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Novel Ring Systems in Morphinoides II [1]: C8,17-Ethano-Bridged 4,5-Epoxyhasubanans[a]

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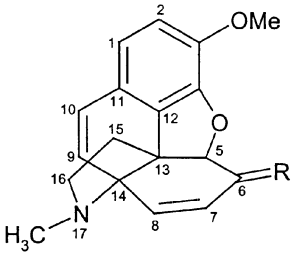
Summary. *Claisen-Eschenmoser* rearrangement of the 9,10-saturated derivative of 4,5-epoxyhasubanan-6β-ol affords the 8β-substituted amide which can be converted to the polycyclic quaternary ammonium salt **7** with an indolizidine substructure. An N-demethylation step with triethylborohydride leads to three products in accordance with the different possible positions of attack of the hydride ion to the strained ring system.

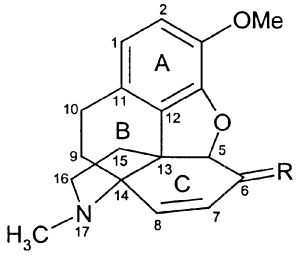
Keywords. Codeine; *Claisen-Eschenmoser* rearrangement; Hasubanan; N-Demethylation.

Introduction

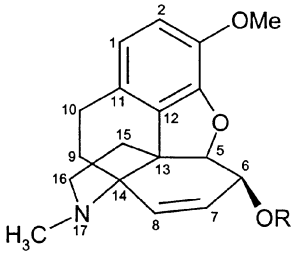
In continuation of our attempts to synthesize derivatives of (5α,13β,14β)-7,8,9,10-tetradehydro-3-methoxy-17-methyl-4,5-epoxyhasubanan-6-on (**1b**) with new ring formation in the electron-donor region of the nucleophilic nitrogen we here report our advances on the 9,10-hydrogenated educt **2**. The question was whether the higher conformative flexibility of ring B in contrast to derivatives of **1** – and, consequently, that of ring C – would give raise to consequences in the cyclization step product formerly reported [1] as well as in the newly synthesized products.



1a: $R = (OCH_3)_2$
1b: $R = O$
1c: $R = H, OH(\alpha)$
1d: $R = H, OH(\beta)$



2a: $R = (OCH_3)_2$
2b: $R = O$



3a: $R = H$
3b: $R = OCO_2C_6H_5$

[a] Dedicated to Prof. *Richard Neidlein* on the occasion of his 70th birthday
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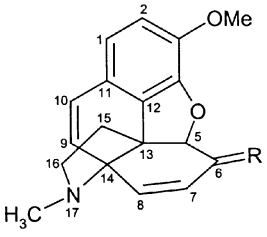
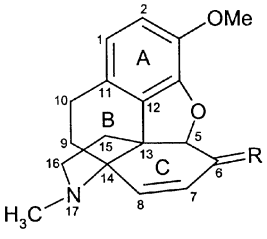
Results and Discussion

Acidic hydrolysis of the acetal **2a** yielded the enone **2b** quantitatively [2]. Since our goal was the synthesis of C-8,N-fused compounds *via* a *Claisen-Eschenmoser* reaction of **3a** with 8β-substituted compounds we forced the formation of the favourable epimer **3a**. In contrast to codeinone, dihydrocodeinone, and 14-hydroxycodeinone, where reduction with metal hydrides proceeds with a high degree of stereoselectivity [3], N,C-14-bridged ketones have been reported being reduced with poor selectivity, leading to mixtures of the C-6-epimer carbinols [4]. Earlier, we have mentioned an acceptable stereoselective behaviour of **1b** yielding the α-carbinol **1c** upon reaction with diisobutylaluminum hydride [1], whereas the selectivity with lithium aluminum hydride was poor. In the course of treating **2b** with sodium borohydride in methanol we isolated a mixture of carbinols **4a**(α) and **3a**(β) in a ratio of 2:3 in addition to 5% of the 7,8-saturated products, whereas application of diisobutylaluminum hydride led to a mixture of **4a**(α) and the favoured isomer **3a**(β) in an epimeric ratio of 7:3. This mixture could not be successfully separated, neither by crystallization nor by chromatographic methods; we were therefore forced to run the separation in any subsequent step of the planned reaction sequence. In order to enrich **3a**, a change of configuration was intended by applying the *Mitsunobu* method [5, 1] followed by separation of the epimeric benzyloxycarbonyloxy derivatives (Route A: *DIBAL*-H reduction of **2b** $\rightarrow$ *Mitsunobu* reaction $\rightarrow$ hydrolysis of **3b** and **4b** $\rightarrow$ *Claisen-Eschenmoser* reaction of the pure epimers to the 8-substituted tertiary amides **5a** and **6a**). Surprisingly, after separation on silicagel only the β-epimer **3b** (in absence of **4b**) could be isolated besides a fraction consisting of a mixture of the carbinols **3a** and **4a** in a ratio of 3:1. The epimer **3b** was purified by crystallization and hydrolized with alkali to the desired β-carbinol **3a**.

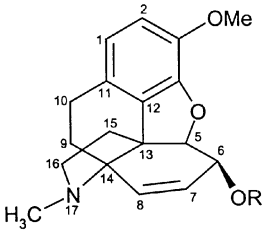
In order to provide structural assignments for all substances, we decided to run the *Mitsunobu* sequence of a carbinol mixture **3a/4a** with an enriched fraction of **3a** which was obtained by reduction of ketone **2b** with lithium aluminum hydride (see below). Surprisingly, we obtained a mixture of three isomeric benzyloxycarboxylates (**3b**, **4b**, and **6c**) which were identified by analytical methods after separation.



4a: $R = H$
4b: $R = OCO_2CH_2C_6H_5$



5a: $R = CH_2CON(CH_3)_2$
5b: $R = CH_2CH_2N(CH_3)_2$
5c: $R = CH_2CH_2OH$
5d: $R = CH_2CH_2OTs$
5e: $R = CH_2CH_2N(CH_3)_2 \cdot CH_3I$
5f: $R = CH_2CHO$
5g: $R = CH_2CH_3$



6a: $R = CH_2CON(CH_3)_2$
6b: $R = CH_2CH_2N(CH_3)_2$
6c: $R = OCO_2CH_2C_6H_5$
6d: $R = OH$
6e: $R = CH_2CH_2N^+(CH_3)_3I^-$
6f: $R = CH_2CH_2N^+(CH_3)_3ClO_4^-$

Table 1. Formation of isomers (%) related to reagent

Reagent	**4a** (α)	**3a** (β)	α:β	7,8-satd.
$NaBH_4$	38	57	2:3	5
DIBAL-H	70	30	7:3	–
LAH	25	75	1:3	–

Using lithium aluminum hydride for the reduction of **2b** resulted quantitatively in a product mixture with a preference of the desired β-isomer **3a** (ratio **3a:4a** = 3:1) which could be directly introduced in the *Claisen-Eschenmoser* step where separation of the epimeric products was intended. This fact was truly surprising because reduction of the olefinic equivalent entity **1b** with lithium aluminum hydride proceeded without any noticeable stereoselectivity [1], whereas reduction of a very similar ketone, 14,17-cyclonorcodeinone [6], with this reagent afforded the reverse epimeric ratio of the carbinols ($\alpha:\beta$ =3:1). Amounts of products with respect to different hydrid reagents are given in Table 1.

An MM2 force field calculation on **2b** gave evidence that the hydrogenation of the double bond 9, 10 results in a much higher flexibility not only of ring B but also of the cyclohexenone ring C. Comparison of **1b** and **2b**, first performed on *Dreiding* models and refined by computation, shows that the distance between the nitrogen and the carbonyl oxygen (Fig. 1) may serve as a parameter of ring mobility. Whereas in the case of the more unsaturated ketone **1b**, which shows an extremely flat ring C, the distance is computed to 4.82 Å (steric energy: 149.6 kJ/mol), there exists an energetically somewhat higher levelled but rather stable boat conformer in the case of **2b** with an N-O-distance of 4.02 Å (201.1 kJ/mol in contrast to a second conformer with a distance of 4.98 Å and a lower steric energy of 177.2 kJ/mol). As a consequence, it may be possible that the energy gap of 23.9 kJ/mol may be compensated by a well established complexation with the metallic center atom of the hydride reagent as *Lewis* acid, and the carbonyl group might become bended in such a way that the attack of the hydride ion may proceed from the α-side. The opposite fact – stereoselection of the α-epimer, which is

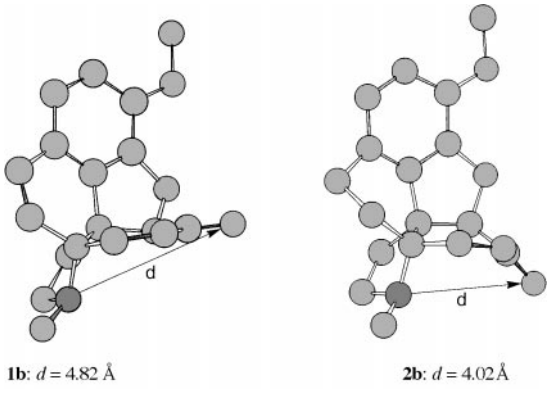
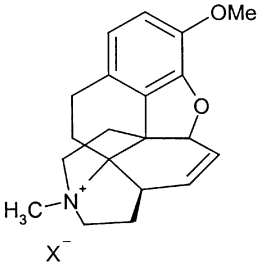


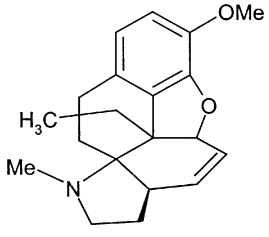
Fig. 1. Distance between N and CO-group of **1b** and **2b**

normally the case in the codeinons [3] – is observed in the reduction of **2b** with diisobutylaluminum hydride and may be explained by the more bulky coordinated reagent which prevents the formation of the metal-substrate complex by means of the insufficient dimension of the pocket. The preference of the normally formed α-epimer correlates with the free flight path of the hydride from the β-side of the molecule like **1b**.

As a consequence of the stereoselective formation of the β-isomer in the reduction of **2b**, the uneconomic *Mitsunobu* reaction had become avoidable. Because of the difficulties in the separation of the epimeric carbinols **3a** and **4a**, the *Claisen-Eschenmoser* step was performed on a mixture of both compounds. As this reaction is assumed to proceed in a strictly stereospecific manner leading to the corresponding 8-substituted products **5a** and **6a**, separation by flash chromatography was performed; **5a** was then used as starting material for the final cyclization (Route B). Reduction of the tertiary amide **5a** with lithium aluminum hydride yielded a mixture of the pure compounds **5b** and **5c** together with a small amount of formylmethyl derivative **5f**; separation was effected by column chromatography. It should be mentioned that reduction of **6a** led only to the corresponding compound **6b** but not to the analogous 6α-hydroxyethyl derivative. Both relevant β-isomers **5b** and **5c** yielded the expected cyclization products by known procedures [1, 7]: esterification of the catenal carbinol of **5c** with *p*-toluenesulfonyl chloride in pyridine led exclusively in one step to **7c** which was isolated and whose structure elucidated as perchlorate **7b**. The reason for not obtaining the intermediate **5d** might be a synergetic effect of the favoured ring closure tendency and the excellent electron withdrawing properties of the tosyl ester group. In an analogous route, *i.e.* by addition of methyl iodide to the amine **5b** – it is known that methylation is performed only on the catenal amine position [7] – we isolated the cyclization product **7a** in one step with spontanous elimination of trimethylamine from the previously formed quaternary methoiodide **5e**. Application of same sequence to the α-epimers (**6a** $\rightarrow$ **6b**) did not show any evidence of cyclization after adding methyl iodide to **6b**, and only the monoquaternary salt **6e** was obtained. This evidence provides a strong and consistent chemical argument for the structural coordination in a retrospective way, since the *Claisen* reaction is



7a: $X = \mathrm{I}$
7b: $X = \mathrm{ClO_4}$
7c: $X = Ts$



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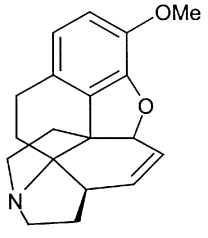

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known to proceed stereospecifically, and the cyclization is unambiguously connected with the β-isomer derived from the educt **2b**.

Reduction of salt **7a** with lithium borohydride [8] led to products distinct from those previously described in connection with the 9,10-unsaturated carbinol derived from **1** [1]. Three compounds (**5g**, **8**, **9**) were isolated which all showed conservation of the 14C-17N-bond which is in contrast with the reported results. Most interesting is compound **9**. For the first time it was observed that the attack of the hydride resulted in a reductive demethylation and conservation of the hitherto unknown hexacyclic ring system with an indolizidine subunit. It is therefore evident that – in contrast to the previously reported derivatives [1] – saturation of the olefinic bond in **1** has a great influence in effecting a higher stability of the 14C-17N-bond due to a higher flexibility of the condensed rings. Interestingly enough, there was no evidence of breaking of the furan ring as had been experienced earlier [1].

Stereochemistry and spectroscopy

All analytical and computational methods afforded results in accordance with the postulated structures of the new substances; however, some of them should be discussed more rigorously. The observed proton coupling constant $J_{5,6}$ of the epimer **4a** suggests that the OH-group is located in a *pseudo*-axial position as also testified by the diamagnetic shift of C-6 in the ^{13}C NMR spectrum (63.27 *vs.* 67.24 ppm in **3a** [9]). The *pseudo*-axial arrangement causes a significant shift difference between C-9 and C-15 (> 5 ppm) in the case of **4a**,**b** *vs.* **3a**,**b** by a vinylogous γ-gauche effect with the strongly twisted C-9. A remarkable high-field shift due to the ring current effect of the aromatic methoxy group of **4b** (3.58 ppm) should be mentioned which is caused by the geometry of the aromatic nucleus of the 6α-benzyloxycarboxyl group with respect to the aromatic part of the scaffold [10].

The *Claisen-Eschemmoser* amide **5a** undergoes axial C-8 substitution, which obviously is a condition for the subsequent formation of bridged derivatives. The solvent dependence of the protons related to the quaternary ammonium group in **7a** is in accordance with literature data [11] (for instance the shift of NCH_3 in $CDCl_3$/*DMS*: 3.81/3.41 ppm). Computations on **8** show a stable conformer ($H_f = 152.3$ kJ/mol) in which the remaining pyrrolidine ring forming bond C8-C19 is equatorially oriented. An NOE is observed at the protons of the free ethyl group at C-13 upon irradiation of H-5 which is in agreement with the measured distances (H5/CH_2: 2.54 Å, H5/CH_3: 2.36 Å) under the postulation that the free rotation of the ethyl group is restricted. Quantum mechanical treatment of derivative **9** yields one stable isomer ($H_f = 207.7$ kJ/mol) in which the torsion angles are in good accordance with the measured coupling constants.

Due to the paramagnetic shift of C-8 (68.18 ppm) in **6d** we propose an equatorial position of the hydroxy substituent [9], which is well confirmed by an NOE between H-5 and H-8. The paramagnetic shift of the NCH_3-group in the ^1H NMR spectrum (2.63 ppm) is accordingly a consequence of *van der Waals* repulsion forces between the axial proton H-8 and the NCH_3-group, which was confirmed by an NOE measurement.

Experimental

Melting points (uncorrected): Kofler melting point microscope; column chromatography: with silica gel (Kieselgel 60, Merck, 70–230 mesh); IR spectra: Perkin Elmer 298, Perkin Elmer Spectrum 1000; NMR spectra: Bruker AC 80, Bruker DPX 200, Varian Unity Plus 300; MS: Shimadzu QP5000, FiniganMAT 8230, Finigan MAT 900S; elementary analyses were performed by the Laboratory of Microanalysis, Institute for Physical Chemistry, University of Vienna; the results were in good agreement with the calculated values. Computations were accomplished by the CS Chem 3D Pro® program, Cambridge, MA.

(5α,13β,14β)-7,8-Didehydro-3-methoxy-17-methyl-4,5-epoxyhasubanan-6-one-dimethylacetal (**2a**; $C_{20}H_{25}NO_4$)

Colourless crystals; ^{1}H NMR ($CDCl_3$): Ref. [2]; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 146.58 (C-4), 141.48 (C-3), 134.51 (C-12), 132.59 (C-8), 129.99 (C-11), 128.51 (C-7), 118.49 (C-1), 113.55 (C-2), 95.52 (C-6), 95.06 (C-5), 63.11 (C-14), 57.25 (C-18), 52.52 (C-13),51.36 (C-16), 50.57, 48.61 (C-19, C-20), 41.87 (C-9), 35.73 (C-15), 34.84 (C-17), 23.76 (C-10) ppm; MS (EI): $m/z = 343$ (100%).

(5α,13β,14β)-7,8-Didehydro-3-methoxy-17-methyl-4,5-epoxyhasubanan-6-one (**2b**; $C_{18}H_{19}NO_3$)

8.33 g (24.4 mmol) **2a** in 15 cm^3 2 *N* HCl were warmed moderately during 5 min followed by addition of 16 cm^3 2 *N* NaOH, extraction with ethyl acetate, and evaporation of the solvent *in vacuo*. Yield: 7.23 g (>99%); colourless crystals (ethyl acetate); ^{1}H NMR ($CDCl_3$): Ref. [2]; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 194.95 (C-6), 149.91 (C-8), 145.16 (C-4), 142.66 (C-3), 128.81 (C-11), 127.13 (C-7), 119.82 (C-1), 113.17 (C-2), 89.38 (C-5), 63.30 (C-14), 56.55 (C-18), 53.81 (C-13), 52.30 (C-16), 39.92 (C-9), 37.15 (C-15), 35.49 (C-17), 23.76 (C-10) ppm; MS (EI): $m/z = 297$ (100%).

Reduction of **2b** *with sodium borohydride*

To a solution of 300 mg (1 mmol) **2b** in 25 cm^3 MeOH at room temperature an excess of $NaBH_4$ (100 mg) was added in portions, and the mixture was left for 30 min until generation of H_2 ended. After evaporation of the solvent and addition of 1 cm^3 H_2O the residue was extracted with ethyl acetate. Drying of the extract over Na_2SO_4 and evaporation *in vacuo* yielded 280 mg (93%) colourless oil (mixture of carbinols **3a** und **4a** and some 7,8-saturated product (5%)). The components were determined by ^{1}H NMR-spectroscopy.

Route A: Reduction of **2b** *with DIBAL-H and Mitsunobu esterification*

To 3.48 g (11.7 mmol) **2b** in 60 cm^3 dry *THF*, 12 cm^3 *DIBAL-H* (1 *M* in *THF*) were added at 0°C under Ar and kept 30 min at room temperature; afterwards, the mixture was refluxed for 1 h. After quenching the cooled mixture with 1 cm^3 H_2O, suction over celite and evaporation of the solvent *in vacuo* followed. Extraction of the residue with ethyl acetate, washing with H_2O/NaCl, drying, and evaporation yielded 3.25 g colourless oil (93%; carbinols **3a** und **4a** in a ratio of 30:70).

To a mixture of 3.25 g (10.9 mmol) **3a** and **4a**, 3.5 g (13.3 mmol) triphenylphosphine and 1.65 g (13.5 mmol) benzoic acid in 50 cm^3 dry ethyl acetate, 2.13 cm^3 (13.5 mmol) diethylazodicarboxylate in 8 cm^3 ethyl acetate were added dropwise within 15 min under Ar. The mixture became slowly warm and clear. After standing for 15 h at room temperature, 12 cm^3 1 *N* HCl were added, and the phases were seperated. The organic phase was washed 3 times with small portions of H_2O, and the H_2O extracts were combined. Alkalization of the water phase with 2 *N* Na_2CO_3, extraction with ethyl acetate, drying, filtration, and evaporation in vacuum afforded 2.50 g (57%) orange coloured oil

which was purified by flash column chromatography on silicagel (eluent: petroleum ether/ethyl acetate/triethyl amine 6/2/1). Fraction 1 ($R_f = 0.56$): 1.26 g pale oil, **3b** (29%); fraction 2 ($R_f = 0.38$): 840 mg **3a** und **4a**.

(5α,13β,14β)-7,8-Didehydro-3-methoxy-17-methyl-4,5-epoxyhasubanan-(6β)-6-ol (**3a**; $C_{18}H_{21}NO_3$)

560 mg (1.39 mmol) **3b** in 20 cm^3 ethanol were refluxed with 1 cm^3 2 *N* NaOH for 1 h. Distillation of the solvent followed by extraction with ethyl acetate, washing with H_2O, drying, and evaporating *in vacuo* yielded 400 mg colorless pure oil **3a**, (96%).

^{1}H NMR ($CDCl_3$, δ, 300 MHz): 6.67 (AB-system, 2H, H-1, H-2, $J_{1,2} = 8.4$ Hz), 5.92 (dd, 1H, H-7, $J_{7,8} = 10.5$ Hz, $J_{6,7} = 3.0$ Hz), 5.74 (dd, 1H, H-8, $J_{6,8} = 1.7$ Hz), 4.29 (d, 1H, H-5, $J_{5,6} = 7.2$ Hz), 3.92 (m, 1H, H-6), 3.84 (s, 3H, H-18), 3.01 (1H, OH), 2.82−2.65 (m, 2H, H-16, H-10), 2.46 (s, 3H, NCH_3) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 144.07 (C-4), 143.03 (C-3), 133.09 (C-12), 130.08 (C-11), 129.33, 129.31 (C-7, C-8), 119.32 (C-1), 111.82 (C-2), 97.30 (C-5), 67.24 (C-6), 64.04 (C-14), 56.23 (C-18), 51.73 (C-13), 51.62 (C-16), 39.26 (C-9), 37.21 (C-15), 35.12 (C-17), 24.09 (C-10) ppm; MS (EI): $m/z = 299$ (100%).

(5α, 13β,14β)-7,8-Didehydro-3-methoxy-17-methyl-4,5-epoxyhasubanan-(6β)-6-benzyloxycarboxylate (**3b**; $C_{25}H_{25}NO_4$)

Colourless crystals; m.p.: 154–156°C (MeOH); IR (KBr): $\nu = 1730$ cm^{-1} (ester); ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 8.10 (bd, 2H, H-1′, H-2′, $J_{1',2'} = 8.5$ Hz), 7.51 (m, 3H, H-3′, H-4′, H-5′), 6.89 (AB-system, 2H, H-1, H-2, $J_{1,2} = 8.1$ Hz), 6.02 (dd, 1H, H-7, $J_{7,8} = 10.74$ Hz, $J_{6,7} = 2.69$ Hz), 5.69 (dd, 1H, H-8, $J_{6,8} = 1.47$ Hz), 5.27 (m, 1H, H-6), 4.64 (d, 1H, H-5, $J_{5,6} = 8.17$ Hz), 3.83 (s, 3H, H-18), 2.90-2.68 (m, 2H), 2.58-2.40 (m, 2H), 2.50 (s, 3H, H-17), 2.28-2.10 (m, 2H), 1.64 (m, 1H, H-15), 0.94 (m, 1H, H-15) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 166.25 (C-19), 144.16 (C-4), 143.29 (C-3), 133.05 (C-7), 132.58 (C-12), 130.72 (C-8), 130.11 (C-1′), 130.00 (C-11), 129.83 (C-2′, C-6′), 128.26 (C-3′, C-5′), 126.43 (C-4′), 119.58 (C-1), 113.10 (C-2), 92.54 (C-5), 70.90 (C-6), 63.80 (C-14), 56.72 (C-18), 51.81 (C-13), 51.75 (C-16), 39.56 (C-9), 37.48 (C-15), 35.22 (C-17), 23.99 (C-10) ppm; MS (EI): $m/z = 403$ (100%).

(5α,13β,14β)-7,8-Didehydro-3-methoxy-17-methyl-4,5-epoxyhasubanan-(6α)-6-ol (**4a**; $C_{18}H_{21}NO_3$)

100 mg **4b** in 10 cm^3 EtOH and 1 cm^3 2 *N* KOH were refluxed for 1 h. Evaporation of the ethanol and basic extraction with ethyl acetate yielded 70 mg colourless oil **4a**, (94%).

^{1}H NMR ($CDCl_3$, δ, 300 MHz): 6.67 (s, 2H, H-1, H-2), 6.10 (d, 1H, H-8, $J_{7,8} = 10.2$ Hz), 5.99 (dd, 1H, H-7, $J_{6,7} = 6.0$ Hz), 4.28 (d, 1H, H-5, $J_{5,6} = 4.8$ Hz), 3.91 (m, 1H, H-6), 3.87 (s, 3H, H-18), 2.48 (s, 3H, H-17) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 145.80 (C-4), 141.55 (C-3), 134.48 (C-12), 133.86 (C-8), 129.08 (C-11), 125.73 (C-7), 119.24 (C-1), 111.60 (C-2), 91.84 (C-5), 63.27 (C-6), 63.16 (C-14), 56.23 (OCH_3), 51.50 (C-16), 50.28 (C-13), 41.88 (C-15), 36.66 (C-9), 35.19 (NCH_3), 23.95 (C-10) ppm; MS (EI): $m/z = 299$ (49%).

Mitsunobu reaction of a favourably enriched mixture of epimers **3a** *and* **4a**

1.5 g (5.05 mmol) of the mixture of epimers **3a** and **4a** obtained by the $LiAlH_4$ reduction (vide infra; ratio 3:1) was dissolved in 25 cm^3 of ethyl acetate together with 1.7 g (6.5 mmol) of triphenylphosphine and 820 mg (6.5 mmol) of benzoic acid. Addition of 1.1 cm^3 diethylazodicarboxylate (6.5 mmol) in 8 cm^3 ethyl acetate induced the *Mitsunobu* reaction, and the mixture was left overnight. After work-up, a mixture of **3b**, **4b**, **6c**, and **3a** was obtained (the percentages were

estimated by NMR spectroscopy). Extensive separation by repeated flash cromatography (solvent: petroleum ether/ethyl acetate/triethyl amine 30/6/1, changing of the eluents to 8/2/1, PSC chromatography) yielded the benzyloxycarbonylates **3b**, **4b**, **6c**, and **3a**.

(5α,13β,14β)-7,8-Didehydro-3-methoxy-17-methyl-4,5-epoxyhasubanan-(6α)-6-benzyloxycarboxylate (**4b**; $C_{25}H_{25}NO_4$)

Yield: 720 mg (47%); colourless oil; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 7.43-7.37 (m, 1H, H-4′), 7.22-7.14 (m, 2H, H-3′, H-5′), 7.06-7.02 (m, 2H, H-4′), 6.76 (d, 1H, H-1, $J_{1,2} = 7.8$ Hz), 6.27-6.18 (m, 2H, H-7, H-8, $J_{7,8} = 10.2$ Hz), 5.55 (dd, 1H, H-6, $J_{6,7} = 6.0$ Hz, $J_{5,6} = 4.9$ Hz), 4.68 (d, 1H, H-5), 3.59 (s, 3H, arom. OCH_3), 2.89-2.76 (m, 2H, H-10, H16), 2.51 (s, 3H, NCH_3), 2.49-2.42 (m, 2H, H-10, H-16), 2.25-2.19 (m, 1H, H-15), 2.14-2.06 (m, 1H, H-9), 1.79-1.68 (m, 1H, H-15), 1.06-0.95 (m, 1H, H-9) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 165.49 (CO), 146.72 (C-4), 142.28 (C-3), 136.20 (C-8), 134.61 (C-12), 132.55 (C-4′), 129.84 (C-1′), 129.70 (C-2′, C-6′), 129.65 (C-11), 127.79 (C-3′, C-5′), 123.48 (C-7), 118.95 (C-1), 112.30 (C-2), 89.27 (C-5), 65.18 (C-6), 63.48 (C-14), 56.40 (arom. OCH_3), 51.63 (C-16), 50.77 (C-13), 41.68 (C-15), 36.61 (C-9), 35.07 (NCH_3), 24.05 (C-10) ppm; MS (EI): $m/z = 403$ (47%).

(5α,13β,14β)-6,7-Didehydro-3-methoxy-17-methyl-4,5-epoxyhasubanan-(8α)-8-benzyloxycarboxylate (**6c**; $C_{25}H_{25}NO_4$)

170 mg pale oil; colourless crystals from MeOH; m.p.: 115–118°C; IR (KBr): $\nu = 1713.6\,cm^{-1}$ (carboxylate); ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 8.03 (d, 2H, H-2′, H-6′), 7.60, 7.46 (m, m, 1H, 2H, H-4′, H-3′, H-5′), 6.70 (s, 2H, H-1, H-2), 5.75 (m, 1H, H-6, $J_{6,7} = 10.3$ Hz), 5.66 (md, 1H, H-8), 5.57 (m, 1H, H-7), 5.00 (m, 1H), 3.88 (s, 3H, OCH_3), 2.96-2.65 (m, 3H, 2H-16, H-10), 2.58-2.44 (m, 2H, H-10, H-9), 2.42 (s, 3H, NCH_3), 2.26 (m, 1H, H-15), 1.71 (m, 1H, H-15), 1.25 (m, 1H, H-9) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 165.62 (CO), 144.20 (C-4), 142.77 (C-3), 133.78 (C-12), 133.25 (C-7), 130.83 (C-6), 129.69 (C-11), 129.58 (C-2′, C-6′), 129.19 (C-4′), 128.49 (C-3′, C-5′), 119.14 (C-1) 112.12 (C-2), 88.79 (C-5), 70.20 (C-8), 66.00 (C-14), 56.37 (arom.OCH_3), 53.90 (C-13), 51.97 (C-16), 39.61 (C-15), 34.45 (NCH_3), 31.54 (C-9), 23.54 (C-10) ppm; MS (EI): $m/z = 403$ (80%).

(5α,13β,14β)-6,7-Didehydro-3-methoxy-17-methyl-4,5-epoxyhasubanan-(8α)-8-ol (**6d**; $C_{18}H_{21}NO_3$)

100 mg (0.25 mmol) of **6c** in 10 cm^3 ethanol and 1 cm^3 2 *N* KOH were hydrolyzed by heating under reflux for 1 h. Distillation of ethanol and extraction with ethyl acetate yielded 70 mg (94%) **6d**, which was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate/triethylamine 4/2/1, $R_f = 0.34$).

^{1}H NMR ($CDCl_3$, δ, 300 MHz): 6.65 (AB-system, 2H, H-1, H-2, $J_{1,2} = 8.1$ Hz), 5.65 (sm, 2H, H-6, H-7), 4.90 (sm, 1H, H-5), 4.46 (sm, 1H, H-8), 3.87 (s, 3H, OCH_3), 2.82-2.65 (m, 3H, 2H-16, H-10), 2.63 (s, 3H, CH_3), 2.54-2.45 (m, 1H, H-10), 2.32-2.20 (m, 2H, H-9, H-15), 2.81-2.72 (m, 1H, H-15), 1.25 (bs, 1H, H-15), 1.09-0.99 (m, 1H, H-9) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 144.29 (C-4), 142.78 (C-3), 134.39, 128.04 (C-6, C-7), 133.70 (C-12), 129.83 (C-11), 119.19 (C-1), 112.13 (C-2), 89.30 (C-5), 68.18 (C-8), 67.18 (C-14), 56.35 (OCH_3), 53.66 (C-13), 52.35 (C-16), 39.55 (C-15), 36.61 (NCH_3), 29.75 (C-9), 23.80 (C-10) ppm; MS (EI): $m/z = 299$ (50%).

Route B: Reduction of **2b** *with* $LiAlH_4$

To 7.23 g (24.3 mmol) **2b** in 80 cm^3 dry *THF* under an argon shield, 6.2 cm^3 lithium aluminum hydride (1 *M* in *THF*) were added under cooling (ice bath). After 30 min for temperature accomodation the mixture was refluxed for 1 h. Quenching with 0.5 cm^3 water under cooling,

separation by suction, and evaporation of the solvent led to a residue of 7.1 g pale oil of **3a** and **4a** (98%). The epimeric mixture (**3a**:**4a** = 3:1, determined by NMR spectroscopy) was used in the *Claisen-Eschenmoser* reaction without further purification.

Claisen-Eschenmoser reaction of the epimers **3a** *and* **4a**

a) 1.2 cm^3 (8.2 mmol) dimethylacetamide-dimethylacetal were added to 1.24 g (4.15 mmol) **3a** in 40 cm^3 xylene (mixture of isomers), and the solution was refluxed for 4 h while the condenser was thermostated at 70°C and dry N_2 was passed through. Evaporation of the red-brown solution yielded 1.40 g dark oil **5a**; crystallisation from MeOH gave 470 mg colourless crystals. From the mother liquor an additional amount was obtained by flash cromatography (petroleum ether/ethyl acetate/triethyl amine 4/2/1): 450 mg (60%) **5a**.

b) 5.6 cm^3 (38.3 mmol) dimethylacetamide-dimethylacetal were added to a mixture (4.0 g, 10.9 mmol) of epimers **3a** und **4a** (3:1) in 140 cm^3 xylene (mixture of isomers), and the solution was refluxed for 4 h while the condenser was thermostated at 70°C and dry N_2 was passed through. After evaporation *in vacuo* there remained 4.66 g red-brown coloured oil; crystallisation from methanol afforded 1.77 g colourless crystals **5a**. The mother liquor was separated by column cromatography (petroleum ether/ethyl acetate/triethyl amine 4/2/1) to yield three further fractions: fraction 1 (R_f = 0.49): 1.81 g pale oil, **3a**; fraction 2 (R_f = 0.28): 1.11 g colourless oil, **5a**; total amount: 2.88 g (40%); this means a yield of 59% by considering 1.81 g recovered **3a**; fraction 3 (R_f = 0.18): 1.25 g **6a**, yield 17.5%.

(5α,13β,14β)-6,7-Didehydro-(8β)-8-dimethylcarbamoylmethyl-3-methoxy-17-methyl-4,5-epoxyhasubanan (**5a**; $C_{22}H_{28}N_2O_3$)

Crystals from MeOH; m.p.: 150–151°C; IR (KBr): ν = 1642 cm^{-1} (*tert*. amide); ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 6.60 (AB-system, 2H, H-1, H-2, $J_{1,2}$ = 8.1 Hz), 6.10 (m, 1H, H-7), 5.72 (dd, 1H, H-6, $J_{6,7}$ = 10.0 Hz, $J_{5,6}$ = 1.9 Hz), 5.05 (sm, 1H, H-5), 3.86 (s, 3H, H-18), 3.00, 2.94 (s, s, 3H, 3H, H-21, H-22), 2.98 (bs, m, 2H, H-8, H-16), 2.84 (m, 1H, H-16), 2.76 (dd, 1H, H-19, J_{gem} = 15.3 Hz, $J_{8,19}$ = 5.4 Hz), 2.56 (m, 1H, H-10), 2.48 (s, 3H, H-17), 2.35 (m, 2H, H-10, H-15), 2.15 (m, 2H, H-9), 1.89 (dd, 1H, H-19, $J_{8,19}$ = 8.7 Hz), 1.10 (m, 1H, H-15) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 172.45 (C-20), 144.73 (C-4), 143.05 (C-3), 135.10 (C-7), 135.01 (C-12), 129.78 (C-11), 128.83 (C-6), 119.20 (C-1), 111.90 (C-2), 91.32 (C-5), 64.11 (C-14), 56.29 (C-18), 54.75 (C-13), 53.95 (C-16), 41.91 (C-9), 40.02 (C-8), 37.38 (C-21), 35.53 (C-22), 35.40 (C-19), 35.31 (C-17), 26.55 (C-10) ppm; MS (EI): m/z = 368 (100%).

(5α,13β,14β)-6,7-Didehydro-(8α)-8-dimethylcarbamoylmethyl-3-methoxy-17-methyl-4,5-epoxyhasubanan (**6a**; $C_{22}H_{28}N_2O_3$)

Glassy residue (ethyl acetate); melting region: 55 to 70°C; IR (KBr): ν = 1636.7 cm^{-1} (*tert*. amide); ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 6.60 (AB-system, 2H, H-1, H-2, $J_{1,2}$ = 8.1 Hz), 5.69 (md, 1H, H-7, $J_{6,7}$ = 10.2 Hz), 5.49 (md, 1H, H-6), 5.01 (bs, 1H, H-5), 3.82 (s, 3H, H-18), 3.04 (m, 1H, H-16), 2.88, 2.77 (s, s, 3H, 3H, H-21, H-22), 2.84 (m, 1H, H-10), 2.70 (m, 1H, H-16), 2.55 (m, 1H, H-10), 2.45 (s, 3H, H-17), 2.42 (m, 1H, H-9), 2.21 (m, 1H, H-19), 2.09 (m, 1H, H-15), 1.97 (dd, 1H, H-9, J_{gem} = 15.9 Hz, $J_{9,10}$ = 11.1 Hz), 1.82 (m, 1H, H-19), 1.26 (m, 1H, H-15) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 171.31 (C-20), 145.02 (C-4), 142.54 (C-3), 133.81 (C-6), 134.00 (C-12), 128.47 (C-11), 118.69 (C-1), 112.40 (C-2), 89.89 (C-5), 64.78 (C-14), 56.32 (C-18), 53.45 (C-13), 51.84 (C-16), 38.94 (C-19), 36.88, 35.37 (C-21, C22), 35.04 (C-8, C-17), 34.86 (C-9), 27.90 (C-15), 24.36 (C-10) ppm; MS (EI): m/z = 368 (40%).

Reduction of **5a** *with* $LiAlH_4$

5.0 cm^3 $LiAlH_4$ (1 *M* in *THF*) were added to 3.46 g (9.40 mmol) **5a** in 100 cm^3 dry *THF* under Ar and refluxed for 2 h. While cooling with an ice bath, 0.5 cm^3 H_2O were added dropwise. Separation by suction and evaporation of the solvent yielded 2.98 g colourless oil which was separated by column chromatography (petroleum ether/ethyl acetate/triethyl amine 5/2/1) to afford 3 fractions: fraction 1 ($R_f = 0.36$): 2.14 g colourless oil, **5b** (64%); fraction 2 ($R_f = 0.25$): 279 mg colourless oil, **5c** (9%); fraction 3 ($R_f < 0.1$): 110 mg yellow oil, **5f** (4%).

(5α,13β,14β)-6,7-Didehydro-(8β)-8-dimethylaminoethyl-3-methoxy-17-methyl-4,5-epoxyhasubanan (**5b**, $C_{22}H_{30}N_2O_3$)

^{1}H NMR ($CDCl_3$, δ, 300 MHz): 6.65 (d, 1H, H-2, $J_{1,2} = 7.8$ Hz), 6.56 (d, 1H, H-1), 5.95 (m, 1H, H-7), 5.74 (d, 1H, H-6, $J_{6,7} = 10.2$ Hz), 5.08 (bs, 1H, H-5), 3.86 (s, 3H, H-18), 2.53 (s, 3H, H-17), 2.21 (s, 6H, H-21, H-22) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 144.17 (C-4), 143.00 (C-3), 135.14 (C-12), 134.67 (C-6), 129.58 (C-11), 128.64 (C-7), 119.06 (C-1), 111.92 (C-2), 91.19 (C-5), 64.50 (C-14), 58.37 (C-20), 56.33 (C-18), 54.63 (C-13), 53.57 (C-16), 45.60 (C-21, C-22), 41.23 (C-9), 40.53 (C-8), 35.22 (C-15), 35.15 (C-17), 30.53 (C-19), 26.35 (C-10) ppm; MS (EI): $m/z = 354$, 296.

(5α,13β,14β)-6,7-Didehydro-(8β)-8-hydroxyethyl-3-methoxy-17-methyl-4,5-epoxyhasubanan (**5c**, $C_{20}H_{25}NO_3$)

^{1}H NMR ($CDCl_3$, δ, 300 MHz): 6.64 (d, 1H, H-2, $J_{1,2} = 8.1$ Hz), 6.56 (d, 1H, H-1), 5.92 (m, 1H, H-7), 5.75 (dd, 1H, H-6, $J_{6,7} = 10.2$ Hz, $J_{5,6} = 1.5$ Hz), 5.09 (sd, 1H, H-5), 3.85 (s, 3H, H-18), 3.68−3.46 (m, 2H, H-20), 3.40 (m, 1H, OH), 2.54 (s, 3H, H-17) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 144.74 (C-4), 142.98 (C-3), 134.93 (C-12), 134.09 (C-6), 129.22 (C-11), 128.94 (C-7), 119.08 (C-1), 112.01 (C-2), 90.85 (C-5), 64.45 (C-14), 61.18 (C-20), 56.27 (C-18), 54.61 (C-13), 53.56 (C-16), 41.60 (C-8), 41.08 (C-9), 35.69 (C-15), 35.45 (C-17), 35.23 (C-19), 26.44 (C-10) ppm; MS (EI): $m/z =$ 327 (100%).

(5α,13β,14β)-6,7-Didehydro-(8β)-8-formylmethyl-3-methoxy-17-methyl-4,5-epoxyhasubanan (**5f**, $C_{20}H_{23}NO_3$)

^{1}H NMR ($CDCl_3$, δ, 300 MHz): 6.68 (d, 1H, H-2, $J_{1,2} = 8.1$ Hz), 6.60 (d, 1H, H-1), 6.00 (m, 1H, H-7), 5.83 (dd, 1H, H-6, $J_{6,7} = 9.68$ Hz, $J_{5,6} = 1.2$ Hz), 5.11 (bs, 1H, H-5), 3.87 (s, 3H, H-18), 2.66 (s, 3H, H-17) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 144.84 (C-4), 143.26 (C-3), 132.76 (C-12), 131.38 (C-6), 130.27 (C-7), 128.92 (C-11), 119.37 (C-1), 112.46 (C-2), 89.71 (C-5), 56.34 (C-18), 54.78 (C-16), 53.68 (C-13), 42.78 (C-8), 42.65 (C-19), 39.76 (C-9), 38.22 (C-17), 36.35 (C-15), 25.64 (C-10) ppm; MS (EI): $m/z = 325$ (31%).

(5α,13β,14β)-6,7-Didehydro-(8α)-8-dimethylaminoethyl-3-methoxy-17-methyl-4,5-epoxyhasubanan (**6b**, $C_{22}H_{30}N_2O_2$)

1.5 cm^3 $LiAlH_4$ (1 *M* in *THF*) were added to 990 mg (2.7 mmol) **6a** in 50 cm^3 dry *THF* under Ar and refluxed for 2 h. While cooling in an ice bath, 0.3 cm^3 H_2O were added dropwise. Separation by suction and evaporation of the solvent yielded 890 mg colourless oil **6b** (93%).

^{1}H NMR ($CDCl_3$, δ, 300 MHz): 6.62 (AB-system, 2H, H-1, H-2, $J_{1,2} = 8.1$ Hz), 5.71 (m, 1H, H-7), 5.50 (m, 1H, H-6), 4.93 (sm, 1H, H-5), 3.85 (s, 3H, H-18), 2.56 (s, 3H, H-17), 2.20 (s, 6H, H-21, H-22) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 144.53 (C-4), 142.66 (C-3), 134.30 (C-12), 133.85 (C-6), 129.68 (C-11), 118.73 (C-1), 111.88 (C-2), 90.18 (C-5), 65.42 (C-14), 58.47 (C-20), 56.30 (C-18), 55.37 (C-13), 52.51 (C-16), 45.59 (C-21, C-22), 39.80 (C-9), 27.37 (C-8), 35.74 (C-17), 30.48 (C-15), 29.51 (C-19), 24.28 (C-10) ppm; MS (EI): $m/z = 354$ (100%).

(5α,13β,14β)-6,7-Didehydro-(8α)-8-dimethylaminoethyl-3-methoxy-17-methyl-4,5-epoxyhasubanan methoiodide (**6b**·CH_3I; $C_{23}H_{33}N_2IO_2$)

1 cm^3 CH_3I was added to 900 mg (2.50 mmol) **6b** in 5 cm^3 methanol. After standing for 5 h in an effective hood the solvent was evaporated; 1250 mg (>99%) colourless oil remained which was not crystallizable.

^{1}H NMR ($CDCl_3$, δ, 300 MHz): 6.63 (AB-system, 2H, H-1, H-2, $J_{1,2}$ = 8.4 Hz), 5.81 (m, 1H, H-6), 5.66 (m, 1H, H-7), 4.95 (bs, 1H, H-5), 3.85 (s, 3H, H-18), 3.38 (s, 9H, H-21, H-22, H-23), 2.58 (s, 3H, H-17) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 142.75 (C-4), 131.48, 129.79 (C-6, C-7), 129.13 (C-11), 119.01 (C-1), 112.47 (C-2), 89.80 (C-5), 65.78 (C-14), 56.50 (C-18), 54.76 (C-20), 53.70 (C-21, C-22, C-23), 52.47 (C-16), 39.28 (C-15), 37.11, 36.22 (C-8, C-17), 25.06 (C-19), 24.45 (C-10) ppm.

(5α,13β,14β)-6,7-Didehydro-(8α)-8-dimethylaminoethyl-3-methoxy-17-methyl-4,5-epoxyhasubanan methoperchlorate (**6b**·CH_3ClO_4; $C_{23}H_{33}N_2ClO_6$)

To 500 mg (1 mmol) **6b**·CH_3I in 5 cm^3 water, an excess of $NaClO_4$ was added; an oily precipitate formed. Crystallisation from ethanol yielded 240 mg colourless pellets.

M.p.: 160–162°C (51%); ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 6.63 (AB-system, 2H, H-1, H-2, $J_{1,2}$ = 8.1 Hz), 5.79 (d, 1H, H-7, $J_{6,7}$ = 10.2 Hz), 5.57 (d, 1H, H-6), 4.97 (s, 1H, H-5), 3.86 (s, 3H, H-18), 3.38 (m, 2H, H-20), 3.13 (s, 9H, H-21, H-22, H-23), 2.58 (s, 3H, H-17) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 144.73 (C-4), 142.68 (C-3), 133.67 (C-12), 131.44, 129.80 (C-6, C-7), 119.08 (C-1), 112.48 (C-2), 89.75 (C-5), 65.95 (C-20), 65.67 (C-14), 56.49 (C-18), 54.94 (C-13), 53.15 (C-21, C-22, C-23), 52.40 (C-16), 39.35 (C-9), 36.85 (C-8), 35.75 (C-17), 29.51 (C-15) 24.82 (C-19), 24.33 (C-10) ppm.

A) Cyclization starting from the catenal quaternary ammonium iodide **5b** · CH_3I *(5α,13β,14β)-6,7-Didehydro-(8β)-8,17-ethano-3-methoxy-17-methyl-4,5-epoxyhasubanan methoiodide* (**7a**·CH_3I; $C_{20}H_{24}NIO_2$)

In an efficient hood 0.4 cm^3 iodomethane were poured to 1.61 g (4.55 mmol) **5b** in 10 cm^3 MeOH. The reaction vessel was connected to a Hg bubbler to maintain a slight pressure and left resting for 1 d. After drying by evaporation, a sample was taken and the composition of the mixture was examined by ^{1}H NMR spectroscopy. The main product was the catenal quaternary salt **5e**; some additional signals suggested a subsequent cyclization product. Further addition of 50 cm^3 MeOH and refluxing the solution under N_2 enforced the cyclization as indicated by the development of triethylamine. As soon as the reaction was terminated the solution was evaporated *in vacuo*.

Yield: 1.97 g pale oil (99%); colourless crystals (MeOH); m. p.: 296–298°C; ^{1}H NMR (*DMSO*-d_6, δ, 300 MHz): 6.77 (AB-system, 2H, H-1, H-2, $J_{1,2}$ = 8.1 Hz), 5.79 (ddd, 1H, H-7, $J_{6,7}$ = 10.5 Hz, $J_{7,8\alpha}$ = 6.3 Hz, $J_{7,19}$ = 2.1 Hz), 5.81 (d, 1H, H-6), 3.34 (s, 1H, H-5), 3.78 (s, 3H, H-18), 3.42 (s, 3H, H-17) ppm; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 6.74 (AB-system, 2H, H-1 H-2, $J_{1,2}$ = 8.1 Hz), 5.96 (AB-system, 2H, H-6, H-7, $J_{6,7}$ = 10.4 Hz), 5.03 (s, 1H, H-5), 4.48−4.20 (m, 3H, 2H-16, H-20), 3.88 (s, 3H, H-18), 3.81 (s, 3H, H-17) ppm.

B) Cyclization by toluolsulfonylation of 8β-hydroxyethyl derivative **5c** *(5α, 13β, 14β)-6,7-Didehydro-(8β)-8,17-ethano-3-methoxy-17-methyl-4,5-epoxyhasubananmethoperchlorate* (**7b**·CH_3ClO_4; $C_{20}H_{24}NClO_6$)

To 340 mg (1 mmol) **5c** in 10 cm^3 CH_2Cl_2, 130 mg dimethylaminopyridine, 0.3 cm^3 triethylamine, and 200 mg toluolsulfonyl chloride were added, and the mixture was kept at room temperature for 1 h. After evaporation *in vacuo* the residue was extracted with ethyl acetate/saturated $NaHCO_3$ in a seperatory funnel. The aqueous phase was treated with an excess of $NaClO_4$ and yielded 300 mg

colourless needles (70%) which were crystallized from MeOH. An alternative way consists in reacting **7a** in H_2O with an excess of $NaClO_4$ and crystallization of the precipitate from methanol.

M.p.: 221–223°C; ^{1}H NMR (*DMSO*-d_6 δ, 300 MHz): 6.77 (AB-system, 2H, H-1, H-2, $J_{1,2} = 8.4$ Hz), 5.97 (ddd, 1H, H-7, $J_{6,7} = 10.2$ Hz, $J_{7,8} = 6.3$ Hz, $J_{7,19} = 2.7$ Hz), 5.80 (d, 1H, H-6, $J_{5,6} = 1$ Hz), 5.32 (sd, 1H, H-5), 3.79 (s, 3H, arom. OCH_3), 3.76-3.55 (m, 4H, H-16, H-18), 3.39 (s, 3H, H-17), 2.93 (m, 1H, H-9), 2.84 (m, 1H, H-8), 2.76, 2.60 (m, m, 1H, 1H, H-10, H-10), 2.50 (m, 1H, H-15), 2.35 (m, 1H, H-19), 2.12 (m, 1H, H-15), 1.72 (m, 1H, H-19), 1.22 (m, 1H, H-9) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 75 MHz): 144.03 (C-4), 142.70 (C-3), 129.13 (C-12), 128.88, 128.51 (C-6, C-7), 127.90 (C-11), 119.43 (C-1), 113.54 (C-2), 84.67 (C-5), 84.35 (C-14), 62.76 (C-18), 61.77 (C-16), 56.08 (arom. OCH_3), 54.38 (C-13), 47.10 (NCH_3), 45.47 (C-8), 36.98 (C-9), 35.08 (C-15), 30.48 (C-19), 23.61 (C-10) ppm.

Reduction of **7a** *with lithium triethylborohydride*

To a suspension of 1.97 g (4.5 mmol) **7a** in 100 cm^3 dry *THF* 11 cm^3 (1.2 equivalents) lithium triethylborohydride (Superhydrid®; 1 *M* in *THF*) were added through a septum under Ar shielding and stirring. After 30 min at room temperature the mixture was refluxed for 2 h. After temperature accomodation, excessive reagent was destroyed by addition of a few drops of H_2O, and the solvent was evaporated under vacuum. Solution of the residue in CH_2Cl_2, washing with small portions of H_2O, drying over Na_2SO_4, and evaporating under vacuum yielded 1.55 g colourless oil which was separated by chromatography on silica gel (petroleum ether/ethyl acetate/trietyl amine 5/2/1): fraction 1 ($R_f = 0.61$): 250 mg **5g**, colourless oil; fraction 2 ($R_f = 0.35$): 140 mg **8**; fraction 3 ($R_F = 0.12$): 780 mg **9**.

(5α, 13β, 14β)-6,7-Didehydro-(8β)-8-ethyl-3-methoxy-17-methyl-4,5-epoxyhasubanan (**5g**; $C_{20}H_{25}NO_2$)

^{1}H NMR ($CDCl_3$, δ, 300 MHz): 6.61 (AB-system, 2H, H-1, H-2, $J_{1,2} = 8.4$ Hz), 5.96 (ddd, 1H, H-7, $J_{6,7} = 9.9$ Hz, $J_{7,8} = 6.3$ Hz, $J_{7,19} = 2.4$ Hz), 5.74 (dd, 1H, H-6, $J_{6,8} = 1.2$ Hz), 5.08 (bs, 1H, H-5), 3.87 (s, 3H, H-18), 2.52 (s, 3H, NCH_3), 2.14-2.06 (m, 1H, H-8), 1.87-1.73 (m, 1H, H-19), 1.09-0.92 (m, 1H, H-19), 0.89 (t, 3H, H-20, $J_{19,20} = 7.5$ Hz) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 142.96 (C-3), 134.95 (C-12), 134.76 (C-7), 129.32 (C-11), 127.96 (C-6), 119.05 (C-1), 111.97 (C-2), 91.19 (C-5), 64.68 (C-14), 56.32 (C-18), 54.45 (C-13), 53.59 (C-16), 44.43 (C-8), 40.98 (C-9), 35.32 (C-17), 34.45 (C-15), 26.26 (C-19), 25.24 (C-10), 12.82 (C-20) ppm; MS (EI): $m/z = 311$ (100%).

(5α,13β,14β)-6,7-Didehydro-(8β)-8,17-ethano-3-methoxy-17-methyl-16,17-seco-4,5-epoxyhasubanan (**8**; $C_{20}H_{25}NO_2$)

Crystals by sublimation in vaccum; m.p.: 108–110°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 6.63 (AB-system, 2H, H-1, H-2, $J_{1,2} = 8.1$ Hz), 5.67 (m, 1H, H-6), 5.52 (dd, 1H, H-7, $J_{6,7} = 10.2$ Hz, $J_{7,8} = 2.1$ Hz), 5.14 (bs, 1H, H-5), 3.83 (s, 3H, arom. OCH_3), 3.30-3.20 (m, 1H, H-18), 3.02-2.93 (m, 1H, H-9), 2.75-2.61 (m, 2H, H-9, H-18), 2.55 (s, 3H, NCH_3), 2.45-2.34 (m, 2H, H-8, H-10), 2.16-2.02 (m, 2H, H-15, H-19), 1.94-1.82 (m, 1H, H-15), 1.75-1.67 (m, 1H, H-10), 1.53-1.43 (m, 1H, H-19), 0.86 (t, 3H, H-16, $J_{15,16} = 7.5$ Hz) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 135.08 (C-7), 125.49 (C-11), 123.60 (C-6), 119.36 (C-1), 113.22 (C-2), 87.66 (C-5), 67.41 (C-14), 56.46 (OCH_3), 55.64 (C-18), 48.99 (C-13), 40.99 (C-8), 39.82 (NCH_3), 30.42 (C-19), 28.62 (C-15), 24.54 (C-9), 22.81 (C-10), 9.42 (C-16) ppm; MS (EI): $m/z = 311$ (85%).

(5α,13β,14β)-6,7-didehydro-(8β)-8,17-ethano-3-methoxy-4,5-epoxyhasubanan (**9**; $C_{19}H_{21}NO_2$)

^{1}H NMR ($CDCl_3$, δ, 300 MHz): 6.64 (AB-system, 2H, H-1, H-2, $J_{1,2} = 8.1$ Hz), 5.91 (ddd, 1H, H-7, $J_{6,7} = 10.5$ Hz, $J_{7,8} = 6.0$ Hz, $J_{7,19} = 2.1$ Hz), 5.75 (d, 1H, H-6), 4.83 (s, 1H, H-5), 3.84 (s, 3H, H-17),

3.10-3.05 (m, 1H, H-16), 2.96-2.81 (m, 2H, H-18), 2.72-2.62 (m, 1H, H-18), 2.56-2.46 (m, 2H, H-10, H-16), 2.46-2.32 (m, 1H, H-8), 2.28-2.02 (m, 3H, H-9, H-15, H-19), 1.92-1.81 (m, 1H, H-15), 1.49-1.42 (m, 1H, H-19), 1.26-1.16 (m, 1H, H-9) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 144.27 (C-4), 142.60 (C-3), 131.91 (C-12), 131.31 (C-7), 129.60 (C-11), 126.03 (C-6), 118.72 (C-1), 111.97 (C-2), 87.35 (C-5), 70.92 (C-14), 56.18 (C-17), 52.77 (C-13), 51.35 (C-16), 50.64 (C-18), 46.48 (C-8), 42.22 (C-9), 40.23 (C-15), 33.17 (C-19), 25.07 (C-10) ppm; MS (EI): $m/z = 295$ (100%).

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