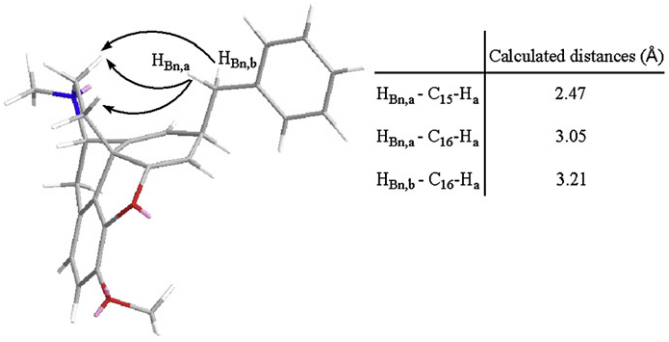


Figure 2. Representative structures of optimized TS of benzyl chloride with thebaine-5-anion **16a** and thebaine-7-anion **16b** (green represents chlorine).



	Calculated distances (Å)
$H_{Bn,a}$ - C_{15}-H_a	2.47
$H_{Bn,a}$ - C_{16}-H_a	3.05
$H_{Bn,b}$ - C_{16}-H_a	3.21

Figure 3. Determining NOE correlations presented on the structure of **20a** optimized at the B3LYP/6-31G* level.

In order to estimate the extent of steric hindrance in the case of thebaine-5-anion **16a** and thebaine-7-anion **16b**, a model was established using the Gaussian 98 program to optimize transition state (TS) structures at the B3LYP/6-31G* level for benzyl chloride with both nucleophiles (Fig. 2 and Table 3).[8,9]

The weaker the electrophilic character of the benzyl chloride, the higher the ratio of the thermodynamically more stable 5β-substituted derivative in the product mixture. Referring to the calculated NBO atomic charges, 2-CF_3– and 4-NO_2–benzyl chlorides were found to be more reactive partners whereas 2-Cl, 2-F and unsubstituted benzyl chlorides were less reactive, which were in accordance with the observed product ratios.

We also considered the possibility of a direct *ortho*-metalation-like (DoM)[10] lithium-coordination to the methoxy group, deprotonation and lithiation of 5- and 7-positions as the initiation of the benzylation procedure and as an explanation of the observed product ratios. Taking into consideration the two important factors of the evolution of DoM, steric hindrance and charge deactivation properties, thebaine (**1**) was found to be an appropriate partner for this mechanism. The complexes formed using *tert*-BuLi and compound **1** towards a potential 5β- and 7-lithiation were investigated as a starting point. It was found that the formation of a complex involving the coordination of lithium to both C_6–methoxy and C_4–O–C_5 etheral oxygen atoms and C_5 carbon as the reactive centre is much more probable with respect to the calculated formation properties of the structures optimized at the B3LYP/6-31G* level. Moreover, we compared our data to the calculation results of García et al.[11] They reported most recently the synthesis and characterization of a stable *ortho*-deprotonated carbamate dimer containing Li–O and Li–N dative bonds and DFT calculations explaining the formation of this product. The comparison between the bond lengths and angles around the centres of the kinetically and thermodynamically most probable monomer of García et al. and our complex towards C_5-lithiation revealed significant similarity.

The benzylation of 6-demethoxythebaine (**3**) was performed according to the same methodology in order to compare the structure and the proportion of the isolated products. Compound **3** was synthesized using the original procedure reported by our research group in 1982.[5b] It was found in each run that the crude product mixtures contained three components, two benzylated morphinans and some unreacted diene **3**. The 1D and 2D NMR spectroscopic characterization of the two products proved that benzylation was taken place again at 5β- and 7-positions, however, besides the expected 5β-benzyl-6-demethoxythebaines **19a**–**e**, we found 7β-benzyl-morphinan-5,8-diene-type products **20a**–**e** (Scheme 4). The 7β-position of the benzyl moiety was confirmed by NOE correlations observed between benzyl hydrogens and C_{15}–H_a/C_{16}–H_a as presented on the optimized structure of **20a** (Fig. 3). As was mentioned in Section 1, these facts and the analytical data for **20a**–**e** were in accord with Maat's observation[3] regarding the methylation of **3**.

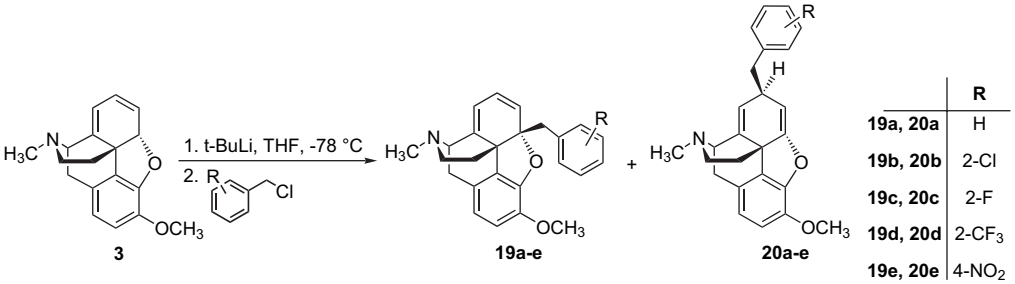
The ratio of the isolated products **19a**–**e** and **20a**–**e** is summarized in Table 4.

These data suggested the loss of thermodynamic dominance of 5β-benzyl product versus 7β-benzyl one in comparison to the benzylation of thebaine (**1**). This observation was confirmed by the

Table 3
Calculated parameters of optimized TS of benzyl chloride with thebaine-5-anion **16a** and thebaine-7-anion **16b**

Substrate	Nucleophile	Bond angle (°) Cl···C_{Bn}···C_{RC}	Mulliken charge			Distance (Å)	
			Cl	C_{Bn}	C_{RC}	Cl···C_{Bn}	C_{Bn}···C_{RC}
Benzyl chloride	**16a**	154	−0.387	0.625	−0.712	2.47	1.97
	16b	173	−0.391	0.656	−0.735	2.61	2.07

C_{RC}=charge carrier C atom of ring C; C_{Bn}=benzyl C atom.



	R
19a, 20a	H
19b, 20b	2-Cl
19c, 20c	2-F
19d, 20d	2-CF_3
19e, 20e	4-NO_2

Scheme 4. Benzylation of 6-demethoxythebaine (**3**).

Table 4
Observed yields in benzylations of 6-demethoxythebaine (**3**)

Product	Isolated yield[a] (%)	Product ratio (**19**:**20**)
19a	26	1:2.15
20a	56	
Unreacted diene **3**	10	
19b	23	1:2.52
20b	58	
Unreacted diene **3**	12	
19c	21	1:2.62
20c	55	
Unreacted diene **3**	11	
19d	25	1:2.40
20d	60	
Unreacted diene **3**	6	
19e	24	1:2.63
20e	63	
Unreacted diene **3**	8	

[a] Reported yields are averages of three reactions and were calculated for **19a**–**e** and **20a**–**e** on the basis of the reacted amount of diene **3**.

calculated data for the heat of formation of **19a**–**e** and **20a**–**e**, and explained by the electronic and conformational effects of the absence of the 6-methoxy group. On the one hand, the absence of the 6-OMe led to the loss of a clearly favourable energetic character of the conjugated 6,8-type diene structure having a stabilizing *O*-ether moiety at the 6-position over a hypothetical product structure with a cumulated 5,8-diene structure and *O*-ethers at positions 5 and 6. On the other hand, the main effect of the loss of 6-OMe on the conformation of the ring C of the morphinan-5,8-diene-7-anion **21** was the occurrence of a more stable, less stretched boat conformation in comparison to thebaine-7-anion **16b** (Fig. 4).

However, no remarkable conformational change was observed at the ring C of the morphinan-6,8-diene skeleton during the elimination of the 6-OMe function of thebaine-5-anion **16a**. On the basis of these reasons, the remarkable change in the product ratios was a clear consequence of the growth of the importance of the kinetic effect of the reactions via the change in the conformational background of the reaction, besides the loss of the thermodynamic one. The modification of the electronic structure of ring C of the 7-benzyl products (**18a**–**e** vs **20a**–**e**) was originated directly from the electronic modification of the target ring affected by the loss of the 6-methoxy moiety.

In summary of the results of benzylations we emphasize that these reactions give rise to some new precursors to semisynthetic aporphinoids with hitherto unknown substitution patterns on the A-ring. The overall conversion of the starting morphinandienes **1** and **3** into the benzylated ones was found to be very high. These are the main reasons for not focussing on the optimization of the ratio of regioisomers, although we are aware the fact that the influence of co-solvents and additives could have dramatic influences on the outcome of such alkylations. In other words these benzylations were proven to be an effective procedure in the synthesis of potentially dopamine-active aporphinoids.

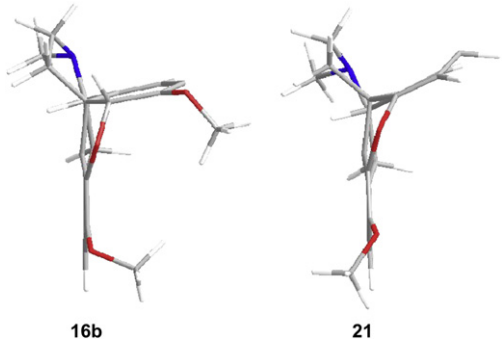
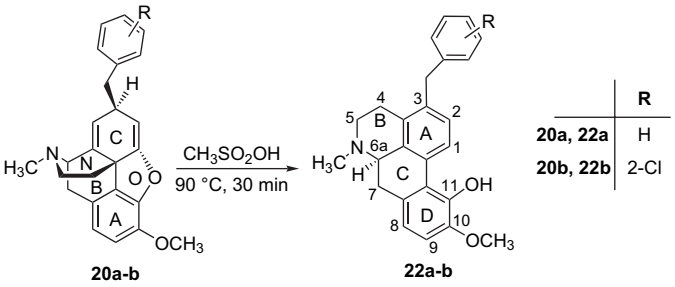


Figure 4. Optimized structure for thebaine-7-anion **16b** and morphinan-5,8-diene-7-anion **21** at the B3LYP/6-31G* level.

2.2. Acid-catalyzed rearrangements

It was decided to study the acid-catalyzed rearrangement of the morphinan-5,8-diene-type products **20a**–**b**. The procedure was performed in line with our original procedure elaborated for the morphinan-6,8-dienes as presented in Section 1. It involved the heating of the methanesulfonic acid solution of the diene **20a**–**e** for 30 min. In both cases we obtained a single component crude product. After isolation and full characterization of these products we concluded that this type of reaction resulted in 3-benzylapocodeines **22a**–**b** (Scheme 5).



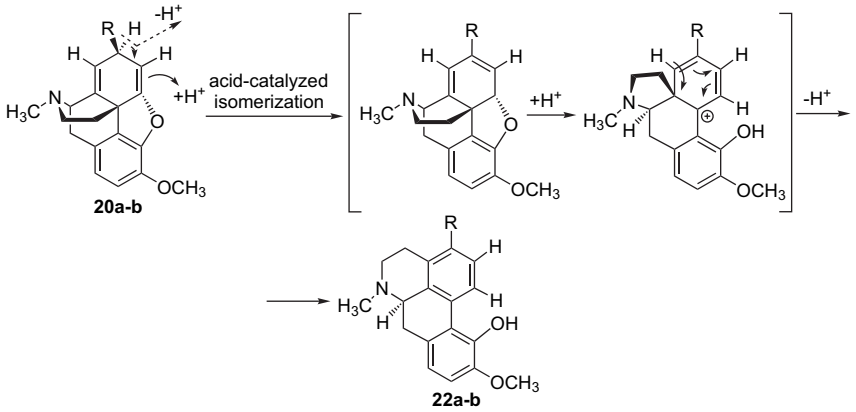
Scheme 5. Acid-catalyzed rearrangement of morphinan-5,8-dienes **20a**–**b**.

The conventional explanation[5a,12] for the acid-catalyzed rearrangement of the thebaine-like molecules involves the proton-promoted cleavage of the C5–O ether bond as the first step, resulting in a cation at ring C. Meanwhile the bridgehead bond of ring N at the fusion of rings B and C relocates from 13-position to 14-position. As the next steps of the mechanism, a series of electron pair shifts take place at ring C in order to form the aromatic structure; these rearrangements are terminated with a further relocation of ring N from 14-position to 8-position of the late morphinan backbone. The aporphine skeleton is stabilized by a proton release. This general theory was applied for the morphinan-5,8-diene structure presuming an acid-catalyzed isomerization of the 5,8-diene structure into the more stable conjugated 6,8-diene intermediate (Scheme 6).

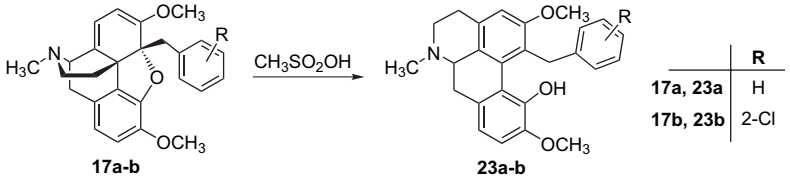
In order to further study the capabilities of acid-catalyzed rearrangement on morphinandiene backbone and to obtain a novel class of semisynthetic aporphines, we performed the rearrangements of some representatives of the newly synthesized 5,6- and 6,7-disubstituted morphinan-6,8-dienes (Schemes 7 and 8).

In the backbone rearrangement of both groups of disubstituted morphinandienes **17**–**18** we found the formation of the corresponding 1,2- or 2,3-disubstituted apocodeines **23**–**24** in high yield. The presence of two substituents or the relative steric bulk on the C ring of the morphinans has no disturbing effect on these acid-catalyzed reactions. The mechanism of them is considered to be the same as the generally accepted one for morphinan-6,8-dienes.

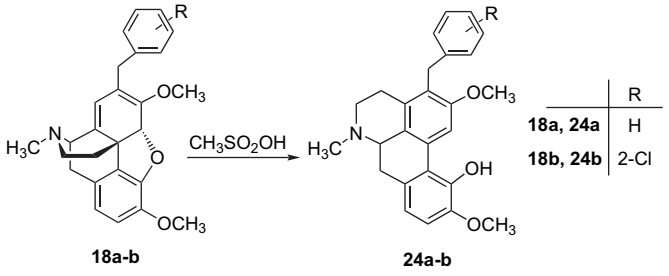
With respect to the significant dopamine D_2 affinity of 2-methoxy- and 2-phenylapomorphines and the interpretation of their activity[2a] the presented 1,2- and 2,3-disubstituted aporphinoids **23** and **24** are neuropharmacologically interesting hybrids bearing the H-bond acceptor ability and the large lipophilic moiety in the proximity of the 2-position of the aporphine skeleton. Due to this consideration the extension of the synthetic procedures and the detailed pharmacological study of the existing compounds are in progress.



Scheme 6. Suggested mechanism for the acid-catalyzed rearrangement of morphinan-5,8-dienes.



Scheme 7. Acid-catalyzed rearrangement of 5,6-disubstituted morphinan-6,8-dienes **17a–b**.



Scheme 8. Acid-catalyzed rearrangement of 6,7-disubstituted morphinan-6,8-dienes **18a–b**.

3. Conclusion

We presented the benzylation of thebaine (**1**) and 6-demethoxythebaine (**3**) resulting in different product mixtures. Explanations were given for either the observed differences in the ratio of 5β- versus 7-benzyl products or the deviation of the electronic structure of ring C of 7-benzyl products starting from **1** or **3**. The acid-catalyzed rearrangement of 7-benzyl-morphinan-5,8-dienes **20a–b** was achieved and a mechanistic interpretation of the formation of 3-benzylapocodeines **22a–b** was provided. The same rearrangement of 5,6- and 6,7-disubstituted morphinans yielded a novel class of semisynthetic aporphinoids with disubstituted A-rings. All the presented aporphines have the possibility of remarkable dopamine binding activity considering the same properties of 2-methoxy- and 2-phenylapomorphines. The presented benzylation data could serve as starting consideration of the development of opioid-active compounds derived via 5- or 7-substituted morphinandienes or dopaminergic apomorphines with mono- or disubstituted ring A.

4. Experimental protocols

4.1. General

Melting points were determined with a Kofler hot-stage apparatus. Thin layer chromatography was performed on precoated Merck 5554 Kieselgel 60 F_{254} foils using chloroform/methanol=8:2 mobile phase; the spots were visualized with Dragendorff's reagent. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 360 (360 and 90.6 MHz, respectively), chemical shifts are reported in parts per million (δ) from internal TMS and coupling constants (J) are measured in hertz. Signal assignments are based on standard APT, DEPT, HSQC, HMQC and ^{1}H–^{1}H COSY experiments. Abbreviations s, d, t, m and br are used to designate singlet, doublet, triplet, multiplet and broad, respectively. Mass spectra (EI and HRMS, 70 eV, m/z) were obtained on a Jeol DX 303/DA 5000 instrument. Elementary analyses were carried out on a Perkin–Elmer 2400 CHN analyzer. Compounds were purified by column chromatography using Merck Kieselgel 60 (230–400 mesh). IR spectra were recorded on Perkin–Elmer 283 B spectrometer.

4.2. Chemistry

4.2.1. General procedure for the benzylation of morphinans

To a stirred solution of 1 g of thebaine (**1**) or 1 g of 6-demethoxythebaine (**3**) in 80 mL of dry THF, cooled to −78 °C, was added 1.7 M *tert*-BuLi (in pentane, 1.2 equiv). The mixture was stirred for 30 min before benzyl chloride (1.2 equiv) was added. The solution was stirred at −78 °C for 1 h before it was allowed to come to room temperature over 2 h and stirred at ambient temperature for further 2 h. The work-up was performed in line with Gates' method,[4] products were separated by means of column chromatography (dichloromethane/methanol/concentrated ammonium hydroxide=90:9:1).

*4.2.1.1. 5β-Benzyl-3,6-dimethoxy-4,5α-epoxy-17-methyl-6,7,8,14-tetradehydro-morphinan (**17a**).* Compound **17a** and compound **18a** were separated by means of column chromatography. Compound **17a** was the first eluted component. Yellow cubic crystals were obtained by crystallization from toluene/methanol=8:2; mp: 126–128 °C (lit.[4] 124 °C from anhydrous ether); yield: 542 mg (42%); CHN anal. calcd for $C_{26}H_{27}NO_3$: C, 77.58; H, 7.01; N, 3.48. Found: C, 77.60; H, 7.09; N, 3.52; $[\alpha]_D^{25}$ −376 (c 0.1, chloroform); R_f (90% CH_2Cl_2/9% CH_3OH/1% concentrated ammonium hydroxide): 0.47; ν_{max} (KBr disc): 2940, 2880, 1640, 1150, 1100; MS (EI): m/z (%) 402

(M^++1, 100), 387 (87), 312 (64); HRMS (EI) *m/z* (%) calculated for $C_{26}H_{28}NO_3^+$: 402.2064 (M^++H), found: 402.2049 (M^++H, 100); δ_H (360 MHz, $CDCl_3$): 7.22–7.04 (5H, m, Bn aromatic), 6.61, 6.59 (2H, 2d, C_1–H, C_2–H, J_{1-2} 8.2), 5.66 (1H, d, C_8–H, J_{7-8} 6.8), 4.84 (1H, d, C_7–H, J_{7-8} 6.8), 3.84–3.76 (6H, m, C_9–H, C_5–CH_2–, C_3–OCH_3), 3.34 (3H, s, C_6–OCH_3), 3.09–2.19 (7H, m, C_{10}–H_a, C_{10}–H_b, C_{16}–H_a, C_{16}–H_b, –NCH_3), 2.08–1.93 (2H, m, C_{15}–H_a, C_{15}–H_b); δ_C (50.3 MHz, $CDCl_3$): 157.25 (C_6), 147.22 (C_3), 144.53 (C_4), 136.37–108.61 (10C, aromatic, C_8, C_{14}), 92.34 (C_6), 88.11 (C_5), 64.61 (C_9), 54.44 (C_6–OCH_3), 52.34 (C_3–OCH_3), 48.83 (C_{16}), 45.88 (C_{13}), 42.01 (NCH_3), 39.12 (C_5–CH_2–), 35.64 (C_{15}), 32.68 (C_{10}).

*4.2.1.2. 5β-(2-Chlorobenzyl)-3,6-dimethoxy-4,5α-epoxy-17-methyl-6,7,8,14-tetradehydro-morphinan (**17b**).* Compound **17b** and compound **18b** were separated by means of column chromatography. Compound **17b** was the first eluted component. Pale yellow cubic crystals were obtained by crystallization from toluene/methanol=8:2; mp: 118–120 °C; yield: 657 mg (47%); CHN anal. calcd for $C_{26}H_{26}ClNO_3$: C, 71.47; H, 6.23; N, 3.21. Found: C, 71.52; H, 6.18; N, 3.15; $[\alpha]_D^{25}$ −312 (*c* 0.1, chloroform); R_f (90% CH_2Cl_2/9% CH_3OH/1% concentrated ammonium hydroxide): 0.46; ν_{max} (KBr disc): 2930, 2900, 1640, 1380, 1170, 1090, 710; MS (EI): *m/z* (%) 436 (M^++1, 100), 384 (51), 334 (43); HRMS (EI) *m/z* (%) calculated for $C_{26}H_{27}ClNO_3^+$: 436.1574 (M^++H), found: 436.1566 (M^++H, 100); δ_H (360 MHz, $CDCl_3$): 7.18–7.01 (4H, m, Bn aromatic), 6.68, 6.63 (2H, 2d, C_1–H, C_2–H, J_{1-2} 8.0), 5.69 (1H, d, C_8–H, J_{7-8} 6.6), 4.91 (1H, d, C_7–H, J_{7-8} 6.6), 3.90–3.80 (6H, m, C_9–H, C_5–CH_2–, C_3–OCH_3), 3.40 (3H, s, C_6–OCH_3), 3.14–2.21 (7H, m, C_{10}–H_a, C_{10}–H_b, C_{16}–H_a, C_{16}–H_b, –NCH_3), 2.11–2.01 (2H, m, C_{15}–H_a, C_{15}–H_b); δ_C (50.3 MHz, $CDCl_3$): 158.92 (C_6), 145.76 (C_3), 144.98 (C_4), 138.67–110.11 (10C, aromatic, C_8, C_{14}), 90.45 (C_6), 87.34 (C_5), 66.68 (C_9), 54.23 (C_6–OCH_3), 51.47 (C_3–OCH_3), 49.66 (C_{16}), 46.06 (C_{13}), 43.74 (NCH_3), 40.21 (C_5–CH_2–), 36.98 (C_{15}), 34.16 (C_{10}).

*4.2.1.3. 3,6-Dimethoxy-4,5α-epoxy-5β-(2-fluorobenzyl)-17-methyl-6,7,8,14-tetradehydro-morphinan (**17c**).* Compound **17c** and compound **18c** were separated by means of column chromatography. Compound **17c** was the first eluted component. Bright yellow cubic crystals were obtained by crystallization from toluene/methanol=8:2; mp: 123–125 °C; yield: 627 mg (48%); CHN anal. calcd for $C_{26}H_{26}FNO_3$: C, 74.44; H, 6.25; N, 3.33. Found: C, 74.50; H, 6.19; N, 3.35; $[\alpha]_D^{25}$ −334 (*c* 0.1, chloroform); R_f (90% CH_2Cl_2/9% CH_3OH/1% concentrated ammonium hydroxide): 0.38; ν_{max} (KBr disc): 2910, 2880, 1660, 1310, 1150, 1100; MS (EI): *m/z* (%) 420 (M^++1, 100), 366 (67), 354 (54), 321 (34); HRMS (EI) *m/z* (%) calculated for $C_{26}H_{27}FNO_3^+$: 420.1969 (M^++H), found: 420.1979 (M^++H, 100); δ_H (360 MHz, $CDCl_3$): 7.06–6.87 (4H, m, Bn aromatic), 6.62, 6.55 (2H, 2d, C_1–H, C_2–H, J_{1-2} 8.1), 5.80 (1H, d, C_8–H, J_{7-8} 6.5), 5.01 (1H, d, C_7–H, J_{7-8} 6.5), 3.94–3.86 (6H, m, C_5–CH_2–, C_3–OCH_3), 3.74 (1H, dd, C_9–H, J_{9-10a} 6.1, J_{9-10b} 3.4), 3.37 (3H, s, C_6–OCH_3), 3.19–2.17 (7H, m, C_{10}–H_a, C_{10}–H_b, C_{16}–H_a, C_{16}–H_b, –NCH_3), 2.07–1.89 (2H, m, C_{15}–H_a, C_{15}–H_b); δ_C (50.3 MHz, $CDCl_3$): 159.44 ($C_{2'}$), 155.43 (C_6), 144.87 (C_3), 143.45 (C_4), 136.91–106.32 (9C, aromatic, C_8, C_{14}), 91.63 (C_6), 86.84 (C_5), 67.21 (C_9), 55.16 (C_6–OCH_3), 52.03 (C_3–OCH_3), 49.34 (C_{16}), 45.07 (C_{13}), 43.32 (NCH_3), 40.01 (C_5–CH_2), 35.23 (C_{15}), 32.45 (C_{10}).

*4.2.1.4. 3,6-Dimethoxy-4,5α-epoxy-17-methyl-6,7,8,14-tetradehydro-5β-(2-trifluoro-methylbenzyl)-morphinan (**17d**).* Compound **17d** and compound **18d** were separated by means of column chromatography. Compound **17d** was the first eluted component. Dark yellow cubic crystals were obtained by crystallization from toluene/methanol=8:2; mp: 132–137 °C; yield: 603 mg (40%); CHN anal. calcd for $C_{27}H_{26}F_3NO_3$: C, 69.07; H, 5.58; N, 2.98. Found: C, 69.12; H, 5.61; N, 3.01; $[\alpha]_D^{25}$ −363 (*c* 0.1, chloroform); R_f (90% CH_2Cl_2/9% CH_3OH/1% concentrated ammonium hydroxide): 0.56; ν_{max} (KBr disc): 2920, 2860, 1650, 1420, 1340, 1120; MS (EI): *m/z* (%) 470 (M^++1, 100), 411 (65), 387 (76), 305 (32); HRMS (EI) *m/z* (%) calculated for $C_{27}H_{27}F_3NO_3^+$: 470.1938 (M^++H), found: 470.1950 (M^++H, 100); δ_H (360 MHz, $CDCl_3$): 7.27–7.10 (4H, m, Bn aromatic), 6.51, 6.48 (2H, 2d, C_1–H, C_2–H, J_{1-2} 8.2), 5.64 (1H, d, C_8–H, J_{7-8} 6.2), 4.87 (1H, d, C_7–H, J_{7-8} 6.2), 3.99–3.82 (7H, m, C_5–CH_2–, C_9–H, C_3–OCH_3), 3.44 (3H, s, C_6–OCH_3), 3.10–1.88 (9H, m, C_{10}–H_a, C_{10}–H_b, C_{15}–H_a, C_{15}–H_b, C_{16}–H_a, C_{16}–H_b, –NCH_3); δ_C (50.3 MHz, $CDCl_3$): 153.54 (C_6), 145.34 (C_3), 144.23 (C_4), 134.21–108.56 (10C, aromatic, C_8, C_{14}, –CF_3), 93.21 (C_6), 87.54 (C_5), 66.87 (C_9), 55.43 (C_6–OCH_3), 53.56 (C_3–OCH_3), 49.21 (C_{16}), 44.76 (C_{13}), 43.05 (NCH_3), 39.40 (C_5–CH_2), 36.65 (C_{15}), 31.98 (C_{10}).

*4.2.1.5. 3,6-Dimethoxy-4,5α-epoxy-17-methyl-5β-(4-nitrobenzyl)-6,7,8,14-tetradehydro-morphinan (**17e**).* Compound **17e** and compound **18e** were separated by means of column chromatography. Compound **17e** was the first eluted component. Pale brown cubic crystals were obtained by crystallization from toluene/methanol=8:2; mp: 131–133 °C; yield: 602 mg (42%); CHN anal. calcd for $C_{26}H_{26}N_2O_5$: C, 69.94; H, 5.87; N, 6.27. Found: C, 69.87; H, 6.09; N, 6.31; $[\alpha]_D^{25}$ −411 (*c* 0.1, chloroform); R_f (90% CH_2Cl_2/9% CH_3OH/1% concentrated ammonium hydroxide): 0.49; ν_{max} (KBr disc): 2920, 2990, 1640, 1530, 1350, 1150, 1130; MS (EI): *m/z* (%) 447 (M^++1, 12), 401 (100), 373 (67), 307 (43); HRMS (EI) *m/z* (%) calculated for $C_{26}H_{27}N_2O_5^+$: 447.1914 (M^++H), found: 447.1924 (M^++H, 12); δ_H (360 MHz, $CDCl_3$): 7.87–7.65 (2H, dd, Bn aromatic, A_2B_2, *J* 6.4 and 1.1), 7.52–7.44 (2H, dd, Bn aromatic, A_2B_2, *J* 6.3 and 1.1), 6.52, 6.47 (2H, 2d, C_1–H, C_2–H, J_{1-2} 8.0), 5.84 (1H, d, C_8–H, J_{7-8} 6.1), 4.97 (1H, d, C_7–H, J_{7-8} 6.1), 3.83–3.73 (6H, m, C_5–CH_2–, C_3–OCH_3), 3.66 (1H, dd, C_9–H, J_{9-10a} 6.0, J_{9-10b} 3.2), 3.43 (3H, s, C_6–OCH_3), 3.37–2.11 (7H, m, C_{10}–H_a, C_{10}–H_b, C_{16}–H_a, C_{16}–H_b, –NCH_3), 2.02–1.86 (2H, m, C_{15}–H_a, C_{15}–H_b); δ_C (50.3 MHz, $CDCl_3$): 156.32 (C_6), 145.21 (C_3), 143.77 (C_4), 139.15–106.98 (10C, aromatic, C_8, C_{14}), 90.87 (C_6), 85.43 (C_5), 67.45 (C_9), 56.10 (C_6–OCH_3), 53.43 (C_3–OCH_3), 50.08 (C_{16}), 45.87 (C_{13}), 43.65 (NCH_3), 39.62 (C_5–CH_2), 36.34 (C_{15}), 33.12 (C_{10}).

*4.2.1.6. 7-Benzyl-3,6-dimethoxy-4,5α-epoxy-17-methyl-6,7,8,14-tetradehydro-morphinan (**18a**).* Compound **17a** and compound **18a** were separated by means of column chromatography. Compound **18a** was the second eluted component. Off-white, plate-shaped crystals were obtained by crystallization from toluene/methanol=8:2; mp: 142–144 °C; yield: 361 mg (28%); CHN anal. calcd for $C_{26}H_{27}NO_3$: C, 77.58; H, 7.01; N, 3.48. Found: C, 77.66; H, 7.12; N, 3.44; $[\alpha]_D^{25}$ −456 (*c* 0.1, chloroform); R_f (90% CH_2Cl_2/9% CH_3OH/1% concentrated ammonium hydroxide): 0.23; ν_{max} (KBr disc): 2900, 2850, 1240, 1140; MS (EI): *m/z* (%) 402 (M^++1, 100), 364 (62), 322 (67), 288 (40); HRMS (EI) *m/z* (%) calculated for $C_{26}H_{28}NO_3^+$: 402.2064 (M^++H), found: 402.2063 (M^++H, 100); δ_H (360 MHz, $CDCl_3$): 7.17–7.00 (5H, m, Bn aromatic), 6.51, 6.48 (2H, 2d, C_1–H, C_2–H, J_{1-2} 8.0), 5.77 (1H, s, C_8–H), 4.22 (1H, s, C_5–H), 3.91–3.83 (4H, m, C_9–H, C_3–OCH_3), 3.61 (3H, s, C_6–OCH_3), 3.32 (2H, s, C_7–CH_2–), 3.18–2.26 (7H, m, C_{10}–H_a, C_{10}–H_b, C_{16}–H_a, C_{16}–H_b, –NCH_3), 2.12–2.01 (2H, m, C_{15}–H_a, C_{15}–H_b); δ_C (50.3 MHz, $CDCl_3$): 154.21 (C_6), 147.56 (C_3), 145.89 (C_4), 131.02–110.67 (10C, aromatic, C_8, C_{14}), 99.23 (C_7), 86.45 (C_5), 61.72 (C_9), 56.64 (C_6–OCH_3), 53.38 (C_3–OCH_3), 50.83 (C_{16}), 44.36 (C_{13}), 41.09 (NCH_3), 38.29 (C_7–CH_2–), 34.04 (C_{15}), 30.94 (C_{10}).

*4.2.1.7. 7-(2-Chlorobenzyl)-3,6-dimethoxy-4,5α-epoxy-17-methyl-6,7,8,14-tetradehydro-morphinan (**18b**).* Compound **17b** and compound **18b** were separated by means of column chromatography. Compound **18b** was the second eluted component. Off-white, plate-shaped crystals were obtained by crystallization from toluene/methanol=8:2; mp: 134–136 °C; yield: 280 mg (20%); CHN anal. calcd for $C_{26}H_{26}ClNO_3$: C, 71.47; H, 6.23; N, 3.21. Found: C, 71.40; H, 6.14; N, 3.15; $[\alpha]_D^{25}$ −404 (*c* 0.1, chloroform); R_f (90% CH_2Cl_2/9% CH_3OH/1% concentrated ammonium hydroxide): 0.26; ν_{max} (KBr disc): 2890, 2810, 1630, 1350, 1180, 720; MS (EI): *m/z* (%)

436 (M^++1, 100), 371 (67), 356 (56), 312 (34); HRMS (EI) *m*/*z* (%) calculated for $C_{26}H_{27}ClNO_3^+$: 436.1574 (M^++H), found: 436.1561 (M^++H, 100); δ_H (360 MHz, $CDCl_3$): 7.11–7.02 (4H, m, Bn aromatic), 6.58, 6.54 (2H, 2d, C_1–H, C_2–H, J_{1-2} 8.1), 5.80 (1H, s, C_8–H), 4.09 (1H, s, C_5–H), 3.88–3.75 (4H, m, C_9–H, C_3–OCH_3), 3.54 (3H, s, C_6–OCH_3), 3.30 (2H, s, C_7–CH_2–), 3.34–2.08 (8H, m, C_{10}–H_a, C_{10}–H_b, C_{15}–H_b, C_{16}–H_a, C_{16}–H_b, –NCH_3), 1.98 (1H, td, C_{15}–H_a, $J_{15a,15b;16a,16b}$ 11.4, $J_{15a,15b}$ 4.5); δ_C (50.3 MHz, $CDCl_3$): 151.27 (C_6), 146.76 (C_3), 145.01 (C_4), 128.44–108.37 (10C, aromatic, C_8, C_{14}), 97.66 (C_7), 88.24 (C_5), 61.04 (C_9), 55.18 (C_6–OCH_3), 53.30 (C_3–OCH_3), 49.93 (C_{16}), 43.92 (C_{13}), 41.25 (NCH_3), 40.09 (C_7–CH_2–), 35.53 (C_{15}), 32.45 (C_{10}).

*4.2.1.8. 3,6-Dimethoxy-4,5α-epoxy-7-(2-fluorobenzyl)-17-methyl-6,7,8,14-tetradehydro-morphinan (**18c**).* Compound **17c** and compound **18c** were separated by means of column chromatography. Compound **18c** was the second eluted component. Pale yellow, plate-shaped crystals were obtained by crystallization from toluene/methanol=8:2; mp: 127–129 °C; yield: 323 mg (24%); CHN anal. calcd for $C_{26}H_{26}FNO_3$: C, 74.44; H, 6.25; N, 3.33. Found: C, 74.39; H, 6.32; N, 3.37; $[\alpha]_D^{25}$ −424 (*c* 0.1, chloroform); R_f (90% CH_2Cl_2/9% CH_3OH/1% concentrated ammonium hydroxide): 0.19; ν_{max} (KBr disc): 2890, 2870, 1630, 1330, 1080; MS (EI): *m*/*z* (%) 420 (M^++1, 100), 366 (54), 342 (32), 307 (74); HRMS (EI) *m*/*z* (%) calculated for $C_{26}H_{27}FNO_3^+$: 420.1969 (M^++H), found: 420.1957 (M^++H, 100); δ_H (360 MHz, $CDCl_3$): 7.02–6.87 (4H, m, Bn aromatic), 6.51, 6.48 (2H, 2d, C_1–H, C_2–H, J_{1-2} 8.2), 5.68 (1H, s, C_8–H), 4.03 (1H, s, C_5–H), 3.91–3.85 (4H, m, C_9–H, C_3–OCH_3), 3.61 (3H, s, C_6–OCH_3), 3.46 (2H, s, C_7–CH_2–), 3.27–2.02 (8H, m, C_{10}–H_a, C_{10}–H_b, C_{15}–H_b, C_{16}–H_a, C_{16}–H_b, –NCH_3), 1.84 (1H, td, C_{15}–H_a, $J_{15a,15b;16a,16b}$ 10.6, $J_{15a,15b}$ 4.3); δ_C (50.3 MHz, $CDCl_3$): 161.11 ($C_{2'}$), 160.67 (C_6), 146.10 (C_3), 145.79 (C_4), 133.65–110.67 (9C, aromatic, C_8, C_{14}), 98.89 (C_7), 88.27 (C_5), 61.56 (C_9), 56.05 (C_6–OCH_3), 53.78 (C_3–OCH_3), 51.12 (C_{16}), 44.12 (C_{13}), 41.78 (NCH_3), 35.33 (C_{15}), 33.27 (C_{10}), 27.62 (C_7–CH_2–).

*4.2.1.9. 3,6-Dimethoxy-4,5α-epoxy-17-methyl-6,7,8,14-tetradehydro-7-(2-trifluoro-methylbenzyl)-morphinan (**18d**).* Compound **17d** and compound **18d** were separated by means of column chromatography. Compound **18d** was the second eluted component. Yellow, plate-shaped crystals were obtained by crystallization from toluene/methanol=8:2; mp: 141–143 °C; yield: 437 mg (29%); CHN anal. calcd for $C_{27}H_{26}F_3NO_3$: C, 69.07; H, 5.58; N, 2.98. Found: C, 69.00; H, 5.64; N, 3.06; $[\alpha]_D^{25}$ −423 (*c* 0.1, chloroform); R_f (90% CH_2Cl_2/9% CH_3OH/1% concentrated ammonium hydroxide): 0.23; ν_{max} (KBr disc): 2910, 2870, 1670, 1420, 1340, 1130; MS (EI): *m*/*z* (%) 470 (M^++1, 100), 441 (78), 408 (34), 374 (72), 332 (32); HRMS (EI) *m*/*z* (%) calculated for $C_{27}H_{27}F_3NO_3^+$: 470.1938 (M^++H), found: 470.1930 (M^++H, 100); δ_H (360 MHz, $CDCl_3$): 7.23–7.18 (2H, m, Bn aromatic), 7.10–7.04 (2H, m, Bn aromatic), 6.63, 6.57 (2H, 2d, C_1–H, C_2–H, J_{1-2} 7.9), 5.85 (1H, s, C_8–H), 3.99 (1H, s, C_5–H), 3.84 (3H, s, C_3–OCH_3), 3.71–3.63 (4H, m, C_9–H, C_6–OCH_3), 3.31 (2H, s, C_7–CH_2–), 3.15–2.00 (8H, m, C_{10}–H_a, C_{10}–H_b, C_{15}–H_b, C_{16}–H_a, C_{16}–H_b, –NCH_3), 1.87 (1H, td, C_{15}–H_a, $J_{15a,15b;16a,16b}$ 11.0, $J_{15a,15b}$ 4.4); δ_C (50.3 MHz, $CDCl_3$): 159.44 (C_6), 147.45 (C_3), 146.10 (C_4), 133.21–109.34 (9C, aromatic, C_8, C_{14}, –CF_3), 98.54 (C_7), 89.65 (C_5), 61.67 (C_9), 56.34 (C_6–OCH_3), 53.10 (C_3–OCH_3), 51.04 (C_{16}), 44.12 (C_{13}), 41.39 (NCH_3), 35.34 (C_{15}), 33.78 (C_{10}), 31.42 (C_7–CH_2–).

*4.2.1.10. 3,6-Dimethoxy-4,5α-epoxy-17-methyl-7-(4-nitrobenzyl)-6,7,8,14-tetradehydro-morphinan (**18e**).* Compound **17e** and compound **18e** were separated by means of column chromatography. Compound **18e** was the second eluted component. Dark yellow, plate-shaped crystals were obtained by crystallization from toluene/methanol=8:2; mp: 148–150 °C; yield: 430 mg (30%); CHN anal. calcd for $C_{26}H_{26}N_2O_5$: C, 69.94; H, 5.87; N, 6.27. Found: C, 69.99; H, 6.11; N, 6.19; $[\alpha]_D^{25}$ −476 (*c* 0.1, chloroform); R_f (90% CH_2Cl_2/9% CH_3OH/1% concentrated ammonium hydroxide): 0.31; ν_{max} (KBr disc): 2930, 2890, 1660, 1550, 1520, 1360, 1150, 1120; MS (EI): *m*/*z* (%) 447 (M^++1, 4), 401 (100), 369 (74), 354 (55), 302 (23); HRMS (EI) *m*/*z* (%) calculated for $C_{26}H_{27}N_2O_5^+$: 447.1914 (M^++H), found: 447.1909 (M^++H, 4); δ_H (360 MHz, $CDCl_3$): 8.01–7.89 (2H, dd, Bn aromatic, A_2B_2, *J* 6.3 and <1), 7.52–7.44 (2H, dd, Bn aromatic, A_2B_2, *J* 6.5 and <1), 6.54, 6.49 (2H, 2d, C_1–H, C_2–H, J_{1-2} 8.2), 5.80 (1H, s, C_8–H), 4.21 (1H, s, C_5–H), 3.91 (3H, s, C_3–OCH_3), 3.82–3.71 (4H, m, C_9–H, C_6–OCH_3), 3.38 (2H, s, C_7–CH_2–), 3.31–2.00 (8H, m, C_{10}–H_a, C_{10}–H_b, C_{15}–H_b, C_{16}–H_a, C_{16}–H_b, –NCH_3), 1.91 (1H, td, C_{15}–H_a, $J_{15a,15b;16a,16b}$ 10.4, $J_{15a,15b}$ 4.3); δ_C (50.3 MHz, $CDCl_3$): 162.23 (C_6), 147.19 (C_3), 146.31 (C_4), 144.54 ($C_{4'}$), 141.78 ($C_{1'}$), 130.07–111.82 (8C, aromatic, C_8, C_{14}), 99.21 (C_7), 89.49 (C_5), 60.09 (C_9), 56.36 (C_6–OCH_3), 53.49 (C_3–OCH_3), 51.45 (C_{16}), 43.89 (C_{13}), 41.10 (NCH_3), 39.62 (C_7–CH_2–), 35.21 (C_{15}), 33.23 (C_{10}).

*4.2.1.11. 5β-Benzyl-4,5α-epoxy-3-methoxy-17-methyl-6,7,8,14-tetradehydro-morphinan (**19a**).* Compound **19a** and compound **20a** were separated by means of column chromatography. Compound **19a** was the first eluted component. Off-white, plate-shaped crystals were obtained by crystallization from toluene/methanol=6:4; mp: 116–118 °C; yield: 309 mg (26%) and 100 mg of unreacted diene **3** also was recovered; CHN anal. calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.73; H, 6.70; N, 3.82; $[\alpha]_D^{25}$ −321 (*c* 0.1, chloroform); R_f (90% CH_2Cl_2/9% CH_3OH/1% concentrated ammonium hydroxide): 0.59; ν_{max} (KBr disc): 2880, 2860, 1610, 1140; MS (EI): *m*/*z* (%) 372 (M^++1, 100), 357 (47), 321 (66); HRMS (EI) *m*/*z* (%) calculated for $C_{25}H_{26}NO_2^+$: 372.1958 (M^++H), found: 372.1964 (M^++H, 100); δ_H (360 MHz, $CDCl_3$): 7.14–7.01 (5H, m, Bn aromatic), 6.65, 6.61 (2H, 2d, C_1–H, C_2–H, J_{1-2} 8.1), 5.84–5.72 (3H, m, C_6–H, C_7–H, C_8–H), 3.84–3.76 (6H, m, C_9–H, C_5–CH_2–, C_3–OCH_3), 3.12–2.09 (8H, m, C_{10}–H_a, C_{10}–H_b, C_{15}–H_b, C_{16}–H_a, C_{16}–H_b, –NCH_3), 1.90 (1H, td, C_{15}–H_a, $J_{15a,15b;16a,16b}$ 11.1, $J_{15a,15b}$ 4.5); δ_C (50.3 MHz, $CDCl_3$): 147.56 (C_3), 145.89 (C_4), 138.37–108.17 (10C, aromatic, C_6, C_7, C_8, C_{14}), 86.75 (C_5), 62.67 (C_9), 56.49 (C_6–OCH_3), 50.17 (C_{16}), 49.34 (C_{13}), 41.56 (NCH_3), 40.67 (C_5–CH_2–), 35.89 (C_{15}), 33.09 (C_{10}).

*4.2.1.12. 5β-(2-Chlorobenzyl)-4,5α-epoxy-3-methoxy-17-methyl-6,7,8,14-tetradehydro-morphinan (**19b**).* Compound **19b** and compound **20b** were separated by means of column chromatography. Compound **19b** was the first eluted component. Pale yellow, plate-shaped crystals were obtained by crystallization from toluene/methanol=6:4; mp: 111–113 °C; yield: 291 mg (23%) and 120 mg of unreacted diene **3** also was recovered; CHN anal. calcd for $C_{25}H_{24}ClNO_2$: C, 73.97; H, 5.96; N, 3.45. Found: C, 73.91; H, 5.97; N, 3.40; $[\alpha]_D^{25}$ −356 (*c* 0.1, chloroform); R_f (90% CH_2Cl_2/9% CH_3OH/1% concentrated ammonium hydroxide): 0.64; ν_{max} (KBr disc): 2900, 2810, 1640, 1360, 1140, 720; MS (EI): *m*/*z* (%) 406 (M^++1, 100), 391 (84), 360 (60); HRMS (EI) *m*/*z* (%) calculated for $C_{25}H_{25}ClNO_2^+$: 406.1568 (M^++H), found: 406.1564 (M^++H, 100); δ_H (360 MHz, $CDCl_3$): 7.16–7.06 (4H, m, Bn aromatic), 6.56, 6.52 (2H, 2d, C_1–H, C_2–H, J_{1-2} 7.9), 5.91 (1H, dd, C_7–H, J_1 6.6, J_2 6.8); 5.80–5.71 (2H, m, C_6–H, C_8–H), 3.78–3.64 (6H, m, C_9–H, C_5–CH_2–, C_3–OCH_3), 3.21–2.11 (8H, m, C_{10}–H_a, C_{10}–H_b, C_{15}–H_b, C_{16}–H_a, C_{16}–H_b, –NCH_3), 1.94 (1H, td, C_{15}–H_a, $J_{15a,15b;16a,16b}$ 10.6, $J_{15a,15b}$ 4.2); δ_C (50.3 MHz, $CDCl_3$): 147.32 (C_3), 146.16 (C_4), 143.56 ($C_{2'}$), 136.45–109.23 (9C, aromatic, C_6, C_7, C_8, C_{14}), 85.42 (C_5), 62.75 (C_9), 56.33 (C_6–OCH_3), 49.69 (C_{16}), 49.11 (C_{13}), 42.14 (NCH_3), 41.23 (C_5–CH_2–), 36.03 (C_{15}), 33.34 (C_{10}).

*4.2.1.13. 4,5α-Epoxy-5β-(2-fluorobenzyl)-3-methoxy-17-methyl-6,7,8,14-tetradehydro-morphinan (**19c**).* Compound **19c** and compound **20c** were separated by means of column chromatography. Compound **19c** was the first eluted component. Pale grey, plate-shaped crystals were obtained by crystallization from toluene/methanol=6:4; mp: 118–120 °C; yield: 259 mg (21%) and 110 mg of unreacted diene **3** also was recovered; CHN anal. calcd for

$C_{25}H_{24}FNO_2$: C, 77.10; H, 6.21; N, 3.60. Found: C, 77.14; H, 6.27; N, 3.51; $[\alpha]_D^{25}$ −399 (*c* 0.1, chloroform); R_f (90% CH_2Cl_2/9% CH_3OH/1% concentrated ammonium hydroxide): 0.53; ν_{max} (KBr disc): 2900, 2880, 1600, 1350, 1070; MS (EI): *m*/*z* (%) 390 (M^++1, 100), 375 (65), 323 (54); HRMS (EI) *m*/*z* (%) calculated for $C_{25}H_{25}FNO_2^+$: 390.1864 (M^++H), found: 390.1860 (M^++H, 100); δ_H (360 MHz, $CDCl_3$): 7.10–6.94 (4H, m, Bn aromatic), 6.45, 6.42 (2H, 2d, C_1–H, C_2–H, J_{1-2} 8.3), 5.95 (1H, dd, C_7–H, J_1 6.5, J_2 6.6); 5.81–5.74 (2H, m, C_6–H, C_8–H), 3.82–3.71 (6H, m, C_9–H, C_5–CH_2–, C_3–OCH_3), 3.21–2.04 (9H, m, C_{10}–H_a, C_{10}–H_b, C_{15}–H_a, C_{15}–H_b, C_{16}–H_a, C_{16}–H_b, NCH_3); δ_C (50.3 MHz, $CDCl_3$): 158.34 ($C_{2'}$), 147.45 (C_3), 146.23 (C_4), 135.12–110.78 (9C, aromatic, C_6, C_7, C_8, C_{14}), 86.01 (C_5), 61.76 (C_9), 56.52 (C_6–OCH_3), 50.44 (C_{16}), 49.76 (C_{13}), 42.56 (NCH_3), 36.32 (C_{15}), 33.49 (C_{10}), 32.10 (C_5–CH_2–).

*4.2.1.14. 4,5α-Epoxy-3-methoxy-17-methyl-6,7,8,14-tetradehydro-5β-(2-trifluoromethylbenzyl)-morphinan (**19d**).* Compound **19d** and compound **20d** were separated by means of column chromatography. Compound **19d** was the first eluted component. Off-white, plate-shaped crystals were obtained by crystallization from toluene/methanol=6:4; mp: 129–131 °C; yield: 367 mg (25%) and 60 mg of unreacted diene **3** also was recovered; CHN anal. calcd for $C_{26}H_{24}F_3NO_2$: C, 71.06; H, 5.50; N, 3.19. Found: C, 71.01; H, 5.55; N, 3.20; $[\alpha]_D^{25}$ −432 (*c* 0.1, chloroform); R_f (90% CH_2Cl_2/9% CH_3OH/1% concentrated ammonium hydroxide): 0.64; ν_{max} (KBr disc): 2900, 2870, 1640, 1410, 1350, 1130; MS (EI): *m*/*z* (%) 440 (M^++1, 100), 425 (61), 379 (87), 351 (56); HRMS (EI) *m*/*z* (%) calculated for $C_{26}H_{25}F_3NO_2^+$: 440.1832 (M^++H), found: 440.1821 (M^++H, 100); δ_H (360 MHz, $CDCl_3$): 7.28–7.21 (2H, m, Bn aromatic), 7.11–7.07 (2H, m, Bn aromatic), 6.56, 6.52 (2H, 2d, C_1–H, C_2–H, J_{1-2} 8.1), 5.84 (1H, dd, C_7–H, J_1 7.0, J_2 6.8); 5.79–5.73 (2H, m, C_6–H, C_8–H), 3.84–3.69 (6H, m, C_9–H, C_5–CH_2–, C_3–OCH_3), 3.27–2.01 (9H, m, C_{10}–H_a, C_{10}–H_b, C_{15}–H_a, C_{15}–H_b, C_{16}–H_a, C_{16}–H_b, NCH_3); δ_C (50.3 MHz, $CDCl_3$): 147.21 (C_3), 146.45 (C_4), 133.83–107.12 (10C, aromatic, C_6, C_7, C_8, C_{14}, CF_3), 86.34 (C_5), 61.20 (C_9), 56.91 (C_6–OCH_3), 51.12 (C_{16}), 50.07 (C_{13}), 41.87 (NCH_3), 37.24 (C_5–CH_2–), 36.07 (C_{15}), 33.54 (C_{10}).

*4.2.1.15. 4,5α-Epoxy-3-methoxy-17-methyl-5β-(4-nitrobenzyl)-6,7,8,14-tetradehydro-morphinan (**19e**).* Compound **19e** and compound **20e** were separated by means of column chromatography. Compound **19e** was the first eluted component. Yellow, plate-shaped crystals were obtained by crystallization from toluene/methanol=1:1; mp: 121–123 °C; yield: 327 mg (24%) and 80 mg of unreacted diene **3** also was recovered; CHN anal. calcd for $C_{25}H_{24}N_2O_4$: C, 72.10; H, 5.81; N, 6.73. Found: C, 72.01; H, 5.87; N, 6.67; $[\alpha]_D^{25}$ −408 (*c* 0.1, chloroform); R_f (90% CH_2Cl_2/9% CH_3OH/1% concentrated ammonium hydroxide): 0.67; ν_{max} (KBr disc): 2910, 2880, 1660, 1540, 1510, 1360, 1120, 1110; MS (EI): *m*/*z* (%) 417 (M^++1, 12), 371 (100), 356 (59); HRMS (EI) *m*/*z* (%) calculated for $C_{25}H_{25}N_2O_4^+$: 417.1809 (M^++H), found: 417.1814 (M^++H, 12); δ_H (360 MHz, $CDCl_3$): 8.09–7.90 (2H, dd, Bn aromatic, A_2B_2, *J* 6.1 and <1), 7.64–7.47 (2H, dd, Bn aromatic, A_2B_2, *J* 6.5 and <1), 6.59, 6.55 (2H, 2d, C_1–H, C_2–H, J_{1-2} 8.0), 5.84–5.73 (3H, m, C_6–H, C_7–H, C_8–H), 3.81–3.65 (6H, m, C_9–H, C_5–CH_2–, C_3–OCH_3), 3.30–2.03 (9H, m, C_{10}–H_a, C_{10}–H_b, C_{15}–H_a, C_{15}–H_b, C_{16}–H_a, C_{16}–H_b, $-NCH_3$); δ_C (50.3 MHz, $CDCl_3$): 146.43 (C_3), 145.65 (C_4), 142.12 ($C_{4'}$), 139.10 ($C_{1'}$), 131.67–109.82 (8C, aromatic, C_6, C_7, C_8, C_{14}), 85.69 (C_5), 61.17 (C_9), 56.43 (C_6–OCH_3), 51.67 (C_{16}), 50.98 (C_{13}), 43.24 (C_5–CH_2–), 41.36 (NCH_3), 35.43 (C_{15}), 32.81 (C_{10}).

*4.2.1.16. 7β-Benzyl-4,5α-epoxy-3-methoxy-17-methyl-5,6,8,14-tetradehydro-morphinan (**20a**).* Compound **19a** and compound **20a** were separated by means of column chromatography. Compound **20a** was the second eluted component. Yellow, cubic crystals were obtained by crystallization from toluene/methanol=1:1; mp: 124–126 °C; yield: 665 mg (56%) and 100 mg of unreacted diene **3** also was recovered; CHN anal. calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.87; H, 6.79; N, 3.84; $[\alpha]_D^{25}$ −67 (*c* 0.1, chloroform); R_f (90% CH_2Cl_2/9% CH_3OH/1% concentrated ammonium hydroxide): 0.34; ν_{max} (KBr disc): 2920, 2880, 1650, 1420, 1120; MS (EI): *m*/*z* (%) 372 (M^++1, 100), 357 (73), 318 (32); HRMS (EI) *m*/*z* (%) calculated for $C_{25}H_{26}NO_2^+$: 372.1958 (M^++H), found: 372.1950 (M^++H, 100); δ_H (360 MHz, $CDCl_3$): 7.20–7.09 (5H, m, Bn aromatic), 6.51, 6.49 (2H, 2d, C_1–H, C_2–H, J_{1-2} 7.9), 5.34 (1H, d, C_8–H, J_{7a-8} 5.5), 4.78 (1H, d, C_6–H, J_{6-7a} 4.9), 3.84–3.77 (4H, m, C_9–H, C_3–OCH_3), 3.31 (1H, dd, C_7–H, J_{7a-8} 5.5, J_{6-7a} 4.9), 3.14–2.09 (10H, m, C_5–CH_2–, C_{10}–H_a, C_{10}–H_b, C_{15}–H_b, C_{16}–H_a, C_{16}–H_b, $-NCH_3$), 1.97 (1H, td, C_{15}–H_a, $J_{15a,15b;16a,16b}$ 10.8, $J_{15a,15b}$ 4.3); δ_C (50.3 MHz, $CDCl_3$): 161.12 (C_5), 146.49 (C_3), 145.31 (C_4), 140.11 ($C_{1'}$), 138.32 (C_{14}), 134.59–108.47 (9C, aromatic, C_6, C_8), 61.84 (C_9), 56.34 (C_6–OCH_3), 51.14 (C_{16}), 43.24 (C_5–CH_2–), 41.67 (C_{13}), 41.18 (NCH_3), 37.56 (C_7), 34.39 (C_{15}), 31.69 (C_{10}).

*4.2.1.17. 7β-(2-Chlorobenzyl)-4,5α-epoxy-3-methoxy-17-methyl-5,6,8,14-tetradehydro-morphinan (**20b**).* Compound **19b** and compound **20b** were separated by means of column chromatography. Compound **20b** was the second eluted component. Pale yellow, cubic crystals were obtained by crystallization from toluene/methanol=1:1; mp: 127–129 °C; yield: 736 mg (58%) and 120 mg of unreacted diene **3** also was recovered; CHN anal. calcd for $C_{25}H_{24}ClNO_2$: C, 73.97; H, 5.96; N, 3.45. Found: C, 74.04; H, 6.04; N, 3.41; $[\alpha]_D^{25}$ −43 (*c* 0.1, chloroform); R_f (90% CH_2Cl_2/9% CH_3OH/1% concentrated ammonium hydroxide): 0.44; ν_{max} (KBr disc): 2920, 2870, 1640, 1350, 1450, 1130, 720; MS (EI): *m*/*z* (%) 406 (M^++1, 100), 391 (78), 377 (89), 352 (48); HRMS (EI) *m*/*z* (%) calculated for $C_{25}H_{25}ClNO_2^+$: 406.1568 (M^++H), found: 406.1575 (M^++H, 100); δ_H (360 MHz, $CDCl_3$): 7.16–7.03 (4H, m, Bn aromatic), 6.56, 6.52 (2H, 2d, C_1–H, C_2–H, J_{1-2} 8.0), 5.29 (1H, d, C_8–H, J_{7a-8} 5.2), 4.65 (1H, d, C_6–H, J_{6-7a} 5.1), 3.90–3.79 (4H, m, C_9–H, C_3–OCH_3), 3.37 (1H, dd, C_7–H, J_{7a-8} 5.2, J_{6-7a} 5.1), 3.27–2.04 (11H, m, C_5–CH_2–, C_{10}–H_a, C_{10}–H_b, C_{15}–H_a, C_{15}–H_b, C_{16}–H_a, C_{16}–H_b, $-NCH_3$); δ_C (50.3 MHz, $CDCl_3$): 163.08 (C_5), 146.23 (C_3), 144.27 (C_4), 141.48 ($C_{1'}$), 137.67 (C_{14}), 133.17–108.78 (9C, aromatic, C_6, C_8), 61.23 (C_9), 56.93 (C_6–OCH_3), 51.08 (C_{16}), 41.89 (C_{13}), 41.03 (NCH_3), 37.28 (C_7), 34.59 (C_5–CH_2–), 33.67 (C_{15}), 30.12 (C_{10}).

*4.2.1.18. 4,5α-Epoxy-7β-(2-fluorobenzyl)-3-methoxy-17-methyl-5,6,8,14-tetradehydro-morphinan (**20c**).* Compound **19c** and compound **20c** were separated by means of column chromatography. Compound **20c** was the second eluted component. Pale yellow, cubic crystals were obtained by crystallization from toluene/methanol=1:1; mp: 133–135 °C; yield: 678 mg (55%) and 110 mg of unreacted diene **3** also was recovered; CHN anal. calcd for $C_{25}H_{24}FNO_2$: C, 77.10; H, 6.21; N, 3.60. Found: C, 77.02; H, 6.25; N, 3.66; $[\alpha]_D^{25}$ −78 (*c* 0.1, chloroform); R_f (90% CH_2Cl_2/9% CH_3OH/1% concentrated ammonium hydroxide): 0.32; ν_{max} (KBr disc): 2910, 2860, 1620, 1460, 1340, 1040; MS (EI): *m*/*z* (%) 390 (M^++1, 100), 375 (87), 361 (89), 334 (34); HRMS (EI) *m*/*z* (%) calculated for $C_{25}H_{25}FNO_2^+$: 390.1864 (M^++H), found: 390.1856 (M^++H, 100); δ_H (360 MHz, $CDCl_3$): 7.09–6.93 (4H, m, Bn aromatic), 6.50, 6.47 (2H, 2d, C_1–H, C_2–H, J_{1-2} 8.1), 5.39 (1H, d, C_8–H, J_{7a-8} 5.5), 4.88 (1H, d, C_6–H, J_{6-7a} 5.3), 3.92–3.81 (4H, m, C_9–H, C_3–OCH_3), 3.44 (1H, dd, C_7–H, J_{7a-8} 5.5, J_{6-7a} 5.3), 3.26–1.98 (11H, m, C_5–CH_2–, C_{10}–H_a, C_{10}–H_b, C_{15}–H_a, C_{15}–H_b, C_{16}–H_a, C_{16}–H_b, $-NCH_3$); δ_C (50.3 MHz, $CDCl_3$): 163.66 (C_5), 159.14 ($C_{2'}$), 147.11 (C_3), 143.73 (C_4), 136.23 (C_{14}), 133.40–109.69 (9C, aromatic, C_6, C_8), 61.73 (C_9), 56.23 (C_6–OCH_3), 51.48 (C_{16}), 41.45 (C_{13}), 40.66 (NCH_3), 35.19 (C_7), 34.08 (C_5–CH_2–), 32.99 (C_{15}), 31.49 (C_{10}).

*4.2.1.19. 4,5α-Epoxy-3-methoxy-17-methyl-5,6,8,14-tetradehydro-7β-(2-trifluoro-methylbenzyl)-morphinan (**20d**).* Compound **19d** and compound **20d** were separated by means of column chromatography. Compound **20d** was the second eluted component.

Off-white, cubic crystals were obtained by crystallization from toluene/methanol=1:1; mp: 130–132 °C; yield: 881 mg (60%) and 60 mg of unreacted diene **3** also was recovered; CHN anal. calcd for $C_{26}H_{24}F_3NO_2$: C, 71.06; H, 5.50; N, 3.19. Found: C, 71.09; H, 5.53; N, 3.18; $[\alpha]_D^{25}$ −48 (*c* 0.1, chloroform); R_f (90% CH_2Cl_2/9% CH_3OH/1% concentrated ammonium hydroxide): 0.44; ν_{max} (KBr disc): 2920, 2870, 2840, 1630, 1460, 1420, 1350, 1130; MS (EI): *m*/*z* (%) 440 (M^++1, 100), 382 (78), 366 (62), 340 (50); HRMS (EI) *m*/*z* (%) calculated for $C_{26}H_{25}F_3NO_2^+$: 440.1832 (M^++H), found: 440.1837 (M^++H, 100); δ_H (360 MHz, $CDCl_3$): 7.35–7.28 (2H, m, Bn aromatic), 7.17–7.09 (2H, m, Bn aromatic), 6.57, 6.54 (2H, 2d, C_1–H, C_2–H, J_{1-2} 8.0), 5.30 (1H, d, C_8–H, J_{7a-8} 5.0), 4.91 (1H, d, C_6–H, J_{6-7a} 5.1), 3.87–3.72 (4H, m, C_9–H, C_3–OCH_3), 3.35 (1H, dd, C_7–H, J_{7a-8} 5.0, J_{6-7a} 5.1), 3.23–1.94 (11H, m, C_5–CH_2–, C_{10}–H_a, C_{10}–H_b, C_{15}–H_a, C_{15}–H_b, C_{16}–H_a, C_{16}–H_b, –NCH_3); δ_C (50.3 MHz, $CDCl_3$): 160.16 (C_5), 146.34 (C_3), 144.70 (C_4), 137.29 (C_{14}), 134.39–110.26 (10C, aromatic, C_6, C_8, CF_3), 61.24 (C_9), 56.79 (C_6–OCH_3), 51.30 (C_{16}), 42.08 (C_{13}), 41.63 (NCH_3), 36.51 (C_5–CH_2–), 35.03 (C_7), 32.39 (C_{15}), 30.98 (C_{10}).

*4.2.1.20. 4,5α-Epoxy-3-methoxy-17-methyl-7β-(4-nitrobenzyl)-5,6,8,14-tetradehydro-morphinan (**20e**).* Compound **19e** and compound **20e** were separated by means of column chromatography. Compound **20e** was the second eluted component. Off-white, cubic crystals were obtained by crystallization from toluene/methanol=1:1; mp: 140–142 °C; yield: 858 mg (63%) and 80 mg of unreacted diene **3** also was recovered; CHN anal. calcd for $C_{25}H_{24}N_2O_4$: C, 72.10; H, 5.81; N, 6.73. Found: C, 72.12; H, 5.85; N, 6.72; $[\alpha]_D^{25}$ −48 (*c* 0.1, chloroform); R_f (90% CH_2Cl_2/9% CH_3OH/1% concentrated ammonium hydroxide): 0.51; ν_{max} (KBr disc): 2920, 2870, 2860, 1650, 1540, 1440, 1330, 1110; MS (EI): *m*/*z* (%) 417 (M^++1, 4), 371 (100), 356 (42), 321 (43); HRMS (EI) *m*/*z* (%) calculated for $C_{25}H_{25}N_2O_4^+$: 417.1809 (M^++H), found: 417.1800 (M^++H, 4); δ_H (360 MHz, $CDCl_3$): 8.14–7.94 (2H, dd, Bn aromatic, A_2B_2, *J* 6.6 and <1), 7.78–7.61 (2H, dd, Bn aromatic, A_2B_2, *J* 6.1 and <1), 6.52, 6.48 (2H, 2d, C_1–H, C_2–H, J_{1-2} 8.3), 5.42 (1H, d, C_8–H, J_{7a-8} 5.4), 4.84 (1H, d, C_6–H, J_{6-7a} 4.9), 3.90–3.81 (4H, m, C_9–H, C_3–OCH_3), 3.47 (1H, dd, C_7–H, J_{7a-8} 5.4, J_{6-7a} 4.9), 3.30–2.07 (10H, m, C_5–CH_2–, C_{10}–H_a, C_{10}–H_b, C_{15}–H_b, C_{16}–H_a, C_{16}–H_b, –NCH_3), 1.97 (1H, td, C_{15}–H_a, $J_{15a,15b;16a,16b}$ 11.1, $J_{15a,15b}$ 4.5); δ_C (50.3 MHz, $CDCl_3$): 161.84 (C_5), 146.37 (C_3), 145.11 ($C_{4'}$), 144.47 ($C_{1'}$), 143.74 (C_4), 138.44 (C_{14}), 135.10–109.82 (8C, aromatic, C_6, C_8), 61.44 (C_9), 56.10 (C_6–OCH_3), 51.67 (C_{16}), 43.58 (C_5–CH_2–), 42.21 (C_{13}), 41.83 (NCH_3), 34.70 (C_7), 32.67 (C_{15}), 31.27 (C_{10}).

4.2.2. General procedure for acid-catalyzed rearrangement of dienes

A mixture of the diene (1.00 g) and 98% methanesulfonic acid (5 mL) was stirred for 20 min at 0 °C and then for 30 min at 90–95 °C (the progress of the reaction was followed by TLC). After completion the reaction mixture was added dropwise, with stirring and external ice cooling, to a solution of potassium hydrogen carbonate (10 g) in water (50 mL). After extraction with chloroform (3×15 mL), the combined organic extracts were washed with saturated brine, dried ($MgSO_4$) and concentrated under vacuum to yield crude apocodeine. Recrystallization from anhydrous ether gave pure apocodeine.

*4.2.2.1. (−)-R-3-Benzyl-11-hydroxy-10-methoxy-aporphine (**22a**).* Off-white, needle-shaped crystals; mp: 212–214 °C (ether); yield: 790 mg (79%); CHN anal. calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.73; H, 6.83; N, 3.71; $[\alpha]_D^{25}$ −124 (*c* 0.1, chloroform); R_f (chloroform/methanol=8:2): 0.61; ν_{max} (KBr disc): 3550, 3050, 2940, 2840, 1630, 1590, 1480, 1300, 1120; MS (EI): *m*/*z* (%) 372 (M^++1, 100), 342 (46), 308 (30); HRMS (EI) *m*/*z* (%) calculated for $C_{25}H_{26}NO_2^+$: 372.1958 (M^++H), found: 372.1966 (M^++H, 100); δ_H (360 MHz, $CDCl_3$): 7.18–7.04 (6H, m, Bn aromatic, C_1–H), 6.84 (1H, d, C_2–H, J_{1-2} 8.4), 6.59, 6.55 (2H, 2d, C_8–H, C_9–H, J_{8-9} 7.9), 6.12 (1H, br s, OH), 4.17 (1H, td, C_{6a}–H, J_{6a-7a} 10.5, J_{6a-7b} 2.8), 3.87 (3H, s, C_{10}–OCH_3), 3.81 (2H, s, C_3–CH_2–), 3.22–2.41 (9H, m, C_4–H_a, C_4–H_b, C_5–H_a, C_5–H_b, C_7–H_a, C_7–H_b, –NCH_3); δ_C (50.3 MHz, $CDCl_3$): 146.49 (C_9), 144.12 (C_{10}), 141.63 ($C_{1'}$), 138.54–113.17 (15C, aromatic), 61.24 (C_{6a}), 56.47 (C_{10}–OCH_3), 54.74 (C_5), 41.18 (NCH_3), 40.24 (C_3–CH_2–), 35.51 (C_7), 32.10 (C_4).

*4.2.2.2. (−)-R-3-(2-Chlorobenzyl)-11-hydroxy-10-methoxy-aporphine (**22b**).* Pale yellow, needle-shaped crystals; mp: 233–235 °C (ether); yield: 730 mg (73%); CHN anal. calcd for $C_{25}H_{24}ClNO_2$: C, 73.97; H, 5.96; N, 3.45. Found: C, 74.07; H, 6.01; N, 3.44; $[\alpha]_D^{25}$ −147 (*c* 0.1, chloroform); R_f (chloroform/methanol=8:2): 0.51; ν_{max} (KBr disc): 3560, 3080, 2950, 1630, 1590, 1480, 1300, 1120, 730; MS (EI): *m*/*z* (%) 406 (M^++1, 100), 391 (62), 361 (71), 332 (21); HRMS (EI) *m*/*z* (%) calculated for $C_{25}H_{25}ClNO_2^+$: 406.1568 (M^++H), found: 406.1560 (M^++H, 100); δ_H (360 MHz, $CDCl_3$): 7.12–7.03 (5H, m, Bn aromatic, C_1–H), 6.89 (1H, d, C_2–H, J_{1-2} 8.1), 6.55, 6.52 (2H, 2d, C_8–H, C_9–H, J_{8-9} 8.0), 6.24 (1H, br s, OH), 4.21 (1H, td, C_{6a}–H, J_{6a-7a} 10.1, J_{6a-7b} 3.0), 3.81 (2H, s, C_3–CH_2–), 3.74 (3H, s, C_{10}–OCH_3), 3.31–2.44 (9H, m, C_4–H_a, C_4–H_b, C_5–H_a, C_5–H_b, C_7–H_a, C_7–H_b, –NCH_3); δ_C (50.3 MHz, $CDCl_3$): 145.67 (C_9), 143.20 (C_{10}), 142.69 ($C_{1'}$), 137.89–112.59 (15C, aromatic), 61.07 (C_{6a}), 56.23 (C_{10}–OCH_3), 55.01 (C_5), 42.03 (NCH_3), 35.56 (C_7), 33.28 (C_3–CH_2–), 32.54 (C_4).

*4.2.2.3. (−)-R-1-Benzyl-11-hydroxy-2,10-dimethoxy-aporphine (**23a**).* White, plate-shaped crystals; mp: 178–182 °C (ether); yield: 710 mg (71%); CHN anal. calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.84; H, 6.85; N, 3.44; $[\alpha]_D^{25}$ −62 (*c* 0.1, chloroform); R_f (chloroform/methanol=8:2): 0.43; ν_{max} (KBr disc): 3470, 3010, 2830, 1620, 1530, 1510, 1440; MS (EI): *m*/*z* (%) 402 (M^++1, 78), 387 (100), 343 (38); HRMS (EI) *m*/*z* (%) calculated for $C_{25}H_{28}NO_3^+$: 402.2069 (M^++H), found: 402.2071 (M^++H, 78); δ_H (360 MHz, $CDCl_3$): 7.22–7.04 (5H, m, Bn aromatic), 6.61, 6.56 (2H, 2d, C_8–H, C_9–H, J_{8-9} 8.0), 6.33 (1H, s, C_3–H), 6.02 (1H, br s, OH), 4.29 (1H, td, C_{6a}–H, J_{6a-7a} 9.7, J_{6a-7b} 2.4), 3.78 (3H, s, C_{10}–OCH_3), 3.71 (3H, s, C_2–OCH_3), 3.68 (2H, s, C_1–CH_2–), 3.41–2.35 (9H, m, C_4–H_a, C_4–H_b, C_5–H_a, C_5–H_b, C_7–H_a, C_7–H_b, –NCH_3); δ_C (50.3 MHz, $CDCl_3$): 154.23 (C_2), 147.78 (C_9), 146.27 (C_{10}), 137.12–112.66 (15C, aromatic), 6.87 (C_{6a}), 57.12 (C_2–OCH_3), 56.34 (C_{10}–OCH_3), 52.71 (C_5), 40.81 (NCH_3), 34.56 (C_7), 32.56 (C_4), 30.24 (C_1–CH_2–).

*4.2.2.4. (−)-R-1-(2-Chlorobenzyl)-11-hydroxy-2,10-dimethoxy-aporphine (**23b**).* Yellow, plate-shaped crystals; mp: 168–171 °C (ether); yield: 740 mg (74%); CHN anal. calcd for $C_{26}H_{26}ClNO_3$: C, 71.63; H, 6.01; N, 3.21. Found: C, 71.57; H, 6.09; N, 3.27; $[\alpha]_D^{25}$ −81 (*c* 0.1, chloroform); R_f (chloroform/methanol=8:2): 0.52; ν_{max} (KBr disc): 3520, 3010, 2960, 1600, 1580, 1500, 1340, 1120, 740; MS (EI): *m*/*z* (%) 436 (M^++1, 91), 421 (100), 398 (67), 337 (32); HRMS (EI) *m*/*z* (%) calculated for $C_{26}H_{27}ClNO_3^+$: 436.1679 (M^++H), found: 436.1670 (M^++H, 91); δ_H (360 MHz, $CDCl_3$): 7.16–7.02 (4H, m, Bn aromatic), 6.63, 6.60 (2H, 2d, C_8–H, C_9–H, J_{8-9} 8.3), 6.44 (1H, s, C_3–H), 6.12 (1H, br s, OH), 4.29 (1H, td, C_{6a}–H, J_{6a-7a} 9.9, J_{6a-7b} 2.7), 3.84 (3H, s, C_{10}–OCH_3), 3.81 (2H, s, C_1–CH_2–), 3.77 (3H, s, C_2–OCH_3), 3.43–2.41 (9H, m, C_4–H_a, C_4–H_b, C_5–H_a, C_5–H_b, C_7–H_a, C_7–H_b, –NCH_3); δ_C (50.3 MHz, $CDCl_3$): 161.12 (C_2), 149.56 (C_9), 146.32 (C_{10}), 141.43 ($C_{1'}$), 139.56–114.51 (14C, aromatic), 61.44 (C_{6a}), 56.23–56.01 (C_{10}–OCH_3, C_{10}–OCH_3), 53.78 (C_5), 42.11 (NCH_3), 35.10 (C_7), 32.52 (C_4), 29.16 (C_1–CH_2–).

*4.2.2.5. (−)-R-3-Benzyl-11-hydroxy-2,10-dimethoxy-aporphine (**24a**).* Off-white, plate-shaped crystals; mp: 167–169 °C (ether); yield: 800 mg (80%); CHN anal. calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.73; H, 6.82; N, 3.50; $[\alpha]_D^{25}$ −101 (*c* 0.1, chloroform); R_f (chloroform/methanol=8:2): 0.61; ν_{max} (KBr disc): 3580, 3100, 2870, 2810, 1640, 1500, 1350; MS (EI): *m*/*z* (%) 402 (M^++1, 100), 387 (78), 351 (89); HRMS (EI) *m*/*z* (%) calculated for $C_{25}H_{26}NO_2^+$: 402.2069 (M^++H), found: 402.2066 (M^++H, 100); δ_H (360 MHz, $CDCl_3$): 7.14–7.04 (5H, m, Bn aromatic), 6.53, 6.50 (2H,

2d, C_8–H, C_9–H, J_{8-9} 8.0), 6.47 (1H, s, C_1–H), 6.20 (1H, br s, OH), 4.26 (1H, td, C_{6a}–H, J_{6a-7a} 10.0, J_{6a-7b} 2.6), 3.87 (3H, s, C_{10}–OCH_3), 3.84 (3H, s, C_2–OCH_3), 3.75 (2H, s, C_3–CH_2–), 3.37–2.34 (9H, m, C_4–H_a, C_4–H_b, C_5–H_a, C_5–H_b, C_7–H_a, C_7–H_b, –NCH_3); δ_C (50.3 MHz, $CDCl_3$): 156.56 (C_2), 146.59 (C_9), 145.36 (C_{10}), 142.48 ($C_{1'}$), 139.66–115.25 (14C, aromatic), 61.30 (C_{6a}), 56.40–56.09 (C_2–OCH_3, C_{10}–OCH_3), 55.03 (C_5), 42.45 (NCH_3), 35.57 (C_7), 33.24 (C_3–CH_2–), 33.44 (C_4).

*4.2.2.6. (−)-R-3-(2-Chlorobenzyl)-11-hydroxy-2,10-dimethoxy-aporphine (**24b**).* Pale yellow, plate-shaped crystals; mp: 173–175 °C (ether); yield: 730 mg (73%); CHN anal. calcd for $C_{26}H_{26}ClNO_3$: C, 71.63; H, 6.01; N, 3.21. Found: C, 71.67; H, 6.04; N, 3.30; $[\alpha]_D^{25}$ −111 (*c* 0.1, chloroform); R_f (chloroform/methanol=8:2): 0.65; ν_{max} (KBr disc): 3520, 2940, 1660, 1600, 1440, 1330, 1140, 730; MS (EI): *m*/*z* (%) 436 (M^++1, 100), 421 (89), 400 (14), 376 (71), 356 (27); HRMS (EI) *m*/*z* (%) calculated for $C_{26}H_{27}ClNO_3^+$: 436.1679 (M^++H), found: 436.1677 (M^++H, 100); δ_H (360 MHz, $CDCl_3$): 7.18–7.07 (4H, m, Bn aromatic), 6.60, 6.57 (2H, 2d, C_8–H, C_9–H, J_{8-9} 8.1), 6.39 (1H, s, C_1–H), 6.13 (1H, br s, OH), 4.24 (1H, td, C_{6a}–H, J_{6a-7a} 9.7, J_{6a-7b} 2.5), 3.87 (3H, s, C_{10}–OCH_3), 3.81 (2H, s, C_3–CH_2–), 3.76 (2H, s, C_3–CH_2–), 3.36–2.40 (9H, m, C_4–H_a, C_4–H_b, C_5–H_a, C_5–H_b, C_7–H_a, C_7–H_b, –NCH_3); δ_C (50.3 MHz, $CDCl_3$): 154.12 (C_2), 146.60 (C_9), 144.67 (C_{10}), 142.34 ($C_{1'}$), 139.29–115.78 (14C, aromatic), 62.00 (C_{6a}), 56.23–56.20 (C_2–OCH_3, C_{10}–OCH_3), 55.56 (C_5), 42.36 (NCH_3), 34.89 (C_7), 33.34 (C_3–CH_2–), 32.26 (C_4).

4.3. Computational procedure

We have carried out the geometry optimization at Becke's three-parameter hybrid (B3LYP)[13] levels in the DFT with the basis set 6-31G* using Gaussian 98.[9] The solvent effect was not considered. We assumed that the morphinans **1** or **3** and the benzyl chlorides were far apart in the initial state. After optimizing the TS structure, vibrational calculation was performed to confirm that the TS had only one imaginary vibrational frequency. Intrinsic reaction coordinate calculation was also carried out to ensure that the TS connected the initial and the intended final states. The reported net atomic charges were obtained for the geometry optimized structures using the NBO (natural bond orbital) analysis implemented in Gaussian 98 package. Mulliken population analyses for optimized TS structures were calculated by Fragment Reassociation method.[8]

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