

An unexpected ring formation in morphine chemistry

Wilhelm Fleischhacker,*^a Bernd Richter,^a Gerald Giester,^b and Thomas H. Brehmer^b

^a *Institute of Pharmaceutical Chemistry, University of Vienna, Althanstraße 14, A-1090 Wien, Austria*

E-mail: wilhelm.fleischhacker@univie.ac.at

^b *Institute of Crystallography and Mineralogy, University of Vienna, Althanstraße 14, A-1090 Wien, Austria*

E-mail: gerald.giester@univie.ac.at

Dedicated to Prof. Fritz Sauter on the occasion of his 70th birthday

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Abstract

Reaction of (7*R*)-*N*-benzyl-*N*-nor-7-bromoneopinone dimethyl acetal (**2**) with primary or secondary amines (RNH₂, R₁R₂NH) resulted in 9-amino-substituted hasubanan derivatives; in particular, modification of the 9-(2-hydroxyethyl)amino derivative in subsequent steps gave products **8** with a 9-(oxazolidin-2'-one-3'-yl) substituent. ¹H and ¹³C NMR spectra did not provide definitive evidence for the supposed structure and reaction mechanism, but X-ray analyses of compounds **8a** and **8d** confirmed both structures.

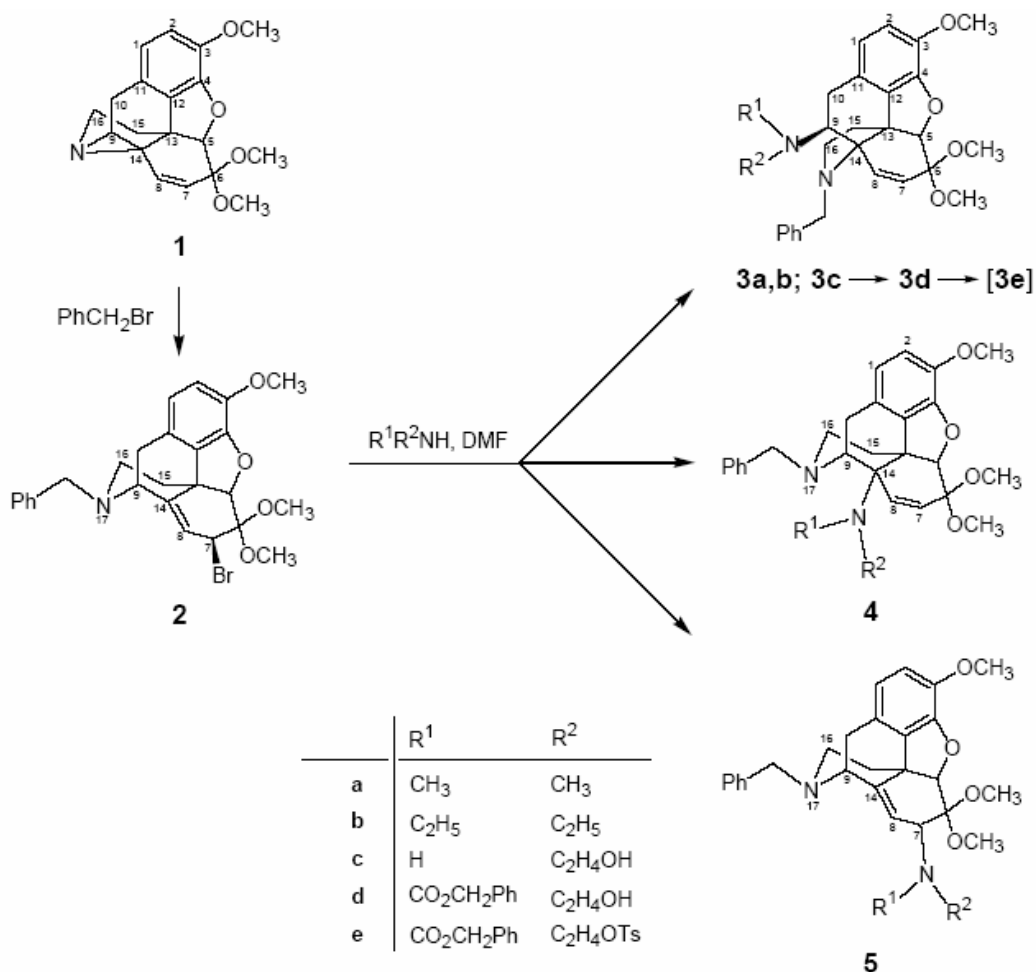
Keywords: Morphine derivatives, neopine derivatives, hasubanan, ring formation, 9-(oxazolidin-2'-one-3'-yl)-substitution, X-ray structure analysis

Introduction

It is known that the position of basic nitrogen in the morphine scaffold as well as the type of its substituents are of great importance with regard to the interaction with the anionic site of the receptor. The goal of our approach was to introduce a second basic group in the vicinity to the nitrogen attached to C-9. The subsequent step should turn the original nitrogen atom into a non-basic group, incapable of interaction with the anionic site of the receptor. In this way the scaffold nitrogen would be changed to inefficiency whereas the newly inserted one could be capable of pharmacologic interactions.

Two more points of consideration should be mentioned: 1. A second nitrogen offers the advantage to insert an intramolecular bridge. 2. The synthesis of dimers by inserting suitable bivalent reagents should be possible; such compounds are known to possess higher

antinociceptive potency and receptor selectivity by entropic reasons.¹

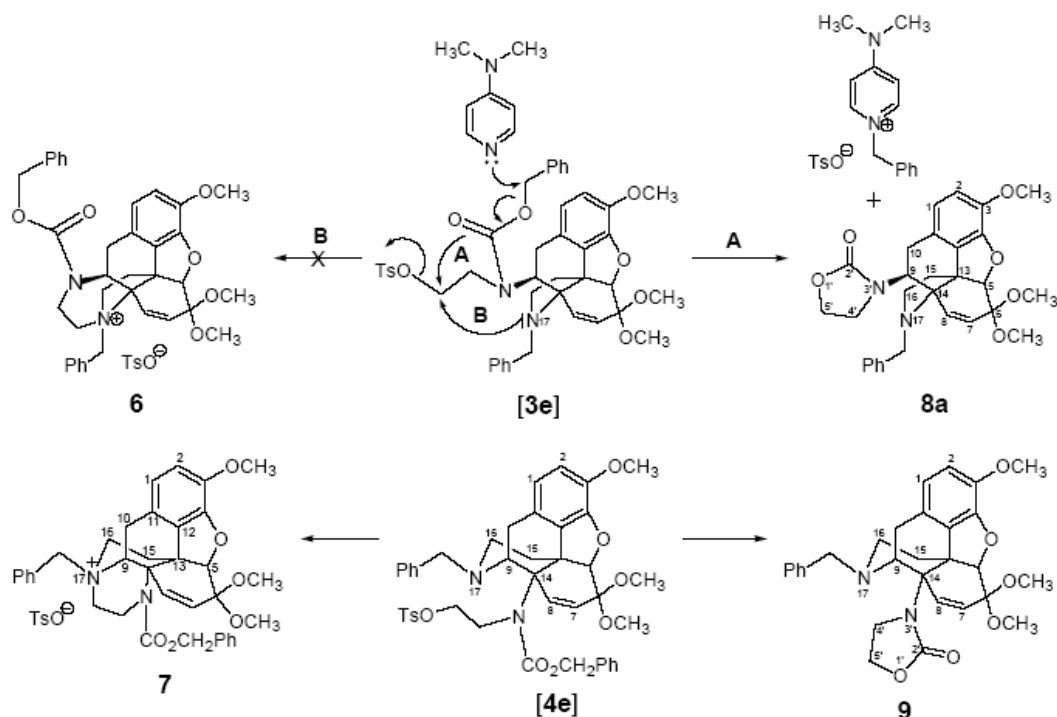


Scheme 1

We started as follows (Scheme 1): Reaction of the known 14,17-cyclonorcodeinone dimethyl acetal **1**² with benzyl bromide yielded quantitatively the neopinone derivative **2**.³ Generally, hydrolysis, methanolysis, acetolysis, *i.e.* nucleophilic substitution of 7-bromoneopinone or 14-bromocodeinone acetal derivatives are assumed to occur via an ionic intermediate (a quaternary aziridinium ion derived from **1**), which results in a mixture of 7-, 14- and 9-substituted derivatives.⁴ Therefore, the straightforward reaction with primary and secondary amines furnishing single, defined products was a surprise at first sight. Inspection of the NMR spectra of the product eliminated structure **5**, but it was not possible to discriminate unambiguously between amine substitution at C-9 (as in **3**) or C-14 (as in **4**) by any routine analytical method. Only the ¹H NMR spectrum of derivative **3d**, obtained later, gave evidence in support of the proposed structure based on the paramagnetic shift of the H-9 signal as a consequence of carbamate formation. We expected that synthetic steps to be carried out at a later stage and aiming at cyclisation by bridging both nitrogen atoms would support this indication, but at last the X-ray analyses of **8a** and **8d** confirmed the substitution at C-9.

Results and Discussion

In regard to our experience with codeinone derivatives, bridge building between both nitrogen atoms at C-9 and C-14 should be possible.⁵ In **3c** and **4c** ($R_1 = H$, $R_2 = CH_2CH_2OH$) the hydroxyl group is expected to become a good nucleofuge upon conversion into the tosylate such as **3e** or **4e**, thus facilitating ring closure with the other nitrogen (N-17 of the original morphine scaffold) to form ammonium salt **6** or **7**, respectively (Scheme 2), which in turn, could afford a dibasic compound after detachment of the benzyl groups in a subsequent step.



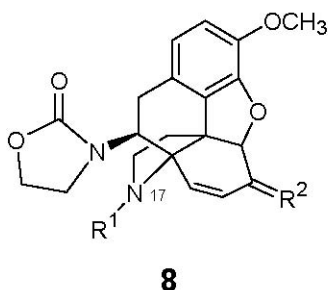
Scheme 2

At this stage we engaged in some mechanistic considerations to evaluate the possibility of an alternative ring formation from **3e** or **4e** (bond lengths, steric energies). It must be argued that at first sight there seemed to be no energy preference for ring formation taking place from a newly inserted *N*-substituent at C-9 to the rearranged N-17, now located at C-14 (in **3**), or alternatively from the alkylamino substituent at C-14 to N-17 bonded to C-9 as in the original scaffold (in **4**). In fact, computation (MM2 force field) of the energies of the alternative bases derived from structures **6** and **7** gave almost identical results (14.7 vs. 14.9 kJmol⁻¹), whereas the quaternary ammonium salts **6** and **7** revealed a rather low steric energy of 16.4 kJmol⁻¹ for **6**, vs. 18.6 kJmol⁻¹ for **7**, obviously due to the more crowded topology caused by substitution with the bulkier *Z*-group in the vicinity of the quaternary C-14. Since the reaction did not work efficiently with the unprotected secondary amine **3c** or **4c**, the benzyloxycarbonyl group (*Z*-group) was introduced as R_1 to give **3d** or **4d**. The subsequent tosylation step to form **3e** or **4e** was carried out without

isolation of the resulting intermediate and was expected to facilitate the desired intramolecular reaction by increasing the electrophilicity of the terminal methylene group (Scheme 2).

Surprisingly, we did not obtain the quaternary ammonium salt **6** or **7**, but rather a product in high yield and with concomitant loss of *one* benzyl group. Later this product was identified as the oxazolidinone derivative **8a** (vide infra). At first, we were not aware of this and believed that a diazine moiety had been formed, and keeping in mind the loss of one benzyl group we set out to distinguish between a product structure derived from either **6** or **7**.

It is noteworthy to mention that the decisive condition for this unique reaction leading to **8a** is the presence of dimethylaminopyridine (DMAP) in the tosylation step which triggered the entire reaction sequence: nucleophilic attack of DMAP at the *O*-benzyl methylene group induced CH₂-O-bond cleavage and ring closure by the carboxyl oxygen at the tosyloxymethylene group with displacement of the tosylate anion. The benzyl group of the *Z*-group was consumed by DMAP affording the *N*-benzyl-4-(dimethyl-amino)pyridinium ion, which was precipitated as the perchlorate salt and analyzed after crystallisation. Without the assistance of DMAP no reaction was detectable.



8	R ¹	R ²
a	CH ₂ Ph	(OCH ₃) ₂
b	H	(OCH ₃) ₂
c	CH ₃	(OCH ₃) ₂
d	CH ₂ CH=CH ₂	(OCH ₃) ₂
e	CH ₂ Ph	O
f	H	O
g	CH ₃	O
h	CH ₂ CH=CH ₂	O
i	CO ₂ CH ₂ Ph	(OCH ₃) ₂

Compound **8a** was debenzylated to **8b** by hydrogenation over Pd/C-catalyst in acetic acid. Finally, the structure elucidation of **8d** and **8a** by X-ray analyses ensured that the oxazolidine derivative had in fact been formed. This result eliminates structure **9** and that of its conceivable precursor **4e**.

Crystal structure discussion

Eventually, the structure of compounds **8a** and **8d** was proven by X-ray analysis (Figures 1 and 2).

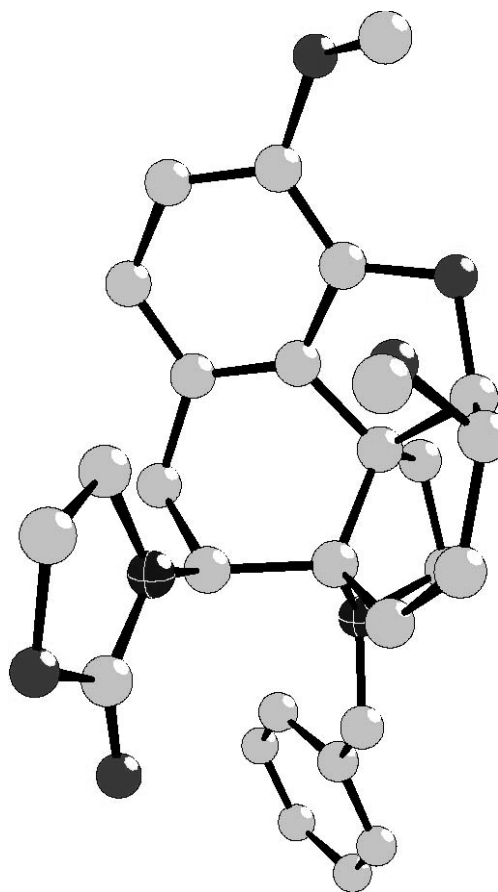


Figure 1. Perspective view of compound **8a**.

The crystal data are summarized in the Experimental part. Lists of structure factors, atomic coordinates and thermal components for non-hydrogen atoms and hydrogen atom parameters are available from T.H.B. and have been deposited at the Cambridge Crystallographic Data Centre. All bond lengths and angles in the molecules **8a** and **8d** lie within the expected ranges. The phenyl rings (C1,C2,C3,C4,C11,C12) and (C24-C29) are planar, whereas the other six-membered rings are characterized by classical conformations (chair, boat, twist-boat) with deviations of some ring atoms. The five-membered rings (O2,C5,C13,C12,C4) and (C13,C14,N1,C16,C15) have envelope conformations with C5 and C16, respectively, deviating from the planes defined by the other ring atoms. The oxazolidine ring (N2,C17,O4,C18,C19) adopts an envelope conformation only in compound **8a**, where C18 deviates from the ring plane. In structure **8d** this ring is planar.

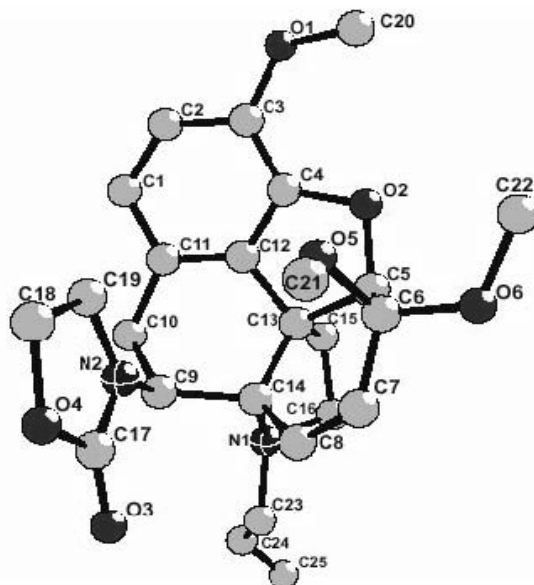


Figure 2 Perspective view of compound **8d** with atom labeling scheme.

Experimental Section

General Procedures. Melting points: Kofler hot stage microscope; column chromatography was performed on silica gel (Kieselgel 60, 70–230 mesh; Merck). IR spectra were recorded on a Perkin Elmer Spectrum 1000 instrument; NMR spectra were recorded on a Varian Unity Plus 300 spectrometer; mass spectra were measured on a Shimadzu QP-5000 mass spectrometer (EI, 70eV). Elemental analyses were performed by the Laboratory of Microanalysis, Institute for Physical Chemistry of the University of Vienna. Energy computations were accomplished using the CS Chem 3D Pro[®] program (MM2 force field), Cambridge, MA.

(7R)-N-Benzyl-N-nor-7-bromoneopinone dimethyl acetal (2). Benzyl bromide (0.75 mL, 6.3 mmol) was added to 14,17-cyclonorcocodeinone dimethyl acetal (**1**, 2.0 g, 6.11 mmol) in CH₂Cl₂ (20 mL) and stirred at 25 °C for 6 h. After addition of a saturated aqueous solution of NaHCO₃ (5 mL) stirring was continued for 1 h. The CH₂Cl₂ layer was separated, washed with water, dried over Na₂SO₄, and concentrated. The residual pale oil **2** (3.0 g, 98%) was purified over silica gel (petrol ether/ethyl acetate/triethylamine 10:2:1, R_f = 0.43). ¹H NMR (CDCl₃): δ 7.45–7.20 (m, 5H, C₆H₅), 6.80 (d, J_{1,2} = 8.1 Hz, 1H, H-2), 6.55 (d, J_{1,2} = 8.1 Hz, 1H, H-1), 5.77 (d, J_{7,8} = 6.3 Hz, 1H, H-8), 5.22 (s, 1H, H-5), 4.59 (d, J_{7,8} = 6.3 Hz, 1H, H-7), 3.90 (s, 3H, 3-OCH₃), 4.01, 3.92 (AB, J_{gem} = 13.4 Hz, 2H, benzyl-HA₁HB), 3.54 (d, J_{9,10β} = 7.1 Hz, 1H, H-9), 3.53 (s, 3H, 6_α- or 6_β-OCH₃), 3.21 (d, J_{gem} = 18.2 Hz, 1H, H_α-10), 3.03 (m, 1H, H_A-16), 3.02 (s, 3H, 6_α- or 6_β-OCH₃), 2.86 (dd, J_{9,10β} = 7.1 Hz, J_{gem} = 18.2 Hz, 1H, H_β-10), 2.68 (m, 1H, H_B-16), 2.50 (m, 1H, H_A-15), 1.69 (m, 1H, H_B-15); ¹³C NMR (CDCl₃): δ 145.68 (C-4), 143.80 (C-14), 142.01 (C-3), 138.91 (C_{Ph}-1), 131.25 (C-12), 128.68, 128.20 (C_{Ph}-2,6, C_{Ph}-3,5), 127.04 (C-11), 126.89 (C_{Ph}-4), 119.04 (C-1), 117.00 (C-8), 114.60 (C-2), 98.48 (C-6), 91.89 (C-5), 57.98 (C-9),

57.02 (benzyl-CH₂), 57.02 (3-OCH₃), 50.42, 49.50 (6 α - and 6 β -OCH₃), 46.69 (C-13), 46.61 (C-7), 43.46 (C-16), 34.79 (C-15), 31.86 (C-10); MS: *m/z* 497, 499 (1:1). Anal Calcd for C₂₆H₂₈BrNO₄ (498.42): C, 62.66; H, 5.66; Br, 16.03; N, 2.81. Found: C, 62.39; H, 5.65; Br, 15.95; N, 2.81.

(9S)-17-Benzyl-4,5-epoxy-9-diethylamino-3-methoxyhasubanan-6-one dimethyl acetal (3b).

To a solution of **2** (580 mg, 1.16 mmol) in DMF (15 mL) was added dry diethylamine (0.6 mL, excess), and the mixture was stirred under Ar at 120 °C for 4 h. After evaporation and flash chromatography (petroleum ether/ethyl acetate/triethylamine 12:2:0.5) **3b** (150 mg, 26%) was obtained as an analytically pure oil. Another pure fraction was **3a** (120 mg, 22%; formed from dimethylamine present in purchased and unpurified diethylamine; Merck 803010, "z. Synthese"). ¹H NMR (CDCl₃): δ 7.38 (m, 5H, C₆H₅), 6.73 (d, *J*_{1,2} = 8.1 Hz, 1H, H-2), 6.67 (d, *J*_{1,2} = 8.1 Hz, 1H, H-1), 6.26 (d, *J*_{7,8} = 11.1 Hz, 1H, H-8), 5.88 (d, *J*_{7,8} = 11.1 Hz, 1H, H-7), 4.64 (s, 1H, H-5), 4.32 (d, *J*_{gem} = 13.5 Hz, 1H, benzyl-H_A), 3.98 (s, 3H, 3-OCH₃), 3.58 (m, 1H, H-9), 3.56 (s, 3H, 6 α - or 6 β -OCH₃), 3.49 (d, *J*_{gem} = 13.5 Hz, 1H, benzyl-H_B), 3.11 (s, 3H, 6 α - or 6 β -OCH₃), 2.99 (d, *J*_{gem} = 15.6 Hz, 1H, H α -10), 2.87 (dd, *J*_{9,10 β} = 4.95 Hz, *J*_{gem} = 15.6 Hz, 1H, H β -10), 2.64 (m, 1H, H α -16), 2.27 (m, 1H, H β -16), 2.11 (broad m, 4H, 2 x CH₂CH₃), 2.02 (m, 1H, H α -15), 1.62 (m, 1H, H β -15), 0.91 (t, 6H, 2 x CH₂CH₃); ¹³C NMR (CDCl₃): δ 146.21 (C-4), 141.48 (C-3), 140.63 (C_{Ph}-1), 133.74 (C-8), 132.19 (C-12), 128.26 (C_{Ph}-2,6), 128.08 (C_{Ph}-3,5), 127.44 (C-11), 126.82 (C_{Ph}-4), 125.29 (C-7), 118.79 (C-1), 115.23 (C-2), 94.49 (C-6), 94.36 (C-5), 67.06 (C-9), 65.97 (C-14), 57.47 (3-OCH₃), 53.23 (benzyl-CH₂), 52.39 (C-13), 50.08, 48.78 (6 α -, 6 β -OCH₃), 46.55 (C-16), 44.29 (CH₂CH₃), 40.75 (C-15), 23.64 (C-10), 15.00 (CH₂CH₃); MS: *m/z* 490, C₃₀H₃₈N₂O₄ (490.63).

(9S)-17-benzyl-4,5-epoxy-3-methoxy-9-dimethylaminohasubanan-6-one dimethyl acetal (3a).

¹H NMR (CDCl₃): δ 7.37 (m, 5H, C₆H₅), 6.72 (d, *J*_{1,2} = 8.0 Hz, 1H, H-2), 6.69 (d, *J*_{1,2} = 8.0 Hz, 1H, H-1), 6.21 (d, *J*_{7,8} = 11.1 Hz, 1H, H-7), 5.93 (d, *J*_{7,8} = 11.1 Hz, 1H, H-8), 4.65 (s, 1H, H-5), 4.28 (d, *J*_{gem} = 13.5 Hz, 1H, benzyl-H_A), 3.97 (s, 3H, 3-OCH₃), 3.56 (s, 3H, 6 α - or 6 β -OCH₃), 3.50 (d, *J*_{gem} = 13.5 Hz, 1H, benzyl-H_B), 3.24 (m, 1H, H-9), 3.09 (s, 3H, 6 α - or 6 β -OCH₃), 2.97 (m, *J*_{gem} = 15.6 Hz, 2H, H-10), 2.68 (m, 1H, H α -16 or H β -16), 2.31 (m, 1H, H α -16 or H β -16), 2.05 (m, 1H, H α -15 or H β -15), 1.97 (s, 6H, 2 x CH₃), 1.62 (m, 1H, H-15 α or H-15 β); ¹³C NMR (CDCl₃): δ 146.20 (C-4), 141.46 (C-3), 140.47 (C_{Ph}-1), 133.31 (C-8), 132.19 (C-12), 128.29 (C_{Ph}-2,6), 127.98 (C_{Ph}-3,5), 127.14 (C-11), 126.85 (C_{Ph}-4), 126.76 (C-7), 119.05 (C-1), 115.25 (C-2), 94.72 (C-6), 94.62 (C-5), 69.90 (C-9), 65.88 (C-14), 57.44 (3-OCH₃), 52.82 (benzyl-CH₂), 52.16 (C-13), 50.19, 48.27 (6 α -, 6 β -OCH₃), 46.69 (C-16), 43.12 (CH₃), 41.49 (C-15), 21.61 (C-10); MS: *m/z* 462, C₃₀H₃₄N₂O₄ (462.59).

(9S)-17-Benzyl-4,5-epoxy-9-hydroxyethylamino-3-methoxyhasubanan-6-one dimethyl acetal (3c).

A solution of **2** (6.08 g, 12.21 mmol) and aminoethanol (7.4 mL, excess) in dry DMF (100 mL) was stirred under Ar at 130 °C (bath temperature) for 4 h. After evaporation of the solvent the residue was taken up with ethyl acetate. The organic extract was washed with brine and water, dried with Na₂SO₄, and after removal of the solvent under reduced pressure **3c** was obtained a pale orange oil (5.73 g, 98%), which was sufficiently pure for further reactions. An analytical sample was crystallized from ethanol and gave colourless crystals, mp

158–160 °C; ^1H NMR (CDCl_3): δ 7.37–7.27 (m, 5H, C_6H_5), 6.74 (d, $J_{1,2} = 8.1$ Hz, 1H, H-1), 6.73 (d, $J_{1,2} = 8.1$ Hz, 1H, H-2), 6.19 (d, $J_{7,8} = 10.8$ Hz, 1H, H-7), 6.00 (d, $J_{7,8} = 10.8$ Hz, 1H, H-8), 4.62 (s, 1H, H-5), 4.27 (d, $J_{\text{gem}} = 13.5$ Hz, 1H, benzyl-H_A), 3.95 (s, 3H, 3-OCH₃), 3.59 (s, 3H, 6 α - or 6 β -OCH₃), 3.52 (d, 1H, benzyl-H_B), 3.45, 3.25 (m, m, 1H, 1H, OCH_AH_B), 3.21 (d, $J_{\text{gem}} = 14.7$ Hz, 1H, H α -10), 3.19 (broad s, 1H, H-9), 3.04 (s, 3H, 6 α - or 6 β -OCH₃), 2.88 (broad d, 1H, H β -10), 2.75 (m, 1H, H α -16), 2.66, 2.48 (m, m, 1H, 1H, NCH_AH_B), 2.34 (m, 1H, H_{eq}-16), 2.12 (m, 1H, H α -15), 1.60 (m, 1H, H_{eq}-15). ^{13}C NMR (CDCl_3): δ 146.12 (C-4), 141.78 (C-3), 140.03 (C_{Ph}-1), 133.16 (C-12), 132.38, 130.58 (C-7, C-8), 128.23, 127.28 (C_{Ph}-2,6, C_{Ph}-3,5), 126.83 (C_{Ph}-4), 123.64 (C-11), 120.53 (C-1), 114.42 (C-2), 95.46 (C-6), 94.63 (C-5), 68.44 (C-14), 60.16 (OCH₂), 59.63 (C-9), 57.17 (3-OCH₃), 53.09 (benzyl-CH₂), 52.27 (C-13), 50.82, 48.49 (6 α - and 6 β -OCH₃), 47.91 (C-16), 47.43 (NCH₂), 41.86 (C-15), 27.45 (C-10); MS: m/z (%) 478 (0.35), 446 (100; M –CH₃OH). Anal. Calcd. for $\text{C}_{28}\text{H}_{34}\text{N}_2\text{O}_5$ (478.59): C, 70.27; H, 7.16; N, 5.85. Found: C, 70.26; H, 7.30; N, 5.78.

(9S)-17-Benzyl-(N-benzoyloxycarbonyl)-4,5-epoxy-9-hydroxyethylamino-3-meth-

oxyhasubanan-6-one dimethyl acetal (3d). To a solution of **3c** (3.10 g, 6.5 mmol) in acetone (65 mL) were added K_2CO_3 (1.0 g, 7.2 mmol) and benzyl chloroformate (1 mL, 1.2 g, 7.0 mmol), and the mixture was stirred at 40 °C (bath temperature) under Ar for 2 h. After concentration, the crude residue (3.81 g, 96%) was found to be sufficiently pure for further reactions. For analytical purpose a sample was purified by flash chromatography on silica gel (petrol ether/ethyl acetate/triethylamine 5:2:1). The NMR spectra show two sets of spectra due to the presence of amide rotamers. ^1H NMR (CDCl_3): δ 7.33–7.08 (m, 10H, 2 C_6H_5), 6.76–6.63 (AB, 2H, H-1, H-2), 5.93–5.71 (m, 2H, H-7, H-8), 5.26–5.04 (m, 2H, benzyl-CH₂), 4.99, 4.82 (d, d, 1H, 1H, H-9), 4.60, 4.56 (s, s, 1H, 1H, H-5), 4.19 (d, 1H, $J_{\text{gem}} = 13.7$ Hz, benzyl-H_A), 3.92 (s, 3H, 3-OCH₃), 3.50 (s, 3H, 6 α - or 6 β -OCH₃), 3.46 – 3.12 (m, 5H, H_A-10, CH₂CH₂O), 3.05 (d, 1H, $J_{\text{gem}} = 13.7$ Hz, benzyl-H_B), 3.02, 2.96 (s, s, 3H, 3H, 2 6 α - and 6 β -OCH₃), 2.85–2.52 (m, 1H, H_B-10, H_A-16), 2.30–1.79 (m, 1H, H-15_A, H_B-16), 1.65–1.45 (m, 1H, H-15_B). ^{13}C NMR (CDCl_3): δ 158.49, 158.00 (2 CO), 146.49, 126.41 (2 C-4), 142.26 (C-3), 140.39, 139.90 (2 *N*-benzyl-C_{Ph}-1), 136.46, 135.11 (2 *O*-benzyl-C_{Ph}-1), 132.92, 132.12 (2 C-12), 130.75, 130.48, 130.14 (C-7, C-8), 128.63, 128.48, 128.41, 128.17, 128.09, 127.90, 127.77 (C_{Ph}), 126.67 (2 C_{Ph}-4), 124.45, 123.86 (2 C-11), 119.02, 118.49 (2 C-1), 114.87, 114.65 (2 C-2), 94.43, 94.15 (2 C-5), 94.27 (C-6), 67.85 (C-14), 68.57, 67.26 (2 benzyl-CH₂O), 64.23, 62.03 (2 CH₂O), 60.53, 60.12 (2 C-9), 57.24 (3-OCH₃), 52.40, 52.03 (CH₂N, benzyl-CH₂N), 50.31, 48.55 (6 α -, 6 β -OCH₃), 46.76, 46.42 (2 C-16), 46.42, 45.15 (2 C-13), 41.21, 40.95 (2 C-15), 29.21, 28.99 (2 C-10); MS: m/z 612. Anal. Calcd. for $\text{C}_{36}\text{H}_{40}\text{N}_2\text{O}_7$ (612.72): C, 70.57; H, 6.58; N, 4.57. Found: C, 70.31; H, 6.62; N, 4.65.

(9S)-17-Benzyl-4,5-epoxy-3-methoxy-9-(oxazolidin-2'-on-3'-yl)hasubanan-6-one dimethyl acetal (8a). A mixture of **3d** (10.3 g, 16.8 mmol), CH_2Cl_2 (120 mL), *p*-toluenesulfonyl chloride (3.2 g, 17 mmol, freshly purified), 4-dimethylaminopyridine (2.1 g, 17.2 mmol) and triethylamine (5 mL, 3.6 g, 36 mmol) was stirred under Ar at 40 °C (bath temperature) for 10 h. After evaporation of the solvent the residue was dissolved in ethyl acetate, the organic extract was washed with a saturated aqueous NaHCO_3 solution, then with brine, dried over Na_2SO_4 , and

concentrated under reduced pressure. After purification of the residue by flash chromatography on silica gel (petrol ether/ethyl acetate/triethylamine 6:4:1) colourless crystals **8a** were isolated (7.95 g, 94%); mp 188–190 °C (MeOH); ¹H NMR (CDCl₃): δ 7.39–7.26 (m, 5H, C₆H₅), 6.75 (d, *J*_{1,2} = 8.2 Hz, 1H, H-1), 6.71 (d, *J*_{1,2} = 8.2 Hz, H, H-1), 6.20 (d, *J*_{7,8} = 10.8 Hz, 1H, H-7), 6.02 (d, *J*_{7,8} = 10.8 Hz, 1H, H-8), 4.67 (d, *J*_{gem} = 12 Hz, 1H, benzyl-H_A), 4.66 (s, 1H, H-5), 4.57 (m, 1H, H-9), 4.55–3.92 (m, 2H, H_AH_B-5'), 3.97 (s, 3H, 3-OCH₃), 3.55 (s, 3H, 6_α- or 6_β-OCH₃), 3.46 (d, *J*_{gem} = 12 Hz, 1H, benzyl-H_B), 3.49, 2.82 (m, m, 1H, 1H, H_AH_B-10), 3.09 (s, 3H, 6_α- or 6_β-OCH₃), 2.93, 2.65 (m, m, 1H, 1H, H_AH_B-4'), 2.77, 2.30 (m, m, 1H, 1H, H_AH_B-16), 2.09, 1.63 (m, m, 1H, 1H, H_AH_B-15). ¹³C NMR (CDCl₃): δ 159.11 (C-2'), 146.08 (C-4), 142.09 (C-3), 140.07 (C_{Ph}-1), 132.44 (C-12), 130.84, 130.60 (C-7, C-8), 128.11 (C_{Ph}-2,3,5,6),, 126.77 (C_{Ph}-4), 124.39 (C-11), 119.51 (C-1), 115.09 (C-2), 94.47 (C-6), 94.23 (C-5), 67.95 (C-14), 62.18 (C-5'), 57.23 (3-OCH₃), 57.13 (C-9), 52.70 (benzyl-CH₂), 51.75 (C-13), 50.36, 48.61 (6_α-, 6_β-OCH₃), 47.05 (C-16), 42.14 (C-4'), 41.78 (C-15), 27.90 (C-10); IR (KBr): 1747.8, 1722.3 cm⁻¹; MS: *m/z* 504. Anal Calcd for C₂₉H₃₂N₂O₆ (504.54): C, 69.03; H, 6.39; N, 5.55. Found C, 68.83; H, 6.49; N, 5.38.

X-ray analysis of compound **8a**

With methylene chloride as solvent inclusion (C₂₉H₃₂N₂O₆ + CH₂Cl₂, M=504.54+84.93). The compound crystallized in monoclinic space group *P*2₁ with unit cell parameters *a* = 9.440(2), *b* = 10.059(2), *c* = 14.889(3) Å, β = 95.51(3)°, *V* = 1407.3(5) Å³, *Z* = 2, *D*_c = 1.391 g/cm⁻³, μ = 0.278 mm⁻¹. Mo-Kα radiation (λ = 0.71073 Å), 5748 reflections measured, 5738 unique, 5549 with *F* = 2σ(*F*) gave *R*₁ = 0.029/*wR*₂ (all data) = 0.073 in a full matrix least squares refinement with 498 parameters. Goodness-of-fit on *F*₂ = 1.073, absolute structure parameter FLACK = 0.02(4). The crystal structure data of **8a** have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; deposition number 155910.

(9*S*)-4,5-Epoxy-3-methoxy-9-(oxazolidin-2'-on-3'-yl)hasubanan-6-one dimethyl acetal (**8b**).

A solution of **8a** (1.45 g, 2.9 mmol) and Pd/C-hydrogenation catalyst (1.5 g, 5% Pd; Sigma) in acetic acid (50 mL) was vigorously stirred under hydrogen gas at 1 bar at room temperature for 1h. After filtration through celite on a glass suction sinter funnel the filtrate was concentrated to afford a pale oil of fair purity (1.08 g, 91%), which crystallized from ethyl acetate; mp 208–211°C; IR (KBr): 1751.8 cm⁻¹; ¹H NMR (CDCl₃): δ 6.70 (d, *J*_{1,2} = 8.1 Hz, 1H, H-1), 6.66 (d, *J*_{1,2} = 8.1 Hz, 1H, H-2), 5.87 (d, *J*_{7,8} = 10.5 Hz, 1H, H-8), 5.79 (d, *J*_{7,8} = 10.5 Hz, 1H, H-7), 4.60 (s, 1H, H-5), 4.34 (dd, *J*_{9,10} = 3.0 Hz, *J*_{9,10} = 2.3 Hz, 1H, H-9), 4.06–3.85 (m, 2H, H_AH_B-5'), 3.90 (s, 3H, 3-OCH₃), 3.48 (s, 3H, 6_α- or 6_β-OCH₃), 3.33 (dd, *J*_{gem} = 15.9 Hz, *J*_{9,10} = 3.0 Hz, 1H, H_A-10), 3.03 (s, 3H, 6_α- or 6_β-OCH₃), 2.97–2.91 (m, 1H, H_A-16), 2.88–2.80 (m, 1H, H_A-4'), 2.81–2.75 (m, 1H, H_B-16), 2.73–2.66 (m, 1H, H_B-10), 2.58–2.51 (m, 1H, H_B-4'), 2.17–2.11 (dd, *J*_{gem} = 12.3 Hz, 1H, H_A-15), 1.72–1.58 (m, 1H, H_B-15). ¹³C NMR (CDCl₃): δ 158.95 (C-2'), 146.11 (C-4), 141.95 (C-3), 135.03 (C-8), 131.95 (C-12), 127.93 (C-7), 124.25 (C-11), 119.55 (C-1), 114.95 (C-2), 94.80 (C-6), 94.11 (C-5), 66.12 (C-14), 62.03 (C-5'), 59.72 (C-9), 57.07, 50.20, 48.50 (3-

OCH₃, 6 α - and 6 β -OCH₃), 50.10 (C-13), 43.98 (C-15), 41.91, 41.87 (C-16, C-4'), 27.19 (C-10); MS: *m/z* 414.46. Anal. Calcd. for C₂₂H₂₆N₂O₆ (414.46): C, 63.76; H, 6.32; N, 6.76. Found: C, 63.64; H, 6.39; N, 6.70.

(9S)-4,5-Epoxy-3-methoxy-17-methyl-9-(oxazolidin-2'-on-3'-yl)hasubanan-6-one dimethyl acetal (8c). MeI (1 mL, 2.28 g, 16 mmol) was added to a solution of **8b** (410 mg, 1 mmol) in CH₂Cl₂ (8 mL), and the mixture was stirred under Ar at room temperature for 24 h. After concentrating the solution, the residue was dissolved in ethyl acetate. The solution was placed in a separatory funnel and washed with 2 M NaOH and subsequently with brine. The organic layer was separated and dried over Na₂SO₄. After evaporation of the solvent, the residue was subjected to flash chromatography on silica gel (petrol ether/ethyl acetate/triethylamine 5:2:1, R_f = 0.35) affording **8c** (240 mg, 57%), which crystallized from methanol; mp 195–197 °C; IR (KBr): 1745.6 cm⁻¹; ¹H NMR (CDCl₃): δ 6.68 (d, *J*_{1,2} = 8.2 Hz, 1H, H-2), 6.63 (d, *J*_{1,2} = 8.2 Hz, 1H, H-1), 5.97 (d, *J*_{7,8} = 11.1 Hz, 1H, H-8), 5.91 (d, *J*_{7,8} = 11.1 Hz, 1H, H-7), 4.57 (s, 1H, H-5), 4.35 (dd, 1H, H-9), 4.05–3.82 (m, 2H, HAHB-5'), 3.91 (s, 3H, 3-OCH₃), 3.49 (s, 3H, 6 α - or 6 β -OCH₃), 3.25 (dd, *J*_{gem} = 15.6 Hz, *J*_{9,10} = 4.5 Hz, 1H, HA-10), 3.01 (s, 3H, 6 α - or 6 β -OCH₃), 2.87–2.77 (m, 2H, HA-4', HA-16), 2.66 (dd, *J*_{9,10} = 2.4 Hz, 1H, HB-10), 2.58 (s, 3H, NCH₃), 2.57–2.50 (m, 1H, HB-4'), 2.42–2.33 (m, 1H, HB-16), 2.09–2.04 (m, 1H, HA-15), 1.67–1.57 (m, 1H, HB-15). ¹³C NMR (CDCl₃): δ 158.99 (C-2'), 146.08 (C-4), 142.03 (C-3), 132.35 (C-12), 130.28 (C-7, C-8), 124.53 (C-11), 119.39 (C-1), 115.08 (C-2), 94.31 (C-6), 94.15 (C-5), 67.39 (C-14), 62.11 (C-5'), 57.22 (3-OCH₃), 56.76 (C-9), 51.59 (C-13), 50.82 (C-16), 50.28 (6 α - or 6 β -OCH₃), 48.51 (6 α - or 6 β -OCH₃), 42.03 (C-4'), 41.47 (C-15), 35.27 (NCH₃), 27.82 (C-10). MS: *m/z* 428. Anal. Calcd. for C₂₃H₂₈N₂O₆ (428.48): C, 64.47; H, 6.59; N, 6.54. Found: C, 64.34; H, 6.63; N, 6.41.

(9S) 17-Allyl-4,5-epoxy-3-methoxy-9-(oxazolidin-2'-on-3'-yl)hasubanan-6-one dimethyl acetal (8d). To a solution of **8b** (320 mg, 0.8 mmol) in CH₂Cl₂ (10 mL) was added 3-bromopropene (0.75 mL, 1.05g, 8.7 mmol), and the mixture was stirred under Ar at room temperature for 48 h. After concentrating, the mixture was taken up in ethyl acetate, placed in a separatory funnel, and sodium carbonate (2 mL, 2 M aqueous solution) was added. Washing the organic layer with brine, drying over Na₂SO₄ and evaporation of the solvent furnished a crude oil (240 mg), which was purified by flash chromatography on silica gel (petrol ether/ethyl acetate/triethylamine 3:2:1, R_f 0.54) to yield crystalline **8d** (160 mg, 46%); mp 158–160 °C (ethyl acetate); IR (KBr): 1736.3cm⁻¹; ¹H NMR (CDCl₃): δ 6.00 (d, *J*_{1,2} = 8.1 Hz, 1H, H-2), 5.89 (d, *J*_{1,2} = 8.1 Hz, 1H, H-1), 6.01 (d, *J*_{7,8} = 11.1 Hz, 1H, H-8), 5.89 (d, *J*_{7,8} = 11.1 Hz, 1H, H-7), 5.90–5.77 (m, 1H, CH=), 5.18 (d, *J*_{vic} = 16.8 Hz, 1H, =CHA), 5.06 (d, *J*_{vic} = 9.9 Hz, 1H, =CHB), 4.57 (s, 1H, H-5), 4.33 (dd, 1H, H-9), 4.05–3.82 (m, 3H, HAHB-5', NCHA), 3.90 (s, 3H, 3-OCH₃), 3.48 (s, 3H, 6 α - or 6 β -OCH₃), 3.15 (dd, 1H, HA-10), 3.01 (s, 3H, 6 α - or 6 β -OCH₃), 2.99–2.70 (m, 3H, HA-4', HA-16, NCHB), 2.65 (dd, 1H, HB-10), 2.60–2.45 (m, 1H, HB-4'), 2.25–2.18 (m, 1H, HB-16), 2.08–2.01 (m, 1H, HA-15), 1.64–1.53 (m, 1H, HB-15); ¹³C NMR (CDCl₃): δ 159.02 (C-2'), 146.01 (C-4), 141.99 (C-3), 137.05 (=CH), 132.38 (C-12), 130.64, 130.18 (C-7, C-8), 124.44 (C-11), 119.38 (C-1), 115.93 (CH₂), 115.05 (C-2), 94.39 (C-6), 94.12 (C-5), 67.71 (C-14), 62.11 (C-5'), 57.18 (3-OCH₃), 57.03 (C-9), 51.70 (C-13), 51.41 (NCH₂), 50.27 (6 α - or 6 β -OCH₃), 48.51

(6 α - or 6 β -OCH₃), 47.15 (C-16), 42.04 (C-4'), 41.57 (C-15), 27.74 (C-10). MS: *m/z* 453. Anal. Calcd. for C₂₅H₃₀N₂O₆ (454.52): C, 66.06; H, 6.65; N, 6.16. Found: C, 65.98; H, 6.77; N, 6.21.

X-ray analysis of 8d (C₂₅H₃₀N₂O₆, M = 454.52): The compound crystallized in orthorhombic space group *P*2₁2₁2₁ with unit cell parameters *a* = 9.4720(1), *b* = 11.8370(2), *c* = 19.8010(3) Å, $\alpha = \beta = \gamma = 90^\circ$, *V* = 2220.09(6) Å³, *Z* = 4, *D*_c = 1.360 g cm⁻³, $\mu = 0.090$ mm⁻¹. Mo-K α radiation ($\lambda = 0.71073$ Å), 6736 reflections measured, 6711 unique, 6098 with *F* = 2 σ (*F*) gave *R*₁ = 0.036 / *wR*₂ (all data) = 0.0827 in a full matrix least squares refinement with 419 parameters. Goodness-of-fit on *F*₂ = 1.027, absolute structure parameter *FLACK* = 0.0(6). The crystal structure of **8d** has been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; deposition number 155909.

(9S)-17-Benzyl-4,5-epoxy-3-methoxy-9-(oxazolidin-2'-on-3'-yl)hasubanan-6-one (8e). A solution of **8a** (1.22 g, 2.4 mmol) in EtOH (10 mL) and 1 N HCl (3 mL) was heated for 5 min. After cooling the mixture was made alkaline with 2 M NaOH (4 mL) and extracted with ethyl acetate. The extract was washed with water and dried over Na₂SO₄ to yield colourless crystals **8e** (1.07 g, 97%); mp 134–136 °C (MeOH); IR (KBr): 1724.1, 1711.2 cm⁻¹; ¹H NMR (CDCl₃): δ 7.36–7.27 (m, 5H, C₆H₅), 7.04 (d, *J*_{7,8} = 10.8 Hz, 1H, H-8), 6.77 (d, *J*_{1,2} = 8.1 Hz, 1H, H-1), 6.74 (d, *J*_{1,2} = 8.1 Hz, 1H, H-2), 6.28 (d, *J*_{1,2} = 8.1 Hz, 1H, H-7), 4.84 (s, 1H, H-5), 4.68 (d, *J*_{gem} = 13.2 Hz, 1H, benzyl-H_A), 4.68 (m, 1H, H-9), 3.97–3.77 (m, 2H, H_AH_B-5'), 3.92 (s, 3H, 3-OCH₃), 3.53 (d, *J*_{gem} = 13.2 Hz, 1H, benzyl-H_B), 3.50 (m, 1H, H_A-10), 2.91 (m, 2H, H_B-10, H_A-16), 2.63 (m, 1H, H_A-4'), 2.51 (m, 1H, H_B-16), 2.22 (m, 1H, H_A-15), 1.96 (m, 1H, H_B-4'), 1.77 (m, 1H, H_B-15). ¹³C NMR (CDCl₃): δ 195.16 (C-6), 159.02 (C-2'), 148.37 (C-8), 144.80 (C-4), 143.38 (C-3), 139.20 (C_{Ph}-1), 130.02 (C-12), 129.59 (C-7), 128.40, 128.10 (C_{Ph}-2,3,5,6), 127.19 (C_{Ph}-4), 124.12 (C-11), 120.85 (C-1), 114.36 (C-2), 89.71 (C-5), 67.82 (C-14), 62.03 (C-5'), 57.11 (C-9), 56.58 (3-OCH₃), 54.07 (C-13), 52.85 (benzyl-CH₂), 48.13 (C-16), 41.76 (C-4'), 28.47 (C-10); MS: *m/z* 458. Anal. Calcd. for C₂₇H₂₆N₂O₅ (458.51): C, 70.73; H, 5.72; N, 6.11. Found: C, 70.51; H, 5.81; N, 5.98.

(9S)-4,5-Epoxy-3-methoxy-9-(oxazolidin-2'-on-3'-yl)hasubanan-6-one (8f). A solution of **8b** (550 mg, 1.3 mmol) in 1 N HCl (4 mL) was heated for 5 min. After cooling, the mixture was made alkaline with 2 M NaOH (3 mL) and extracted with ethyl acetate. The organic extract was washed with brine, dried over Na₂SO₄, and after evaporation of the solvent pale yellow crystals **8f** (470 mg, 96%) were obtained; mp 213–215 °C (MeOH); IR (KBr): 3440.3, 3296.9, 1745.1, 1704.4 cm⁻¹; ¹H NMR (CDCl₃): δ 6.73 (s, 2H, H-1, H-2), 6.68 (d, *J*_{7,8} = 10.8 Hz, 1H, H-8), 6.09 (d, *J*_{7,8} = 10.8 Hz, 1H, H-7), 4.81 (s, 1H, H-5), 4.46 (m, 1H, H-9), 3.90 (s, 3H, 3-OCH₃), 3.93–3.70 (m, 2H, H_AH_B-5'), 3.34 (dd, *J*_{gem} = 15.9 Hz, *J*_{9,10} = 4.2 Hz, 1H, H_A-10), 3.14–2.95 (m, 2H, H_AH_B-16), 2.72 (dd, *J*_{9,10} = 2.4 Hz, 1H, H_B-10), 2.58–2.42 (m, 1H, H_A-4'), 2.29 (dd, *J*_{gem} = 12.6 Hz, *J*_{15A,16} = 3.9 Hz, 1H, H_A-15), 1.96–1.87 (m, 1H, H_B-4'), 1.86–1.77 (m, 1H, H_B-15). ¹³C NMR (CDCl₃): δ 195.23 (C-6), 158.88 (C-2'), 150.32 (C-8), 144.99 (C-4), 143.29 (C-3), 129.67 (C-12), 126.73 (C-7), 124.10 (C-11), 120.88 (C-1), 114.24 (C-2), 89.40 (C-5), 65.73 (C-14), 61.95 (C-5'), 59.67 (C-9), 56.50 (3-OCH₃), 52.42 (C-13), 43.17 (C-15, C-16), 41.54 (C-4'), 27.95 (C-10); MS: *m/z* 368. Anal. Calcd. for C₂₀H₂₀N₂O₅ (368.39): C, 65.21; H, 5.47; N, 7.60. Found: C,

65.01; H, 5.64; N, 7.41.

(9S)-4,5-Epoxy-3-methoxy-17-methyl-9-(oxazolidin-2'-on-3'-yl)hasubanan-6-one (8g). A solution of **8c** (100 mg, 0.23 mmol) in 1 N HCl (3 mL) was heated for 5 min. After cooling the mixture was made alkaline with 2 M NaOH (3 mL) and extracted with ethyl acetate. The extract was washed with brine and dried over Na₂SO₄. After evaporation of the solvent colourless crystals **8g** (80 mg, 90%) were obtained; mp 209–211 °C (ethyl acetate); IR (KBr): 1724.2, 1706.6 cm⁻¹; ¹H NMR (CDCl₃): δ 6.93 (d, *J*_{7,8} = 10.8 Hz, 1H, H-8), 6.71 (s, 2H, H-1, H-2), 6.20 (d, *J*_{7,8} = 10.8 Hz, 1H, H-7), 4.78 (s, 1H, H-5), 4.48 (dd, 1H, H-9), 3.89 (s, 3H, 3-OCH₃), 3.92–3.70 (m, 2H, H_AH_B-5'), 3.26 (dd, *J*_{gem} = 15.6 Hz, *J*_{9,10} = 4.5 Hz, 1H, H_A-10), 2.96 (dd, 1H, H_A-16), 2.70 (dd, *J*_{gem} = 15.6 Hz, *J*_{9,10} = 2.4 Hz, 1H, H_B-10), 2.67 (s, 3H, NCH₃), 2.64 (m, 1H, H_B-16), 2.57 (m, 1H, H_A-4'), 2.21 (m, 1H, H_A-15), 1.91 (m, 1H, H_B-4'), 1.79 (m, 1H, H_B-15); ¹³C NMR (CDCl₃): δ 195.04 (C-6), 158.86 (C-2'), 148.28 (C-8), 144.71 (C-4), 143.21 (C-3), 129.98 (C-12), 129.36 (C-7), 124.22 (C-11), 120.70 (C-1), 114.21 (C-2), 89.59 (C-5), 67.27 (C-14), 61.89 (C-5'), 56.75 (C-9), 56.49 (3-OCH₃), 53.82 (C-13), 51.87 (C-16), 41.62 (C-4'), 40.17 (C-15), 35.42 (17-NCH₃), 28.32 (C-10); MS: *m/z* 382. Anal. Calcd. for C₂₁H₂₂N₂O₅ (382.42): C, 65.96; H, 5.80; N, 7.33. Found: C, 65.69; H, 5.97; N, 7.17.

(9S)-17-Allyl-4,5-epoxy-3-methoxy-9-(oxazolidin-2'-on-3'-yl)hasubanan-6-one (8h). A solution of **8d** (100 mg, 0.22 mmol) in 1 N HCl (3 mL) was heated for 5 min. After cooling, the mixture was made alkaline with 2 M NaOH (3 mL) and extracted with ethyl acetate. The extract was washed with brine, dried over Na₂SO₄. After evaporation of the solvent, **8h** (80 mg, 89%) was obtained as solid material; IR (KBr): 1738.4, 1701.2 cm⁻¹; ¹H NMR (CDCl₃): δ 6.90 (d, *J*_{7,8} = 10.8 Hz, 1H, H-8), 6.71 (s, 2H, H-1, H-2), 6.18 (d, *J*_{7,8} = 10.8 Hz, 1H, H-7), 6.22–5.76 (m, 1H, =CH), 5.24 (d, *J*_{vic} = 17.1 Hz, 1H, =CH_A), 5.12 (d, *J*_{vic} = 10.2 Hz, 1H, =CH_B), 4.78 (s, 1H, H-5), 4.48 (m, 1H, H-9), 3.98 (m, 1H, NCH_A), 3.95–3.68 (m, 2H, H_AH_B-5'), 3.89 (s, 3H, 3-OCH₃), 3.31 (dd, *J*_{gem} = 15.7 Hz, *J*_{9,10} = 4.5 Hz, 1H, H_A-10), 3.11–3.04 (m, 2H, H_A-16, NCH_B), 2.70 (dd, *J*_{gem} = 15.7 Hz, *J*_{9,10} = 2.5 Hz, 1H, H_B-10), 2.59–2.38 (m, 2H, H_A-4', H_B-16), 2.21 (m, 1H, H_A-15), 1.90 (m, 1H, H_B-4'), 1.76 (m, 1H, H_B-15); ¹³C NMR (CDCl₃): δ 195.09 (C-6), 158.90 (C-2'), 148.27 (C-8), 144.68 (C-4), 143.21 (C-3), 136.25 (=CH), 129.93 (C-12), 129.14 (C-7), 124.15 (C-11), 120.71 (C-1), 116.79 (=CH₂), 114.23 (C-2), 89.54 (5), 67.50 (C-14), 61.93 (C-5'), 56.99 (C-9), 56.49 (3-OCH₃), 54.00 (C-13), 51.49 (NCH₂), 48.22 (C-16), 41.63 (C-4'), 40.23 (C-15), 28.27 (C-10); MS: *m/z* 408. Anal. Calcd. for C₂₃H₂₄N₂O₅ (408.45): C, 67.63; H, 5.92; N, 6.86. Found: C, 67.54; H, 6.21; N, 6.92.

(9S) 17-Benzoyloxycarbonyl-4,5-epoxy-3-methoxy-9-(oxazolidin-2'-on-3'-yl)hasubanan-6-one (8i). To a solution of **8b** (250 mg, 0.6 mmol) in acetone (20 mL) was added K₂CO₃ (100 mg) and benzyl chloroformate (0.1 mL, 120mg, 0.7 mmol). The mixture was stirred under Ar at room temperature for 10 h. After concentration under reduced pressure the residue was extracted with ethyl acetate. The extract was washed with brine, dried over Na₂SO₄, and after removal of the solvent an orange oil **8i** (330 mg, 100%) was isolated which was purified by flash chromatography on silica gel (petrol ether/ethyl acetate/triethylamine 3:2:1, *R*_f 0.22); IR (KBr): 1754.4, 1698.5 cm⁻¹; ¹H NMR (CDCl₃) δ: 7.44–7.23 (m, 5H, C₆H₅), 6.74 (d, *J*_{1,2} = 8.1 Hz, 1H, H-

2), 6.66 (d, $J_{1,2} = 8.1$ Hz, 1H, H-1), 6.43 (d, $J_{7,8} = 10.4$ Hz, 1H, H-8), 5.79 (d, 1H, H-7), 5.31 (m, 1H, H-9), 5.21 (broad s, 2H, benzyl-H_AH_B), 4.71 (s, 1H, H-5), 4.10–3.91 (m, 2H, H_AH_B-5'), 3.92 (s, 3H, 3-OCH₃), 3.86–3.39 (m, 2H, H_AH_B-16), 3.29, 3.23 (2 s, 3H, 3H, 6 α - and 6 β -OCH₃), 3.48, 2.97 (2 m, 1H, 1H, H_AH_B-10), 2.95 (m, 2H, H_AH_B-4'), 2.26–2.03 (m, 2H, H_AH_B-15); ¹³C NMR (CDCl₃): δ 158.23 (C-2'), 154.29 (NCO), 146.94 (C-4), 142.65 (C-3), 136.89 (C_{Ph}-1), 129.93 (C-12), 129.86, 129.62 (C-7, C-8), 128.32 (C_{Ph}-2,3,5,6), 127.85 (C_{Ph}-4), 124.66 (C-11), 119.94 (C-1), 116.48 (C-2), 94.82 (C-6), 93.03 (C-5), 66.97 (benzyl-CH₂), 65.97 (C-14), 62.06 (C-5'), 57.35 (3-OCH₃), 55.93 (C-9), 54.65 (C-13), 49.39, 48.89 (6 α - and 6 β -OCH₃), 44.91 (C-16), 42.29 (C-4'), 38.72 (C-15), 28.84 (C-10); MS: m/z 548, C₃₀H₃₂N₂O₈ (548.59).

X-ray structure analysis

Crystallography. Sample preparation. Crystals suitable for X-ray investigation were prepared by slow evaporation of solutions of the respective compounds. Colourless crystals were grown from ethyl acetate in the case of **8d**. Crystallization from CH₂Cl₂ gave the clathrate (inclusion compound) **8a**•CH₂Cl₂ (1:1).

Data collection, structure analysis, and refinement. Intensity data for **8a** and **8d** were obtained on a Nonius Kappa instrument with CCD detector at 110 K (in detail: **8a/8d**, collection time per frame 65/50 sec., rotation width 1.5/1.0 deg., detector distance 35/35 mm, total number of frames 570/392). The structures **8a** and **8d** were solved by direct methods, using the program *SIR92*⁶ and refined with *SHELXL93*.⁷ The figures were prepared using *DIAMOND 2.1a*.⁸

References and Notes

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