Palladium-Catalyzed 2-Phenylethenylation of Codeine: 8-[(1*E*)-2-Phenylethenyl]codeinone Dimethyl Ketal as the Unexpected 'Masked' Diene for the Preparation of 19-Substituted *Diels–Alder* Adducts of Thebaine

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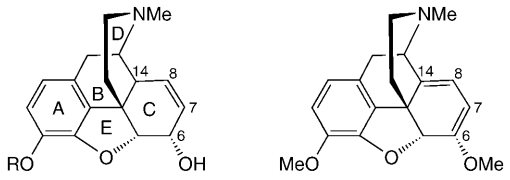
In a search for starting materials for the preparation of 7,8-fused morphine alkaloid derivatives, 8-[(1*E*-2-phenylethenyl]codeinone dimethyl ketal (**4**) and 8-[(1*E*-2-phenylethenyl]codeine (**5**) were prepared. These dienes were used as substrates in the *Diels–Alder* reactions. Compound **5** formed the 'normal' adduct **12** with *N*-phenylmaleimide, while compound **4** behaved in reactions with dienophiles as the 'masked' diene **11**, a 8-[(1*E*)-2-phenylethenyl]-substituted thebaine, yielding the corresponding 19-substituted 6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaines. Specifically, reaction of **4** with methyl vinyl ketone gave rise to 19-[(1*E*)-phenylethenyl]thevinone (**14**) whose structure was elucidated by an X-ray diffraction analysis. The thebaine derivative **11** was also prepared from **4**.

Introduction. – Morphine alkaloids and semisynthetic derivatives thereof form one of the most important groups of non-endogenous opioid-receptor ligands. They can possess both agonist and antagonist properties. Thus, some of them are used as effective analgesics for the treatment of moderate to severe pain or as opioid antagonists for the treatment of narcotic overdosage or opioid addiction; others are used as tools in research [1–3]. The main synthetic route to these compounds is a chemical transformation of the natural alkaloids of the morphine group, *i.e.*, morphine (**1**), codeine (**2**), or thebaine (**3**), obtainable from the opium poppy, *papaver somniferum*, the main object of the transformation being ring *C* of the alkaloids [1][2]. The formation of additional rings fused to ring C essentially affects the pharmacological properties of the alkaloids. In this connection, much attention was paid to the *Diels–Alder* adducts of thebaine (**3**) [1][2]. Ring-constrained analogues of the potent analgesic buprenorphine have been intensively investigated in recent years [4]. Exciting results have been obtained with derivatives bearing an additional 6,7-fused heterocyclic ring. Examples are δ-selective opioid antagonists such as naltrindole and its derivatives [3]. The corresponding carbocyclic derivatives have been less studied. For instance, a *Diels–Alder* reaction of an alkaloid derivative having a diene moiety formed by a C(6)=C(7) bond and a vinyl sub-

stituent at C(6) has been used for their preparation [5]. The vinyl-substituted starting material was preliminarily prepared by a Pd-catalyzed *Stille*-type cross-coupling reaction of the corresponding 6,7-unsaturated 6-triflate with tributylvinylstannane. An alternative route to the ring-C vinyl-substituted alkaloids is a conjugated addition of vinyl cuprate to codeinone leading to (8β)-6,7-dihydro-8-vinylcodeinone [6]. The corresponding 8β-phenyl-substituted derivative was prepared similarly. Pd-Catalyzed reactions of **1** or **2** with aryl iodides giving the 8β-aryl-substituted 6,7-dihydromorphinone or 6,7-dihydrocodeinone, respectively, have also been reported [7].



1 R = H (morphine)
2 R = Me (codeine)

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The target of the present study was a search for routes to morphine-alkaloid-derived dienes useful as starting materials for the preparation of 7,8-fused alkaloids by cycloaddition reactions. Specifically, the aim was to prepare compounds bearing a 1,3-diene moiety formed by the C(6)=C(7) bond of the alkaloid and an exocyclic vinyl substituent at C(8). Here we report on the syntheses of (8β)-8-[(1*E*)-2-phenylethenyl]codeinone dimethyl ketal[1]) (**4**) and (8β)-8-[(1*E*)-2-phenylethenyl]codeine[1]) (**5**) and their different behavior in *Diels–Alder* reactions.

Results. – The syntheses of **4** and **5** from **2** and their reactions are depicted in the *Scheme*. A reaction of **2** with β-bromostyrene (=[(1*E*)-2-bomoethenyl]benzene) in DMF in the presence of $Pd(OAc)_2$ as catalyst and an excess of K_2CO_3 proceeded to **6** as the sole cross-coupling product. The (*E*)-configuration of the styryl group in **6** was derived from the ^{1}H-NMR data ($^3J(18,19) = 15.7$ Hz). Ketone **6** reacted with trimethyl orthoformate in MeOH yielding dimethyl ketal **7** which formed the enol ether **8** after treatment with TsOH in the absence of H_2O. The styryl group at C(8) in **7** occupies the β-position, which was established by the corresponding $^3J(8,14)$ value (10.7 Hz) indicating the presence of an α-positioned H–C(8). Thus, the styryl substituent at C(8) of **6** is also in the β-position because the transformation **6** $\rightarrow$ **7** proceeds without any rearrangement at C(8). In addition, the $^3J(8,14)$ value (10.6 Hz) of **8** similarly indicates the presence of H_α–C(8) both in **8** itself and in its precursor **6**. Further, following the *Rapoport* procedure [8], ether **8** was transformed into the hydrobromide with 48% HBr solution at 0° followed by the reaction with MeOBr in MeOH leading to bromide **9** which has an α-positioned H–C(7) ($^3J(7,8) = 1.8$ Hz). Reaction of **9** with *t*-BuOK in DMSO at 20° yielded diene **4** which was a key intermediate for the synthesis of **5**. Hydrolysis of **4** proceeded smoothly in 20% HCl solution giving

[1]) For systematic names, see *Exper. Part.*

rise to the codeinone derivative **10** which was reduced with $NaBH_4$ in MeOH [9] yielding the targeted codeine derivative **5**. The substituted thebaine **11** was prepared from **4** by refluxing in toluene with concomitant slow distillation of the solvent to remove the MeOH formed as the by-product.

The codeine derivative **5** underwent the cycloaddition reaction with *N*-phenylmaleimide by refluxing in toluene producing the *Diels–Alder* adduct **12**. In contrast, the reaction of diene **4** with *N*-phenylmaleimide under the same conditions led to the 6,14-*endo*-ethano-6,7,8,14-tetrahydrothebaine[1]) derivative **13** as the sole product. Similarly, the 7α-substituted adduct **14** was formed by reacting **4** and methyl vinyl ketone.

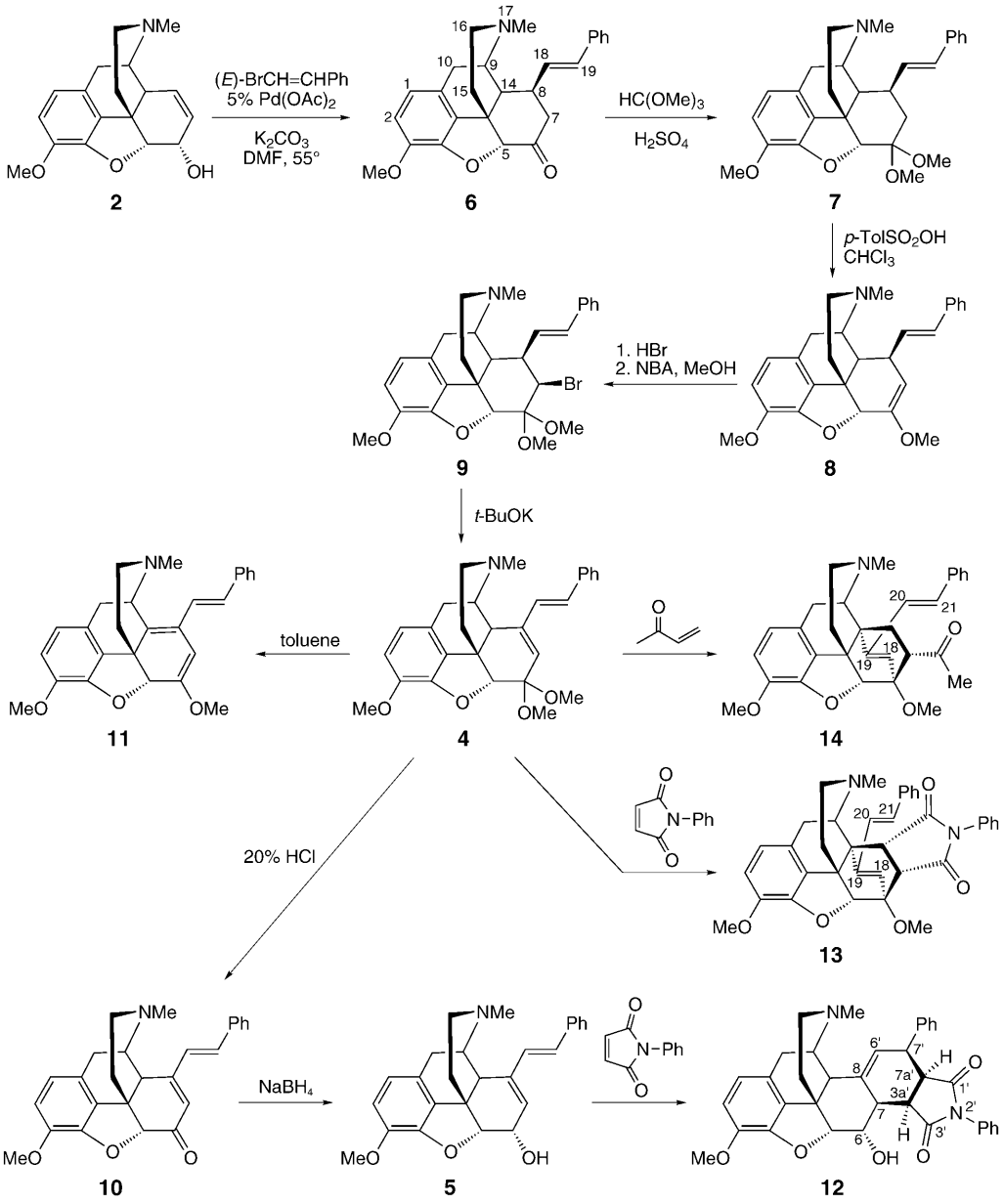
Discussion. – As one might expect, the codeine derivative **5** reveals itself as a typical diene in a *Diels–Alder* reaction yielding the 'normal' adduct **12** with *N*-phenylmaleimide. The presence of any isomeric products was not detected. The structure of **12** was established by a COSY experiment. A type of conjunction of the rings in the adduct, *i.e.* the configuration at C(7), C(3′a), C(7′), and C(7′a), was deduced from the corresponding coupling constants in the ^{1}H-NMR spectrum. A large value of ^3J(6,7) (11.8 Hz) in the strained molecule under consideration indicates the corresponding dihedral angle H–C(6)–C(7)–H to be roughly 180° which can be attributed only to a H_β–C(6)–C(7)–H_α moiety. Similarly, much lower values of ^3J(3′a,7), ^3J(7′,7′a), and ^3J(3′a,7′a), (6.0, 7.6, and 8.6 Hz, resp.) indicate that the corresponding H-atoms do not form such a sterical arrangement. These facts are in a good agreement with the depicted structure of **12**.

It was also found that refluxing of **12** in a AcOEt/heptane 1:3 solution in the absence of *N*-phenylmaleimide gave rise to the codeine derivative **5** as the result of a *retro-Diels–Alder* process.

The diene **4** behaved differently from compound **5** in cycloaddition reactions. The adduct **13** formed by reaction of **4** and *N*-phenylmaleimide has a structure as it would be formed from a cycloaddition reaction of the dienophile with the thebaine derivative **11**. Obviously, **11** was formed from **4** *in situ* under the reaction conditions used. The structure of **13** was deduced from its ^{1}H-NMR spectrum, assuming the stereochemical result of the cycloaddition, *i.e.*, the absolute configurations at C(6), C(7), C(8), and C(14), which is supposed to be the same as in numerous well known adducts of unsubstituted thebaine (**3**) [1–3]. This supposition was corroborated by the regio/stereochemical result of the reaction of diene **4** with the 'unsymmetrical' dienophile methyl vinyl ketone. Again, **4** revealed itself in this reaction as the 'masked' triene **11** yielding the corresponding thebaine-like 7α-substituted adduct **14** as the sole product. The structure of **14** was elucidated by an X-ray crystal structure determination (*Fig.*).

Thus, diene **4** behaves in cycloaddition reactions as the 'masked' 8-styryl-substituted thebaine **11**. In addition, the presence of the substituent at C(8) exerts no influence on both regiochemical and stereochemical results of the reactions. Moreover, the main structural features of **14** appear to be very similar to that found in the usual *Diels–Alder* thebaine adducts [1–3]. The rings B and C of **14** are *trans*-fused, with ring C being in a boat conformation. The piperidine ring has a chair conformation with an equatorial Me group at the N-atom. The torsion angle C(18)–C(19)–C(20)–C(21) of 33.9(3)° indicates an *s-cis* conformation of the diene moiety. The acetyl group at

Scheme



C(7) has α-orientation. Thus, the presence of a styryl substituent exerts also no essential influence on the geometry of the adduct, *i.e.*, it does not prevent the 'normal' course of the cycloaddition reaction.

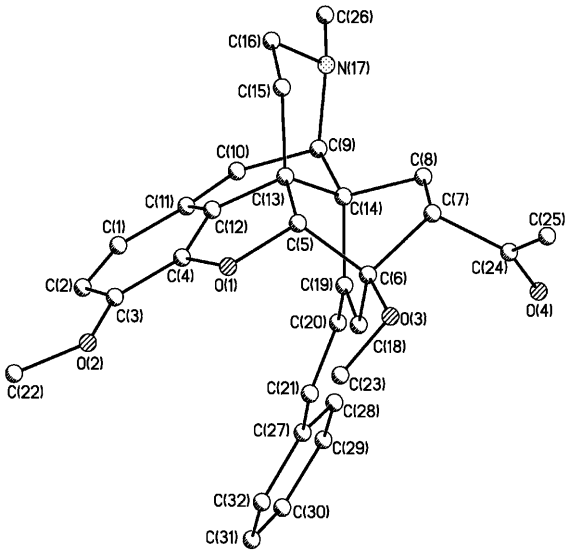


Figure. *Molecular structure of 1-{(5α,6α,7α,14α)-4,5-epoxy-3,6-dimethoxy-17-methyl-19-[(1E)-2-phenylethenyl]-6,14-ethenomorphinan-7-yl}ethanone* (**14**·C_6H_6). H-Atoms and solvated benzene are omitted for clarity. Selected bond lengths [Å]: C(4)–O(1) 1.389(3), O(1)–C(5) 1.470(2), C(6)–C(18) 1.507(3), C(18)–C(19) 1.344(3), C(19)–C(20) 1.466(3), C(20)–C(21) 1.466(3), C(21)–C(27) 1.470(3); torsion angle [°]: C(18)–C(19)–C(20)–C(21) 33.9(3).

We found no evidence of repeated *Diels–Alder* reactions of the diene adducts **13** or **14** with an additional molecule of the dienophiles.

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Experimental Part

General. All solvents were dried and distilled before use. Commercially available reagents were used without further purification unless otherwise specified. All reactions, except for the hydrolysis of dimethyl ketal **4** and the reduction of codeinone derivative **10**, were carried out under Ar. *N*-Bromoacetamide was prepared according to [10], m.p. 104–105° ([10]: m.p. 102–105°). TLC: 'Silufol' plates containing a fluorescent indicator; visualization under UV light, where possible, or by exposure to I_2 vapor for 5 min followed by quenching with H_2O. CC = Column chromatography. ^{1}H-NMR Spectra: *Bruker-AMX-400* spectrometer; at 400 MHz; in $CDCl_3$; δ in ppm relative to $SiMe_4$ as internal reference, J in Hz. Mass spectra: *MS890-KRATOS* spectrometer, 70 eV; in m/z.

Crystal Data of **14**·C_6H_6. For the X-ray study of **14**, a well-formed single crystal obtained by crystallization from C_6H_6 was chosen. At 298 K, crystals of $C_{37}H_{39}NO_4$ are orthorhombic, space group $P2_12_12_1$, $a = 9.156(2)$, $b = 9.809(2)$, $c = 34.073(7)$Å, $V = 3060.3(11)$Å^3, $Z = 4(1)$, $M = 561.69$, $d_{calc} = 1.219\,g\,cm^{-3}$, $\mu(MoK\alpha) = 0.78\,cm^{-1}$, $F(000) = 1200$. Intensities of 5456 independent reflections were measured with a *Siemens P3/Pc* with graphite-monochromated Mo-$K\alpha$ radiation (λ 0.71073 Å, $\theta/2\theta$-scans) and were used in the further refinement. The structure was solved by direct methods and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. H-Atoms were located from the *Fourier* synthesis and refined with a riding model. The absolute configuration of the molecule

was assigned by the known configurations of the codeine fragment. The refinement converged to $wR_2 = 0.1276$ and g.o.f. = 0.944 for all independent reflections ($R_1 = 0.0478$ was calculated against F for 3485 observed reflections with $I > 2\sigma(I)$). All calculations were performed with SHELXTL PLUS 5.0 and an IBM PC AT. CCDC-277686 contains the supplementary crystallographic data for the structure reported in this paper. These data can be obtained free of charge from the *Cambridge Crystallographic Data Center via* www.ccdc.cam.ac.uk/data_request/cif.

*(8β)-7,8-Dihydro-8-[(1*E*)-2-phenylethenyl]codeinone* (*=(5α,8β)-4,5-Epoxy-3-methoxy-17-methyl-8-[(1*E*)-2-phenylethenyl]morphinan-6-one*; **6**). β-Bromostyrene (3.65 ml, 5.21 g, 28.5 mmol) was added to a suspension of codeine (**2**; 7.00 g, 23.4 mmol) and K_2CO_3 (4.04 g, 29.3 mmol) in DMF (60 ml). The suspension was cooled to 0° and palladium acetate (0.25 g, 1.17 mmol) added. The mixture was slowly warmed up to 55° while vigorously stirring and kept under these conditions for 1 h. The mixture was allowed to cool to r.t., poured in Et_2O (300 ml), washed with H_2O (3 × 100 ml), dried (Na_2SO_4), and evaporated. The gummy residue was dissolved in a minimum amount of hot benzene, and crystallization of the product was induced by a very slow addition of hexane. The mixture was allowed to stay at r.t. (3 h), then at −5° (3 h), and at −20° (overnight). The precipitate was filtered off, washed with hexane and dried *in vacuo* over $CaCl_2$/paraffin: 5.60 g (60%) of **6**. The mother liquor was evaporated, the residue dissolved in a minimum amount of CH_2Cl_2 and subjected to CC (silica gel, short (3 cm) column, CH_2Cl_2, then MeOH/CH_2Cl_2 1:10). The MeOH fraction containing the product was evaporated and dried as described above to give 1.0 g (11%) of pure **6** (TLC). Total yield of **6**: 6.6 g (70%). M.p. 179–180°. ^{1}H-NMR: 7.22–7.34 (*m*, Ph); 6.72 (*d*, *J*(1,2) = 8.2, H–C(2)); 6.67 (*d*, H–C(1)); 6.32 (*d*, *J*(18,19) = 15.7, H–C(19)); 6.07 (*dd*, *J*(8,18 = 9.1, H–C(18)); 4.73 (*s*, 1 H–C(5)); 3.91 (*s*, MeO); 3.23 (*dd*, *J*(9,10α) = 5.6, *J*(9,14) = 2.4; H–C(9)); 3.00 (*d*, *J*(10α,10β) = 18.4, H_β–C10)); 2.57 (*m*, *J*(15ax,16eq) = 3.8, H_{eq}–C(16)); 2.40–2.50 (*m*, CH_2(7), H–C(14)); 2.38 (*s*, MeN); 2.27 (*dd*, H_α–C(10)); 2.19 (*ddd*, *J*(16ax,16eq) = 12.0, *J*(15ax,16ax) = 12.1, *J*(15eq,16ax) = 3.3, H_{ax}–C(16)); 2.11–2.18 (*m*, H–C(8)); 2.09 (*m*, *J*(15ax, 15eq) = 12.2, H_{ax}–C(15)); 1.85 (*m*, H_{eq}–C(15)). MS: 401 (M^+). Anal. calc. for $C_{26}H_{27}NO_3$ (401.2): C 77.78, H 6.78, N 3.49; found: C 77.41, H 6.89, N 3.30.

*(8β)-7,8-Dihydro-8-[(1*E*)-2-phenylethenyl]codeinone Dimethyl Ketal* (*=(5α,8β)-4,5-Epoxy-3,6,6-trimethoxy-17-methyl-8-[(1*E*)-2-phenylethenyl]morphinan*; **7**). A mixture of **6** (840 mg, 1.247 mmol), trimethyl orthoformate (1.0 ml, 9.16 mmol), and MeOH (11 ml) was heated to effect dissolution and then cooled. At 15°, conc. H_2SO_4 soln. (0.2 ml) was added dropwise. The soln. was refluxed for 3 h and, additional trimethyl orthoformate (0.5 ml) and H_2SO_4 (0.1 ml) were added followed by refluxing for 5 h. The mixture was poured into an ice-cold mixture of 0.5M Na_2CO_3 (25 ml) and $CHCl_3$ (25 ml). The org. layer was separated, washed with brine, dried (Na_2SO_4), and evaporated. The residue was dried *in vacuo*: **7** (862 mg, 92%). Solid foam. ^{1}H-NMR: 7.26–7.35 (*m*, 2 H_o, 2 H_m of Ph); 7.20 (*tt*, H_p of Ph); 6.72 (*d*, *J*(1,2) = 8.1, H–C(2)); 6.60 (*d*, H–C(1)); 6.30 (*d*, *J*(18,19) = 15.7, H–C(19)); 6.12 (*dd*, *J*(8,18) = 8.9, H–C(18)); 4.54 (*s*, H–C(5)); 3.90 (*s*, 1 MeO); 3.36 (*s*, 1 MeO); 3.15 (*dd*, H–C(9)); 3.11 (*s*, 1 MeO); 2.97 (*d*, *J*(10α,10β) = 18.4, H_β–C(10)); 2.50 (*m*, H_{eq}–C(16)); 2.35 (*s*, MeN); 2.30 (*dd*, *J*(9, 10α) = 5.7, H_α–C(10)); 2.22 (*ddd*, *J*(16ax,16eq) = 12.2, *J*(15eq,16ax) = 3.6, H_{ax}–C(16)); 2.19 (*dd*, *J*(8, 14) = 10.7, *J*(9,14) = 2.6, H–C(14)); 1.93 (*ddd*, *J*(15ax,15eq) = 12.3, *J*(15ax,16ax) = 12.3, *J*(15ax, 16eq) = 5.0, H_{ax}–C(15)); 1.71–1.88 (*m*, CH_2(7), H–C(8), H_{eq}–C(15)).

*(8β)-8,14-Dihydro-8-[(1*E*)-2-phenylethenyl]thebaine* (*=(5α,8β)-6,7-Didehydro-4,5-epoxy-3,6-dimethoxy-17-methyl-8-[(1*E*)-2-phenylethenyl]morphinan*; **8**). To a soln. of TsOH (0.16 g, 0.91 mmol) in anh. $CHCl_3$ (8 ml) was added **7** (0.34 g, 0.76 mmol) in $CHCl_3$ (10 ml). The resulting soln. was heated on an air bath, and the distillate (10 ml) was collected over 30 min. After cooling to 5°, the mixture was poured into cold (5°) 0.5M aq. Na_2CO_3 (10 ml) and stirred. The aq. phase was washed with $CHCl_3$ (10 ml), the combined org. soln. dried (Na_2SO_4) and evaporated, and the crude product crystallized from heptane/AcOEt 5:1: **8** (227 mg, 72%). M.p. 164–166°. ^{1}H-NMR: 7.27–7.36 (*m*, 2 H_o, 2 H_m of Ph); 7.21 (*m*, H_p of Ph); 6.72 (*d*, *J*(1,2) = 8.1, H–C(2)); 6.66 (*d*, H–C(1)); 6.32 (*d*, *J*(18,19) = 15.7, H–C(19)); 6.06 (*dd*, *J*(8,18) = 9.5, H–C(18)); 4.88, 4.56 (2 br. *s*, H–C(5), H–C(7)); 3.85 (*s*, MeO); 3.49 (*s*, MeO); 3.24 (*dd*, *J*(9,10α) = 5.7, H–C(9)); 3.04 (*d*, *J*(10α,10β) = 18.5, H_β–C(10)); 2.52 (*m*, H_{eq}–C(16)); 2.37–2.47 (*m*, H–C(8), H_α–C(10)); 2.37 (*s*, MeN); 2.27 (*ddd*, *J*(16ax,16eq) = 12.1, *J*(15eq,16ax) = 3.3,

H_{ax}–C(16)); 2.14 (*dd*, *J*(8,14) = 10.6, *J*(9,14) = 2.0, H–C(14)); 1.95 (*ddd*, *J*(15ax,15eq) = 12.3, *J*(15ax, 16ax) = 12.3, *J*(15ax,16eq) = 4.9, H_{ax}–C(15)); 1.85 (*m*, H_{eq}–C(15)). MS: 415 (M^+). Anal. calc. for $C_{27}H_{29}NO_3$ (415.2): C 78.04, H 7.03 N 3.37; found: C 77.81, H 7.14, N 3.37.

*(7β,8β)-7-Bromo-7,8-dihydro-8-[(1*E*)-2-phenylethenyl]codeinone Dimethyl Ketal* (= *(5α,7β,8β)-7-Bromo-4,5-epoxy-3,6,6-trimethoxy-17-methyl-8-[(1*E*)-2-phenylethenyl]morphinan*; **9**). A soln. of **8** (2.0 g, 4.82 mmol) in $CHCl_3$ (150 ml) was treated at −5° with 8.8M aq. HBr (0.83 ml, 7.23 mmol). After stirring for 5 min, a cold (0°) sat. NaBr soln. (100 ml) was added and the mixture shaken. The aq. phase was washed with $CHCl_3$ (60 ml) and the combined org. soln. dried (Na_2SO_4) and evaporated. The foamy residue was dissolved in dry MeOH (100 ml), cooled to −5°, and treated dropwise with a cold (0°) soln. of *N*-bromoacetamide (NBA; 0.63 g, 4.58 mmol) in MeOH (20 ml) over 20 min. After stirring at 0° for 15 min, the mixture was treated with 20% aq. NH_3 soln. (50 ml) and H_2O (150 ml), stirred for 30 min, and then filtered. The precipitate was washed with H_2O (3×) and dried *in vacuo*: **9** (2.31 g, 91%). White solid that was used for further transformations. A small sample was further purified by CC (silica gel). M.p. 89–90°. ^{1}H-NMR: 7.34–7.38 (*m*, 2 H_o of Ph); 7.29–7.33 (*m*, 2 H_m of Ph); 7.22–7.26 (*m*, H_p of Ph); 6.72 (*d*, *J*(1,2) = 8.2, H–C(2)); 6.62 (*d*, H–C(1)); 6.42 (*d*, *J*(18,19) = 15.9, H–C(19)); 6.26 (*dd*, *J*(8,18) = 9.1, H–C(18)); 4.88 (*s*, H–C(5)); 4.15 (*d*, *J*(7,8) = 1.8, H–C(7)); 3.89 (*s*, 1 MeO); 3.44 (*s*, 1 MeO); 3.10 (*s*, *m*, 1 MeO, H–C(9)); 3.00 (*d*, *J*(10*α*,10*β*) = 18.2, $H_β$–C(10)); 2.84 (*dd*, *J*(8,14) = 11.9, *J*(9,14) = 2.6, H–C(14)); 2.54 (*m*, H_{eq}–C(16)); 2.37 (*s*, MeN); 2.27 (*dd*, *J*(9,10*α*) = 4.5, $H_α$–C(10)); 2.21 (*m*, H–C(8)); 2.18 (*ddd*, *J*(16ax,16eq) = 12.2, *J*(15eq,16ax) = 3.7, H_{ax}–C(16)); 2.00 (*ddd*, *J*(15ax,15eq) = 12.2, *J*(15ax, 16ax) = 12.2, *J*(15ax,16eq) = 4.8, H_{eq}–C15)); 1.69 (*m*, H_{eq}–C(15)). MS: 525 (M^+). Anal. calc. for $C_{28}H_{32}BrNO_4$ (525.15): C 63.88, H 6.13, N 2.66, Br 15.18; found: C 64.09, H 6.11, N 2.64, Br 15.24.

*(8β)-8-[(1*E*)-2-Phenylethenyl]codeinone Dimethyl Ketal* (= *(5α,8β)-7,8-Didehydro-4,5-epoxy-3,6,6-trimethoxy-17-methyl-8-[(1*E*)-2-phenylethenyl]morphinan*; **4**). To a well stirred suspension of *t*-BuOK (0.85 g, 7.6 mmol) in anh. DMSO (40 ml), **9** (2.0 g, 3.8 mmol) was added. After stirring the mixture at r.t. for 1 h, it was diluted with benzene (150 ml) and washed with H_2O (100 ml). The aq. phase was washed with benzene (60 ml), the combined org. phase washed with H_2O dried (Na_2SO_4) and evaporated, and the solid residue recrystallized from hexane/benzene 10 : 1: **4** (1.0 g) colorless crystals. Additional **4** (0.17 g) was obtained on repeated crystallization of the residue obtained from the mother liquid. Total yield of **4**: 1.17 g (70%). M.p. 166–168° (dec.). ^{1}H-NMR: 7.18–7.29 (*m*, Ph); 6.62 (*d*, *J*(1,2) = 8.2, H–C(2)); 6.47 (br. *d*, H–C(18)); 6.45 (*d*, H–C(1)); 6.36 (*d*, *J*(18,19) = 15.7, H–C19)); 5.72 (*m*, H–C(7)); 4.73 (*d*, *J*(5, 7) = 1.2, H–C(5)); 3.84 (*s*, MeOH); 3.62 (*dd*, *J*(9,10*α*) = 6.5, *J*(9,14) = 2.8, H–C(9)); 3.47 (*s*, 1 MeO); 3.11 (*s*, 1 MeO); 3.04 (*m*, H–C(14)); 2.98 (*d*, *J*(10*α*,10*β*) = 18.6, $H_β$–C(10)); 2.57 (*m*, *J*(16ax, 16eq) = 12.2, H_{eq}–C16)); 2.45 (*s*, MeN); 2.32–2.40 (*m*, $H_α$–C(10), H_{ax}–C(16)); 2.13 (*ddd*, *J*(15ax, 15eq) = 12.5, *J*(15ax,16ax) = 12.5, *J*(15ax,16eq) = 5.2, H_{ax}–C(15)); 1.91 (*m*, H_{eq}–C(15)). MS: 445 (M^+), 430 ($[M-Me]^+$), 413 ($[M-HOMe]^+$). Anal. calc. for $C_{28}H_{31}NO_4$ (445.2): C 75.48, H 7.01, N 3.14; found: C 75.46, H 6.99, N 3.14

*(5α,6α,7α,8α,14α)-4,5-Epoxy-3,6-dimethoxy-17-methyl-1′-phenyl-19-[(1*E*)-2-phenylethenyl]-6,14-ethenopyrrolidino[3′,4′ : 7,8]morphinan-2′,5′-dione* (= *(4*R*,4a*R*,4b*R*,7a*S*,8*R*,8a*R*,13b*S*)-1,2,3,4,4b,7a,8,8a-Octahydro-8,10-dimethoxy-3,6-dimethyl-16-[(1*E*)-2-phenylethenyl]-5*H*-4a,8-etheno-4,13-methanobenzofuro[3,2-*e*]pyrrolo[3,4-*h*]isoquinoline-5,7(6*H*)-dione*; **13**). A soln. of **4** (0.34 g, 0.764 mmol) and *N*-phenylmaleimide (0.21 g, 1.222 mmol) in toluene (20 ml) was refluxed for 4 h. The solvent was evaporated and the residue dissolved in a minimum amount of hot AcOEt. Heptane was added dropwise until the soln. became slightly turbid, and the mixture was kept at r.t. for 3 h. The crystals precipitated were filtered off, washed with AcOEt/heptane 1 : 1 and dried *in vacuo*: **13** (0.39 g). Colorless crystals. The mother liquor was evaporated and the residue purified by prep. TLC (silica gel, $CHCl_3$/MeOH/NH_4OH 320 : 10 : 1): additional **13** (0.05 g). Total yield: 0.44 g (98%). M.p. 265–266° (dec.). ^{1}H-NMR: 7.08–7.39 (*m*, Ph, PhN); 6.62 (*d*, *J*(1,2) = 8.2, H–C(2)); 6.39 (*d*, H–C(1)); 6.21 (*dd*, *J*(20,21) = 15.7, *J*(8,20) = 1.3, H–C(20)); 5.90 (br. *s*, H–C(18)); 5.79 (*d*, H–C(21)); 4.73 (*d*, *J* = 1.5, H–C(5)); 4.59 (*d*, *J*(7,8) = 8.0, H–C(7)); 4.24 (*d*, *J*(9,10*α*) = 7.0, H–C(9)); 3.86 (*s*, MeO); 3.75 (*s*, MeO); 3.26 (*d*, H–C(8)); 3.18 (*d*, *J*(10*α*,10*β*) = 18.7, $H_β$–C(10)); 2.60 (*m*, H_{eq}–C(16)); 2.48–2.56 (*m*, $H_α$–C(10), H_{ax}–C(16)); 2.47 (*s*, MeN); 1.99–2.03 (*m*, $CH_2$15)). MS: 586 (M^+), 413 ($[M-C_{10}H_7NO_2]^+$), 173 ($C_{10}H_7NO_2^+$). Anal. calc. for $C_{37}H_{34}N_2O_5$ (586.2): C 75.75, H 5.84, N 4.77; found: C 75.74, H 5.92, N 4.69.

*8-[(*1E*)-2-Phenylethenyl]thebaine* (*=(5α)-6,7,8,14-Tetradehydro-4,5-epoxy-3,6-dimethoxy-17-methyl-8-[(1*E*)-2-phenylethyl]morphinan*; **11**). A soln. of **4** (0.1 g, 0.223 mmol) in toluene (30 ml) was heated on an oil bath, with concomitant very slow (5 h) distillation of toluene. The volume of toluene in the reaction flask must not be less then 10 ml (additional toluene should be added, if necessary). Then the mixture was evaporated and the residue dried *in vacuo*: **11** (0.09 g, 98%). Solid foam. M.p. 83–86°. ^{1}H-NMR: 7.39 (br. *d*, 2 H_o of Ph); 7.31 (*m*, 2 H_m of Ph); 7.21 (*tt*, H_p of Ph); 7.02 (*d*, *J*(18,19) = 16.0, H–C(18)); 6.65 (*d*, H–C(19)); 6.65 (*d*, *J*(1,2) = 8.2, H–C(2)); 6.59 (*d*, H–C(1)); 5.51, 5.25 (2*s*, H–C(5), H–C(7)); 4.29 (*d*, *J*(9,10α) = 6.7, H–C(9)); 3.84 (*s*, MeO); 3.73 (*s*, MeO); 3.35 (*d*, *J*(10α,10β) = 17.9, $H_β$–C(10)); 2.87 (*ddd*, *J*(16ax,16eq) = 12.6, *J*(15ax,16ax) = 12.6, *J*(15eq,16ax) = 3.6, H_{ax}–C(16)); 2.69 (*dd*, $H_α$–C(10)); 2.64 (*m*, H_{eq}–C(16)); 2.52 (*s*, MeN); 2.26 (*ddd*, *J*(15ax,15eq) = 12.6, *J*(15ax,16eq) = 12.6, *J*(15ax, 16eq) = 5.2, H_{ax}–C(15)); 1.78 (*m*, H_{eq}–C(15)). MS: 413 (M^+). Anal. calc. for $C_{27}H_{27}NO_3$ (413.2): C 78.42, H 6.58, N 3.39; found: C 77.78, H 6.60, N 3.21.

*8-[(1*E*)-2-Phenylethenyl]codeinone* (*=(5α)-7,8-Didehydro-4,5-epoxy-3-methoxy-17-methyl-8-[(1*E*)-2-phenylethenyl]morphinan-6-one*; **10**). Ketal **4** (0.2 g, 0.45 mmol) was stirred at r.t. in 20% aq. HCl soln. (20 ml) for 30 min. The mixture was quenched with $CHCl_3$ (10 ml), cooled to 0–5°, and made alkaline (pH 9) with conc. NH_4OH soln. The aq. layer was washed with $CHCl_3$ (2 × 10 ml), the combined organic extract dried (Na_2SO_4) and evaporated, and the oily residue purified by prep. TLC (silica gel, $CHCl_3$/MeOH/NH_4OH 320 : 10 : 1): **10** (0.16 g, 89%). M.p. 120° (from heptane/AcOEt 5 : 1). ^{1}H-NMR: 7.32–7.44 (*m*, Ph); 6.98 (*d*, *J*(18,19) = 16.0, H–C(18)); 6.78 (*d*, H–C(19)); 6.67 (*d*, *J*(1,2) = 8.2, H–C(2)); 6.57 (*d*, H–C(1)); 6.31 (*d*, *J*(7,14) = 2.2, H–C(7)); 4.70 (*s*, H–C(5)); 3.86 (*s*, MeO); 3.72 (*m*, H–C(9)); 3.42 (*m*, H–C(14)); 3.00 (*d*, *J*(10α,10β) = 18.1, $H_β$–C(10)); 2.64 (*m*, *J*(16ax,16eq) = 11.8, H_{eq}–C(16)); 2.48 (*s*, MeN); 2.30 (*ddd*, *J*(16ax,16eq) = 12.3, *J*(15ax,16ax) = 12.3, *J*(15eq,16ax) = 4.0, H_{ax}–C(16)); 2.28 (*dd*, *J*(9,10α) = 5.7, $H_α$–C(10)); 2.10 (*ddd*, *J*(15ax,15eq) = 12.2, *J*(15ax,16ax) = 12.2, *J*(15ax,16eq) = 4.7, H_{ax}–C(15)); 1.90 (*m*, H_{eq}–C(15)). MS: 399 (M^+). Anal. calc. for $C_{26}H_{25}NO_3$ (399.18): C 78.17, H 6.31, N 3.51; found: C 77.60, H 6.24, N 3.42.

*1-[(5α,6α,7α,14α)-4,5-Epoxy-3,6-dimethoxy-17-methyl-19-[(1*E*)-2-phenylethenyl]-6,14-ethenomorphinan-7-yl)ethanone* (**14**). A mixture of **4** (50 mg, 0.112 mmol) and methyl vinyl ketone (0.07 ml, 0.864 mmol) was refluxed in toluene (5 ml) for 6 h. After evaporation the products were separated by prep. TLC (silica gel, $CHCl_3$/MeOH/NH_4OH 320 : 9 : 1): **14** (50 mg, 87%). Colorless solid. M.p. 65–68°. ^{1}H-NMR: 7.18–7.29 (*m*, Ph); 6.59 (*d*, *J*(1,2) = 8.2, H–C(2)); 6.39 (*d*, H–C(1)); 6.31, 5.98 (2*d*, *J*(20, 21) = 15.6, H–C(20), H–C(21)); 5.96 (*s*, H–C(18)); 4.58 (*s*, H–C(5)); 3.84 (*s*, MeO); 3.62 (*s*, MeO); 3.39 (*d*, *J*(9,10α) = 6.8, H–C(9)); 3.15 (*d*, *J*(10α,10β) = 18.6, $H_β$–C(10)); 3.06 (*dd*, *J*(7,8β) = 9.4, $H_β$–C(8)); 2.95 (*m*, H–C(7)); 2.51 (*m*, H_{eq}–C(16)); 2.49 (*dd*, $H_α$–C(10)); 2.39 (*ddd*, *J*(16ax,16eq) = 12.0, *J*(15ax,16ax) = 12.0, *J*(15eq,16ax) = 4.2, H_{ax}–C(14)); 2.37 (*s*, MeN); 2.11 (*s*, Ac); 1.98 (*ddd*, *J*(15ax, 15eq) = 12.5, *J*(15ax,16ax) = 12.4, *J*(15ax,16eq) = 5.8, H_{ax}–C(15)); 1.92 (*m*, H_{eq}–C(15)); 1.41 (*dd*, *J*(8α, 8β) = 12.5, *J*(7,8α) = 6.6, $H_α$–C(8)). MS: 483 (M^+), 413 ($[M - C_4H_6O]^+$), 70 ($C_4H_6O^+$). Anal. calc. for $C_{31}H_{33}NO_4$ (483.24): C 76.99, H 6.88, N 2.90; found: C 76.80, H 6.82, N 2.61.

Crystals of **14** for X-ray diffraction analysis were obtained by crystallization from a benzene soln. after very slow addition of hexane until the formation of a slightly turbid soln. occurred by standing at r.t. overnight. The product precipitated as **14**·C_6H_6. M.p. 88–90°.

*8-[(1*E*)-2-Phenyletheny])codeine* (*=(5α,6α)-7,8-Didehydro-4,5-epoxy-3-methoxy-17-methyl-8-[(1*E*)-2-phenylethenyl]morphinan*; **5**). $NaBH_4$ (0.10 g, 2.64 mmol) was added in small portions to a stirred soln. of **10** (0.20 g, 0.50 mmol) in MeOH (8 ml). After stirring for 1 h at r.t., the mixture was concentrated to *ca.* $\frac{1}{3}$ of the initial volume and diluted with 10% aq. NaOH soln. (10 ml) and $CHCl_3$ (15 ml). The resulting mixture was heated momentarily to boiling and diluted with H_2O (10 ml), the aq. soln. extracted with $CHCl_3$ (2 × 8 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the oily residue purified by prep. TLC (silica gel, $CHCl_3$/MeOH/NH_4OH 250 : 10 : 1): **5** (170 mg, 83%). M.p. 187–188° (from MeOH). ^{1}H-NMR: 7.26–7.29 (*m*, 2 H_o, 2 H_m of Ph); 7.18–7.23 (*m*, H_p of Ph); 6.64 (*d*, *J*(1,2) = 8.2, H–C(2)); 6.51 (*d*, H–C(1)); 6.36, 6.43 (2*d*, *J*(18,19) = 15.9, H–C(18), H–C(19)); 5.87 (br. *s*, H–C(7)); 4.87 (*dd*, *J*(5,6) = 6.5, *J*(5,7) = 1.0, H–C(5)); 4.26 (*m*, H–C(6)); 3.85 (*s*, MeO); 3.64 (*dd*, *J*(9,10α) = 6.4, *J*(9,14) = 3.0, H–C(9)); 2.98 (*d*, *J*(10α,10β) = 18.6, $H_β$–C(10)); 2.93 (br. *s*, OH); 2.84 (*m*, H–C(14)); 2.58 (*ddd*, *J*(16ax,16eq) = 12.3; *J*(15eq,16eq) = 1.0, H_{eq}–C(16)); 2.45 (*s*, MeN); 2.38 (*ddd*, *J*(15eq,

16ax) = 3.7, H_{ax}–C(16)); 2.37 (*dd*, H_{α}–C(10)); 2.10 (*ddd*, *J*(15ax,16ax) = 12.6, *J*(15ax,16eq) = 5.4, H_{ax}–C(15)); 1.88–1.94 (*m*, *J*(15ax,15eq) = 12.6, H_{eq}–C(15)). MS: 401 (M^+). Anal. calc. for $C_{26}H_{27}NO_3 \cdot 0.5\ H_2O$ (410.52): C 76.07, H 6.87, N 3.41; found: C 76.10, H 6.79, N 3.35.

*(3′a*S*,5α,6α,7β,7*′S*,7′a*R*)-4,5-Epoxy-7,8-didehydro-3′a,7,7′,7′a-tetrahydro-6-hydroxy-3-methoxy-17-methyl-2′,7′-diphenyl-2*H*-isoindolo[4,5 : 7,8]morphinan-1′,3′-dione* (= *(3a*R*,4*S*,5b*R*,6*R*,9a*S*,14a*R*,15*S*, 15b*S*)-3a,4,5b,6,8,9,14a,15,15a,15b-Decahydro-15-hydroxy-13-methoxy-7-methyl-2,4-diphenyl-6,10-methanobenzofuro[3,2-*e*]isoindolo[4,5-*h*]isoquinoline-1,3(2*H*,7*H*)-dione*; **12**). A mixture of **5** (30 mg, 0.072 mmol) and *N*-phenylmaleimide (20 mg, 0.114 mmol) was refluxed in toluene (4 ml) for 5 h. After evaporation the residue was purified by prep. TLC (silica gel, $MeOH/CH_2Cl_2$ 1 : 4: **12** (30 mg, 71%). White powder. M.p. 145–148°. ^{1}H-NMR: 7.38 (*m*, 2 H), 7.38 (*m*, 2 H), 7.32 (*m*, 3 H), 7.25 (*m*, 1 H), 7.17 (*d*, *J* = 7.4, 2 H), 7.11 (*d*, *J* = 7.7, 2 H) (Ph, PhN); 6.65 (*d*, *J*(1,2) = 8.1, H–C(2)); 6.46 (*d*, H–C(1)); 5.78 (*m*, *J*(6′,7′) = 2.6, H–C(6′)); 4.94 (*d*, *J*(5,6) = 4.4, H–C(5)); 4.85 (*dd*, *J*(6,7) = 11.8, H–C(6)); 3.86 (*s*, MeO); 3.67 (*dd*, *J*(3′a,7′a) = 8.6, *J*(3′a,7) = 6.0, H–C(3′a)); 3.63 (br. *d*, *J*(9,10α) = 6.1, H–C(9)); 3.35 (*dd*, *J*(7′,7′a) = 7.6, H–C(7′a)); 3.17 (*m*, H–C(7′)); 2.92 (br. *s*, H–C(14)); 2.91 (*d*, *J*(10α,10β) = 18.2, H_{β}–C(10)); 2.55 (*dd*, *J*(16ax,16eq) = 12.1, *J*(15ax,16eq) = 5.3, H_{eq}–C(16)); 2.45 (*s*, MeN); 2.37 (*dd*, *J*(9, 10α) = 6.8, H_{α}–C(10)); 2.34 (*m*, H_{ax}–C(16)); 2.13 (*dd*, *J*(3′a,7) = 6.0, H–C(7)); 2.11 (*m*, *J*(15ax, 15eq) = 12.6, *J*(15ax,16ax) = 12.5, H_{ax}–C(15)); 1.87 (br. *d*, H_{eq}–C(15)).

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