

Salutaridine and its derivatives as thebaine-equivalents in the synthesis of aporphines

Antal Udvardy and Attila Sipos

Dedicated to the memory of Professor Meinhart H. Zenk

Abstract - Here we report on the transformation of tetracyclic morphinan salutaridine (**1**) into 2,3,10,11-tetrasubstituted (*R*)-aporphines. This method serves as another chemical proof of the previously verified biosynthetic connection with pentacyclic morphinan-6,8-diene-type thebaine. In the presence of nucleophiles, this procedure could lead to pharmacologically interesting new tetrasubstituted aporphinoids. The enantioselective synthesis of 7*S*-salutaridinol (**2**) has been also achieved in order to investigate the acid-catalyzed reactions of this natural morphinan.

Keywords: Alkaloids; Rearrangements; Reductions; Morphinans; Aporphines

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2 Antal Udvardy

3 Department of Physical Chemistry, University of Debrecen, P.O. Box 7, H-
4 4010 Debrecen, Hungary

5

6 Attila Sipos (✉)

7 Department of Pharmaceutical Chemistry, Medical and Health Science
8 Center, University of Debrecen, P.O. Box 70, H-4032 Egyetem Sq. 1,
9 Debrecen, Hungary. Tel.: +36-52-512-900/22478, Fax: +36-52-512-586, e-
10 mail: sipos.attila@pharm.unideb.hu

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Introduction

Salutaridine (**1**) is an alkaloid that is present in the morphinan alkaloid pathway of opium poppy [1]. Barton and co-workers reported the transformation (Scheme 1) of (*R*)-reticuline into salutaridine (**1**) by a regioselective *para-ortho* oxidative coupling [2]. This finding was confirmed and further investigated by Zenk and co-workers pointing out the role of cytochrome P-450 linked microsomal enzymes [3]. On the other hand, salutaridine (**1**) was converted into (*7S*)-salutaridinol (**2**) in the presence of enzyme salutaridine reductase and accompanied by the reduction of NADPH to NADP⁺ [4].

<Scheme 1>

It was also proven that compound **2** could be transformed into thebaine (Fig. 1) in two steps involving the acetyl coenzyme A catalyzed acetylation of 7 β -hydroxyl function followed by the spontaneous loss of an acetate ion and a rearrangement [5]. Generally all the known efforts for the chemical characterization of compound **1** focused on the transformation into (*7S*)-salutaridinol (**2**) or the mixture of *7R* and *7S* stereoisomers of compound **2** [2].

<Figure 1>

The application of thebaine in the preparation of medically important opiate analgesics and (partial or full) antagonists [6], new opioid-active

research derivatives [7] and promising dopaminergic aporphinoids [8] has been considerably increased. Our group reported on the first successful acid-catalyzed rearrangement of morphinan-5,8-dienes into corresponding 3-substituted-aporphines (Fig. 1) [9]. As a consequence of these results, we turned our attention to the investigation of the chemical characteristics of salutaridine (**1**) and its reduced forms, having the morphinan-5,8-dienone structure, to explore the possibility of thebaine-like application of this family of tetracyclic alkaloids.

Results and Discussion

Salutaridine (**1**) is readily available from *Papaver bracteatum* Lindl. [10] cultivated also in Hungary. Alternatively, biosynthetic [11] and preparative procedures [2, 12] were also elaborated for this purpose. The acid-catalyzed rearrangement was performed in accordance with the procedure resulted several selective and active dopaminergic aporphines [13].

<Scheme 2>

The methanesulfonic acid-mediated rearrangement (Scheme 2) resulted (*R*)-3,11-dihydroxy-2,10-dimethoxyaporphine (**3**) in excellent yield (88%). The substitution pattern of ring A was confirmed by NOESY measurements confirming short spatial distance between the H1 and OCH₃ protons (and no coupling between H4 and OCH₃ protons). The *R*

1 configuration of C6a carbon was supported by the optical rotation of the
2 molecule which was found to be $[\alpha]_D^{20} = -108$ ($c=0.2$ in methanol). This
3 value confirms *R* configuration in view of previous results for (*R*)- and (*S*)-
4 aporphines (approx. -130 vs. +130, respectively) with similar substitution
5 [14] as well as ^1H -NMR chemical shifts of H6a (vide infra). It might be
6 interesting to note that 2,3,10,11-tetrasubstituted aporphines form a small
7 family of the aporphinoids [15a], therefore this methodology could lead to
8 preparation and characterization of several new member of this group of
9 alkaloids. Up to now there was no procedure described for the synthesis of
10 such tetrasubstituted aporphines, however the successful isolation of the
11 2,3-dihydroxy-10,11-dimethoxy congener was reported from Chinese
12 *Magnolia cortex* [15b].

13 In view of our previous mechanistic explanation for the rearrangement of
14 morphinan-5,8-dienes [9] the following (Scheme 3) a protonation-induced,
15 aromatization-driven mechanism is suggested for this reaction of
16 salutaridine (**1**).

17 <Scheme 3>

18 The phenomenon of nucleophilic transesterification of the intermediary
19 methoxonium ion was first observed in the course of rearrangement
20 experiments of thebaine in methanesulfonic acid [16]. In the presence of an
21 alcohol (ROH) the main rearrangement product was identified as the

1 corresponding 2-OR-apocodeine besides the 2-OMe-aporphine. This
2 observation was efficiently used in the synthesis of pharmacologically
3 active compounds [17] and tested also in the case of salutaridine (**1**,
4 Scheme 4).

5 <Scheme 4>

6 The application of methanol gave rise to 11-hydroxy-2,3,10-
7 trimethoxyaporphine (**4**) in good yield. As it was expected these reactions
8 with ethanol and *n*-propanol produced mixtures of aporphine derivatives.
9 The confirmation of the substitution pattern of the ring A of these new
10 aporphinoids was based on NOESY measurements. The most relevant
11 couplings were denoted in Scheme 4. The obtained yields of these
12 rearrangements are summarized in Table 1.

13 <Table 1>

14 The usual analytical characterization of the products confirmed the
15 possibility of (trans)etherification at both positions 2 and 3. As the
16 production of 3-hydroxy-type aporphines was not observed it was
17 concluded that position 3 was more sensitive to the ether formation. In
18 view of the commonly accepted mechanism of the acid-catalyzed
19 rearrangement of morphinan-6,8-dienes [18] and our suggested
20 intermediate of the rearrangement of morphinan-5,8-dienes [9] the C3-
21 OH→C3-OR etherification could lead to the stabilization of this structure.

7*S*-Salutaridinol (**2**) is the natural reduction product of compound **1** which plays important role in the biosynthesis of opiates [2, 5, 19]. Besides biosynthetic procedures [5, 19] only one chemical route was schemed [2] for the production of (7*S*)-**2** comprising the nonselective sodium borohydride-mediated reduction of **1** and column chromatography separation of the equimolar mixture of the two epimers. On the basis of literature examples for the enantioselective reductions of highly sensitive ketones with K-Selectride (1.0 M potassium tri-*sec*-butylborohydride in THF) [20] and our previous positive experience with this reagent in the selective reduction of 6-keto function of morphinones [21], salutaridine (**1**) was subjected to a thematic study. Absolute THF was used as a solvent and reactions were run at 0°C meanwhile the applied amount of K-Selectride was changed from 2 equivalents (eq.) to 10 equivalents related to starting alkaloid **1**. It was observed that the treatment of compound **1** with 5 eq. of the borohydride in 16 hours at 0°C and further 5 hours at room temperature gave rise to 7*S*-salutaridinol (**2**) as the main product in 66% yield (Scheme 5) besides minor products and some unreacted salutaridine (**1**).

<Scheme 5>

In order to reveal the basic reason for the observed selectivity of the K-Selectride-mediated reduction, the high level DFT-optimized geometry of salutaridine (**1**) was constructed. In view of the conformation of ring A of

the morphinan (Fig. 2) the spatial hindrance from the direction of ring A could be responsible for the selectivity.

<Figure 2>

Having on one hand the equimolar mixture of 7*S*-salutaridinol (**2**) and 7-epi-salutaridinol (7*R*, **2**) obtained in line with the procedure of Barton et al. [2] and on the other hand the pure 7*S*-salutaridinol (**2**) it was targeted to extend the knowledge on the acid-catalyzed reactions of these tetracyclic alkaloids.

<Scheme 6>

Interestingly, it was observed that regardless of using the equimolar mixture of salutaridinol (**2**) and 7-epi-salutaridinol (7*R*, **2**) or salutaridinol (7*S*, **2**) the resulting mixture contained two well-known aporphinoids (Scheme 6); (*R*)-2,11-dihydroxy-10-methoxyaporphine (morphothebaine, **9**) and its 2-methoxy congener **10**. There was only a slight difference in the ratio of the isolated yields in the two sets of experiments. The explanation for this behavior should be in accordance with a previous observation [16] regarding the formation of 2-hydroxy- and 2-methoxyaporphine-type products from morphinan-6,8-dienes in methanesulfonic acid catalyzed rearrangement in the presence of water traces.

1 Taking into account the suggested mechanism for the rearrangement of **1**
2 (Scheme 3) in this case the formation of methoxonium intermediate occurs
3 via the elimination and successive attack of a water molecule (Scheme 7).

4 <Scheme 7>

5 **Conclusion**

6 In this study we have presented the possibility of the acid-catalyzed
7 rearrangement of tetracyclic morphinan salutaridine (**1**) into 2,3,10,11-
8 tetrasubstituted (*R*)-aporphines. This method is another chemical proof of
9 the previously verified biosynthetic connection with pentacyclic
10 morphinan-6,8-diene-type thebaine. On the other hand, this procedure
11 could lead to pharmacologically interesting new aporphinoids. The
12 enantioselective synthesis of 7*S*-salutaridinol (**2**) has been also achieved in
13 order to investigate the acid-catalyzed reactions of this natural morphinan.
14 These reactions afforded well-known 2,10,11-trisubstituted (*R*)-aporphines.
15 It is worthwhile to note that the dextrorotatory morphinan sinoacutine, the
16 9,13-diastereomer of salutaridine (**1**), also available in nature [22] and with
17 similar rearrangement reactions it would be possible to obtain (*S*)-
18 aporphines for the first time.

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 (DCM)/methanol = 8/2 mobile phase. The spots were visualized with Dragendorff's reagent. ¹H and ¹³C NMR 1D spectra and phase-sensitive 2D NOESY experiments were recorded at 400 MHz using a Bruker Avance DRX400 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. Optical rotation was determined with a Perkin Elmer Model 241 polarimeter. Elemental analyses (C, H) were obtained on a Carlo Erba EA1108 analyzer.

Salutaridine (1) from natural source

The latex of *Papaver bracteatum* Lindl. was processed in accordance with the method of Slavík and Slavíková [23]. Physical and basic spectral characteristics are in accordance with previously reported data [12]. M.p.: 196-199°C (lit. 197-198°C [2]). Calculated for free base C₁₉H₂₁NO₄: C, 69.71; H, 6.74; found: C, 69.29; H, 6.71; MS (ESI) *m/z* 328.2 (M+H⁺), calculated for C₁₉H₂₂NO₄⁺: 328.1; ¹H-NMR (CDCl₃) δ=7.53 (s, 1H, H8),

6.74 (d, 1H, H1, $J_{1-2}=8.1$), 6.65 (d, 1H, H2, $J_{1-2}=8.1$), 6.32 (s, 1H, H5), 6.25 (br s, 1H, OH), 3.88 (s, 3H, OCH₃), 3.75 (s, 3H, OCH₃), 3.67 (dd, 1H, H9, $J=4.6$, <2), 3.32 (d, 1H, H10 α , $J_{10\alpha-10\beta}=16.4$), 2.98 (m, 1H, H10 β), 2.63-2.31 (m, 6H, H15 β , H16 α , H16 β , NCH₃), 1.76 (ddd, 1H, H15 α , $J=5.2$, <2 , <2). ¹³C-NMR (CDCl₃) δ =181.4, 161.4, 151.0, 145.3, 143.3, 129.8, 124.0, 122.2, 120.3, 118.8, 109.4, 61.1, 56.3, 54.8, 47.0, 43.6, 41.7, 37.7, 32.7.

7S-Salutaridinol (2)

Compound **1** (72 mg, 0.22 mmol) was dissolved in absolute THF under argon atmosphere and stirred at 0°C. K-Selectride (1.1 mL, 1M in THF, 1.1 mmol) was added dropwise. The solution was stirred at 0°C for 16 hours and at room temperature for another 5 hours. The reaction mixture was quenched with 4 mL of 96% ethanol and the solvents were removed under reduced pressure. The remaining solid was dissolved in 10 mL of saturated NaHCO₃ solution and extracted with ethyl acetate (3 x 10 mL). After washing with brine, drying on MgSO₄ the solvent was removed completely and the remaining solid was subjected to column chromatography (Kieselgel 40, eluent: DCM/MeOH = 8/2). The off-white solid was found to be 49 mg (yield: 66%). Physical and basic spectral characteristics are in accordance with previously reported data [2, 19]. M.p.: 132-134°C (lit. 132-140°C [2]). Calculated for free base C₁₉H₂₃NO₄: C, 69.28; H, 7.04; found: C, 69.17; H, 7.13; MS (ESI) m/z 330.2 (M+H⁺), calculated for

1 $C_{19}H_{24}NO_4^+$: 330.2; 1H -NMR (CD_3OD) δ =6.77 (d, 1H, H1, J_{1-2} =8.0), 6.68
2 (d, 1H, H2, J_{1-2} =8.0), 6.42 (s, 1H, H5), 5.63 (d, 1H, H8, $J_{8-7\beta}$ =4.1), 4.49 (d,
3 1H, H7 β , $J_{8-7\beta}$ =4.1), 3.86 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃), 3.61 (dd, 1H,
4 H9, J =4.2, <2), 3.29 (d, 1H, H10 α , $J_{10\alpha-10\beta}$ = 15.6), 2.99 (m, 1H, H10 β),
5 2.60-2.25 (m, 6H, H15 β , H16 α , H16 β , NCH₃), 1.80 (ddd, 1H, H15 α , J =5.0,
6 <2, <2). ^{13}C -NMR (CD_3OD) δ =158.3, 145.1, 143.7, 135.8, 128.4, 124.6,
7 121.2, 118.7, 109.8, 91.7, 76.4, 62.1, 56.3, 55.2, 48.0, 43.8, 40.7, 37.7,
8 31.4.

9 **Acid-catalyzed rearrangement of salutaridine (1) and salutaridinols (2)**

10 A mixture of **1** or **2** (0.71 mmol) and 99.5% methanesulfonic acid (1 ml)
11 was stirred for 30 min at 90 °C. Then the reaction mixture was added
12 dropwise, with stirring and external ice-cooling, to a solution of potassium
13 hydrogen carbonate (2 g) in water (10 ml). After extraction with
14 dichloromethane (3x15 ml), the combined extracts were washed with
15 saturated brine, dried (MgSO₄), and concentrated under reduced pressure.
16 The purification was performed by means of column chromatography
17 (Kieselgel 40, eluent: DCM/MeOH = 8/2).

18 **(R)-3,11-dihydroxy-2,10-dimethoxyaporphine (3)**

19 Yield: 88% starting from compound **1**. Pale green solid. M.p.: 132-134°C.
20 $[\alpha]_D^{25}$ -108 (c=0.2 in methanol); calculated for free base $C_{19}H_{21}NO_4$: C,
21 69.71; H, 6.47; found: C, 69.67; H, 6.59; MS (ESI) m/z 327.2 ($M+H^+$),

calculated for $C_{19}H_{22}NO_4^+$: 327.2; 1H -NMR ($CDCl_3$) δ =7.95 (s, 1H, H1), 6.75 (d, 1H, H8, J_{8-9} =7.4), 6.71 (d, 1H, H9, J_{8-9} =7.4), 5.20 (br s, 2H, 2 OH), 3.92 (s, 6H, 2 OCH_3), 3.48 (dd, 1H, H6a, J =4.4, <2), 3.15-2.86 (m, 3H, H7 α , H7 β , H5 α), 2.62-2.41 (m, 6H, H4 α , H4 β , H5 β , NCH_3); ^{13}C -NMR ($CDCl_3$) δ =150.3, 147.4, 144.3, 140.2, 130.9, 128.6, 128.4, 127.2, 126.7, 119.8, 112.2, 110.5, 64.2, 56.4, 56.2, 52.4, 43.8, 34.7, 28.4.

(R)-2,11-dihydroxy-10-methoxyaporphine (morphothebaine, 9)

Yield from the equimolar mixture of **2** epimers: 31%, yield from pure 7*S*-salutaridinol (**2**): 37%. M.p. as an HCl salt: 257-258°C (lit.: 258-260°C [24]). All the physical and spectral data were fully in agreement with previously published data [24].

(R)-2,10-Dimethoxy-11-hydroxyaporphine (10)

Yield from the equimolar mixture of **2** epimers: 37%, yield from pure 7*S*-salutaridinol (**2**): 41%. M.p.: 150-151°C (lit.: 149-151°C [16]). All the physical and spectral data were fully in agreement with previously published data [16].

Acid-catalyzed rearrangement of salutaridine (1) in the presence of alcohols

A mixture of **1** (233 mg, 0.71 mmol), methanesulfonic acid (1 mL) and alcohol (200 μ L) 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 (MgSO₄), and concentrated under reduced pressure. The purification of was performed by means of column chromatography (Kieselgel 40, eluent: DCM/MeOH = 9/1).

(R)-11-Hydroxy-2,3,10-trimethoxyaporphine (4)

Yield: 78% starting from compound 1. Off-white solid. M.p.: 114-116°C.

[α]_D²⁵ -118 (c=0.2 in methanol); calculated for free base C₂₀H₂₃NO₄: C, 70.36; H, 6.79; found: C, 70.19; H, 6.89; MS (ESI) m/z 342.2 (M+H⁺), calculated for C₂₀H₂₄NO₄⁺: 342.2; ¹H-NMR (CDCl₃) δ =8.01 (s, 1H, H1), 6.71 (d, 1H, H8, *J*₈₋₉=7.7), 6.68 (d, 1H, H9, *J*₈₋₉=7.7), 5.15 (br s, 1H, OH), 3.94 (s, 3H, OCH₃), 3.87 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 3.39 (dd, 1H, H6a, *J*=4.5, <2), 3.19-2.87 (m, 3H, H7 α , H7 β , H5 α), 2.67-2.39 (m, 6H, H4 α , H4 β , H5 β , NCH₃); ¹³C-NMR (CDCl₃) δ =149.7, 148.5, 147.3, 144.3, 135.2, 133.9, 127.6, 126.4, 126.2, 120.3, 111.7, 108.5, 66.2, 61.1, 56.4, 56.2, 52.3, 43.5, 34.5, 28.1.

(R)-2,10-Dimethoxy-3-ethoxy-11-hydroxyaporphine (5)

Yield: 48% starting from compound 1. Off-white foam. [α]_D²⁵ -101 (c=0.2 in methanol); calculated for free base C₂₁H₂₅NO₄: C, 70.96; H, 7.01; found: C, 70.77; H, 7.11; MS (ESI) m/z 355.1 (M+H⁺), calculated for C₂₁H₂₆NO₄⁺: 355.2; ¹H-NMR (CDCl₃) δ =8.07 (s, 1H, H1), 6.74 (d, 1H, H8,

1 $J_{8,9}=7.6$), 6.70 (d, 1H, H9, $J_{8,9}=7.6$), 5.09 (br s, 1H, OH), 4.11 (dd, 2H,
2 OCH₂, $J=5.8$), 3.86 (s, 3H, OCH₃), 3.81 (s, 3H, OCH₃), 3.39 (dd, 1H, H6a,
3 $J=4.6$, <2), 3.19-2.83 (m, 3H, H7 α , H7 β , H5 α), 2.59-2.39 (m, 6H, H4 α ,
4 H4 β , H5 β , NCH₃), 1.35 (t, 3H, CH₂CH₃, $J=6.8$); ¹³C-NMR (CDCl₃)
5 δ =148.9, 147.5, 144.3, 143.9, 132.9, 130.8, 127.0, 126.8, 126.2, 120.8,
6 110.6, 109.1, 65.1, 64.2, 56.3, 56.2, 51.7, 43.6, 35.2, 28.4, 17.3.

7 **(R)-2,10-Dimethoxy-11-hydroxy-3-propoxyaporphine (6)**

8 Yield: 40% starting from compound 1. Pale grey solid. M.p.: 121-123°C.
9 $[\alpha]_D^{25}$ -99 (c=0.2 in methanol); calculated for free base C₂₂H₂₇NO₄: C,
10 71.52; H, 7.37; found: C, 71.67; H, 7.44; MS (ESI) m/z 370.2 (M+H⁺),
11 calculated for C₂₂H₂₈NO₄⁺: 370.2; ¹H-NMR (CDCl₃) δ =8.07 (s, 1H, H1),
12 6.71 (d, 1H, H8, $J_{8,9}=7.8$), 6.66 (d, 1H, H9, $J_{8,9}=7.8$), 5.09 (br s, 1H, OH),
13 4.05 (dd, 2H, OCH₂, $J=5.4$), 3.93 (s, 3H, OCH₃), 3.87 (s, 3H, OCH₃), 3.39
14 (dd, 1H, H6a, $J=4.6$, <2), 3.21-2.89 (m, 3H, H7 α , H7 β , H5 α), 2.59-2.33 (m,
15 6H, H4 α , H4 β , H5 β , NCH₃), 1.71 (ddd, 2H, OCH₂CH₂, $J=5.4$), 0.96 (t, 3H,
16 CH₂CH₃, $J=5.4$); ¹³C-NMR (CDCl₃) δ =149.4, 148.3, 145.3, 144.2, 133.6,
17 130.9, 127.4, 126.9, 126.7, 121.0, 112.2, 109.6, 71.1, 64.6, 56.4, 56.3, 51.7,
18 43.4, 35.2, 29.2, 27.6, 10.7.

19 **(R)-2,3-Diethoxy-11-hydroxy-10-methoxyaporphine (7)**

20 Yield: 33% starting from compound 1. Off-white solid. M.p.: 101-103°C;
21 $[\alpha]_D^{25}$ -119 (c=0.2 in methanol); calculated for free base C₂₂H₂₇NO₄: C,

1 71.52; H, 7.37; found: C, 71.77; H, 7.41; MS (ESI) m/z 370.1 ($M+H^+$),
2 calculated for $C_{22}H_{28}NO_4^+$: 370.2; 1H -NMR ($CDCl_3$) δ =8.11 (s, 1H, H1),
3 6.78 (d, 1H, H8, $J_{8,9}$ =7.7), 6.74 (d, 1H, H9, $J_{8,9}$ =7.7), 5.01 (br s, 1H, OH),
4 4.09-4.03 (m, 4H, 2 OCH_2), 3.91 (s, 3H, OCH_3), 3.36 (dd, 1H, H6a, J =4.4,
5 <2), 3.16-2.79 (m, 3H, H7 α , H7 β , H5 α), 2.66-2.32 (m, 6H, H4 α , H4 β , H5 β ,
6 NCH_3), 1.32-1.29 (m, 6H, 2 CH_2CH_3); ^{13}C -NMR ($CDCl_3$) δ =148.2, 146.2,
7 145.1, 144.0, 133.1, 129.8, 126.9, 126.4, 125.9, 121.0, 112.1, 109.6, 65.7,
8 64.3, 64.1, 56.4, 56.2, 51.2, 43.4, 36.5, 28.4, 16.1, 15.9.

9 **(*R*)-2,3-Dipropoxy-11-hydroxy-10-methoxyaporphine (8)**

10 Yield: 29% starting from compound **1**. Grey solid. M.p.: 101-103°C. $[\alpha]_D^{25}$
11 -112 (c =0.2 in methanol); calculated for free base $C_{24}H_{31}NO_4$: C, 72.52; H,
12 7.86; found: C, 72.61; H, 7.92; MS (ESI) m/z 398.2 ($M+H^+$), calculated
13 for $C_{24}H_{32}NO_4^+$: 398.2; 1H -NMR ($CDCl_3$) δ =8.00 (s, 1H, H1), 6.75 (d, 1H,
14 H8, $J_{8,9}$ =7.6), 6.70 (d, 1H, H9, $J_{8,9}$ =7.6), 5.00 (br s, 1H, OH), 4.12-4.05 (m,
15 4H, 2 OCH_2), 3.91 (s, 3H, OCH_3), 3.33 (dd, 1H, H6a, J =4.4, <2), 3.26-2.90
16 (m, 3H, H7 α , H7 β , H5 α), 2.54-2.31 (m, 6H, H4 α , H4 β , H5 β , NCH_3), 1.79-
17 1.71 (m, 4H, 2 OCH_2CH_2), 1.01-0.96 (m, 6H, 2 CH_2CH_3); ^{13}C -NMR
18 ($CDCl_3$) δ =148.1, 147.5, 145.1, 144.6, 133.1, 132.7, 127.5, 127.0, 126.5,
19 121.6, 111.2, 109.7, 71.2, 69.8, 65.7, 56.4, 51.3, 43.7, 34.9, 23.5, 22.9,
20 10.7, 10.5.

21 **Computational procedure**

We have carried out the geometry optimization at Becke's three parameter hybrid (B3LYP) [25] levels in the DFT with the basis set 6-31G* using Gaussian 03 [26] and solvent effect was not considered.

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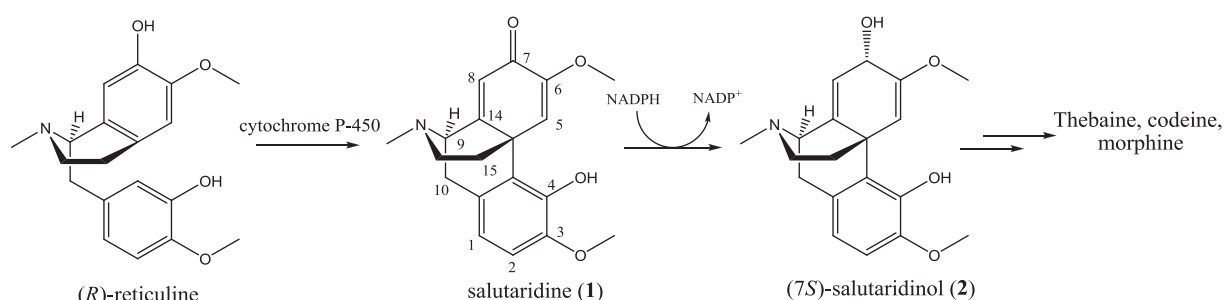
1
2 Tables

3 **Table 1.** Results of the corresponding rearrangement reactions of **1** in the
4 presence of alcohols (ROH)

ROH	Isolated yields (%) [*]	
	2-OMe-3-OR-aporphine (4-6)	2,3-di-OR-aporphine (7, 8)
Methanol	78	-
Ethanol	48	33
<i>n</i> -Propanol	40	29

5 ^{*}after column chromatography
6

Figures and Schemes



Scheme 1. The role of salutaridinone (1) in the formation of opium alkaloids

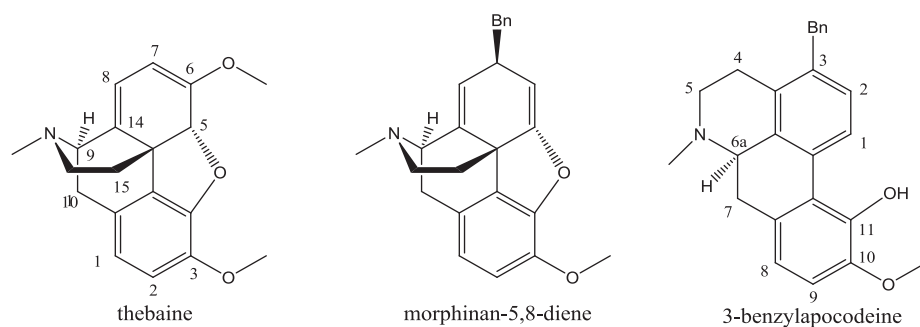
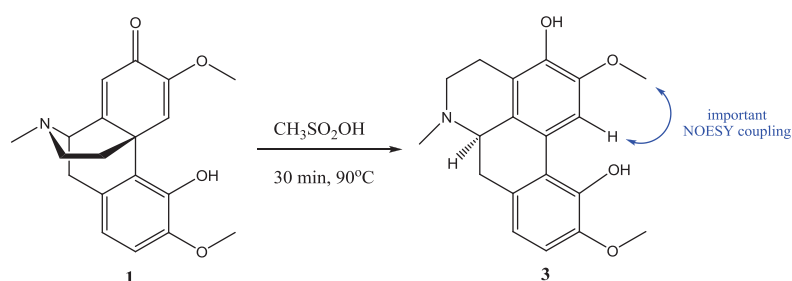
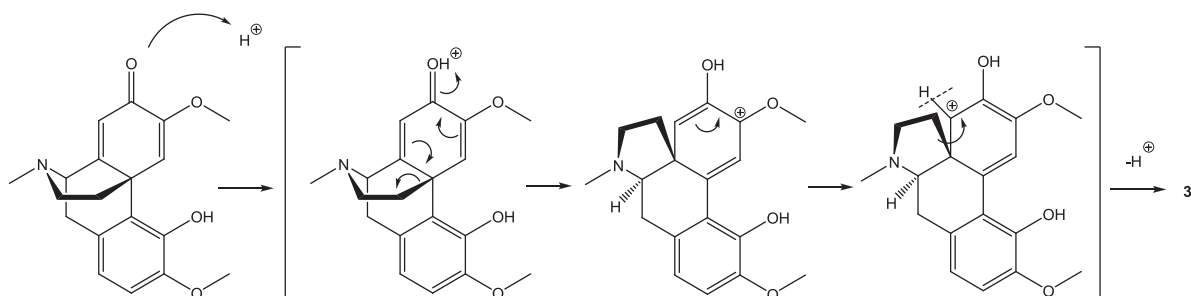


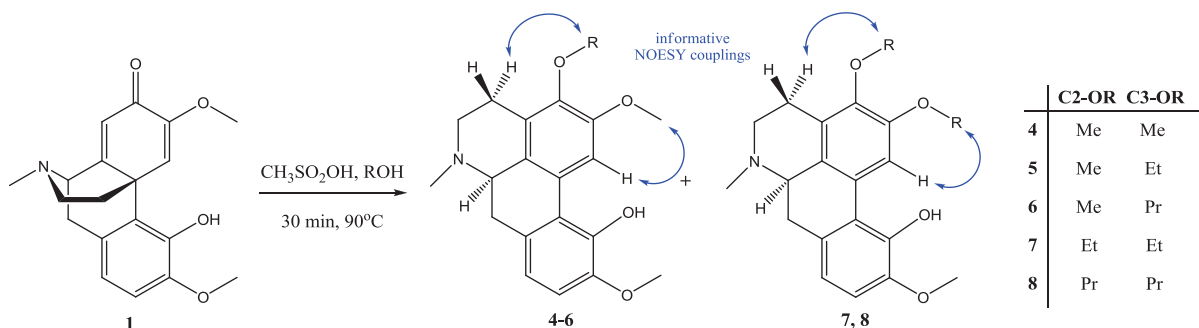
Figure 1. Structure of morphinandienes and their acid-catalyzed rearrangement product, apocodeine



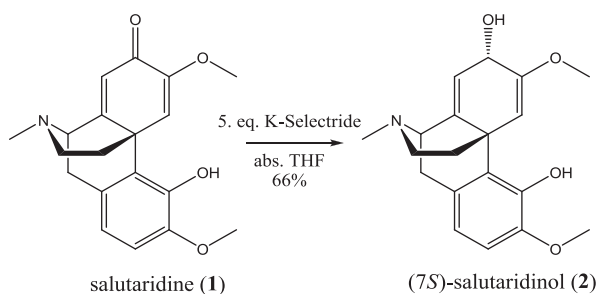
Scheme 2. Acid-catalyzed rearrangement of salutaridinone (1)



Scheme 3. Plausible mechanism for the acid-catalyzed rearrangement of **1**



Scheme 4. Acid-catalyzed rearrangement of **1** in the presence of alcohols



Scheme 5. Modified synthesis of **7*S***-salutaridinol (**2**)

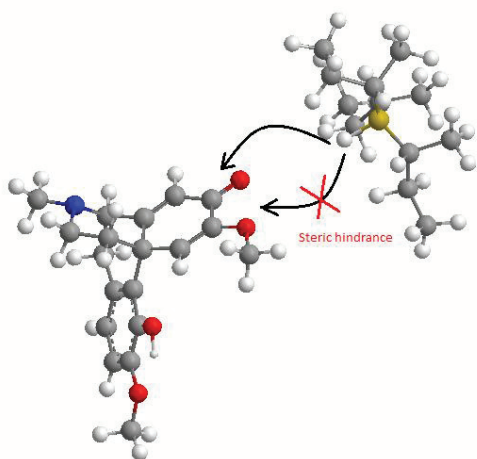
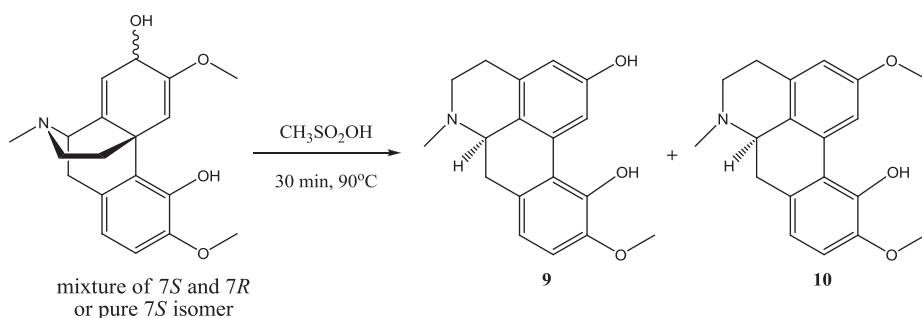
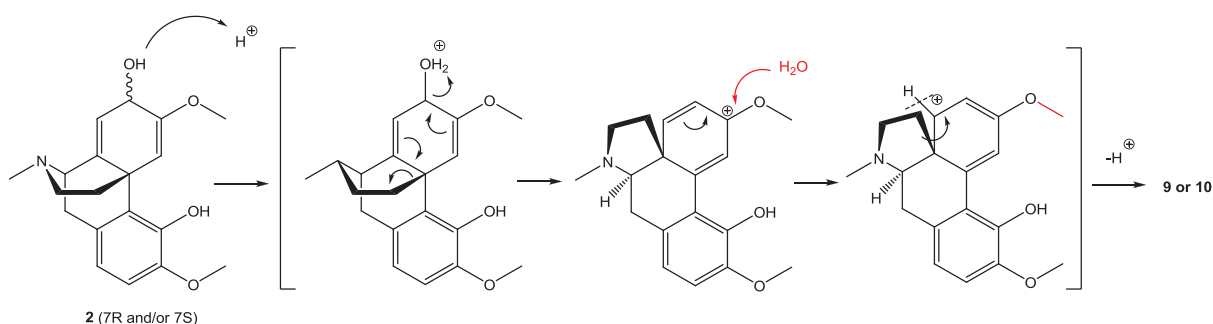


Figure 2. Presentation of the attack of tri-*sec*-butylborohydride ion to the DFT-optimized structure of compound **1**



Scheme 6. Acid-catalyzed rearrangement experiments of salutaridinol (**2**) epimers



Scheme 7. Suggested mechanism for the rearrangement of salutaridinols **2**

Graphical Abstract

Salutaridine and its derivatives as thebaine-equivalents in the synthesis of aporphines

Antal Udvardy • Attila Sipos

