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SYNTHESIS OF THE ASPIDOSPERMA SKELETON THROUGH ALLYLSILANE *N*-ACYLIMINIUM CYCLIZATION

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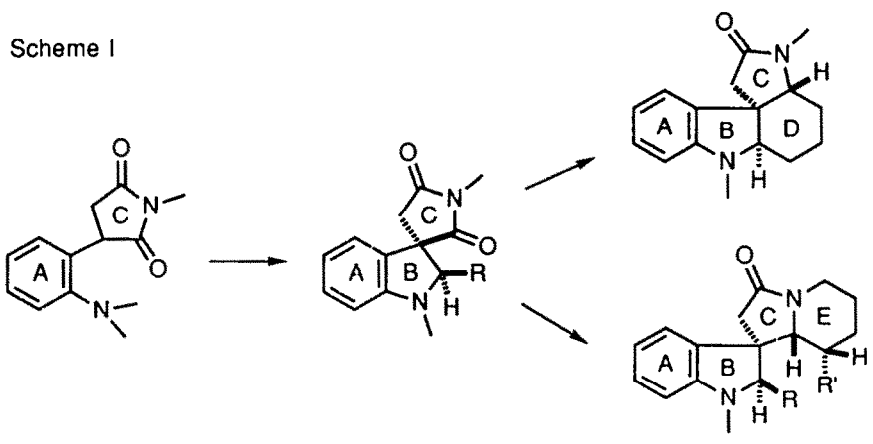
Summary: A highly stereoselective synthesis of the Aspidosperma ring system is described, based on a combination of two stereocontrolled processes. The first features a base-catalyzed cyclization of the imine **5** to generate the indoline **4**. The second involves the formation of tetracycle **2** by the ring closure of *N*-acyliminium ion **3**, whereby an allylsilane moiety functions as π-nucleophile.

INTRODUCTION

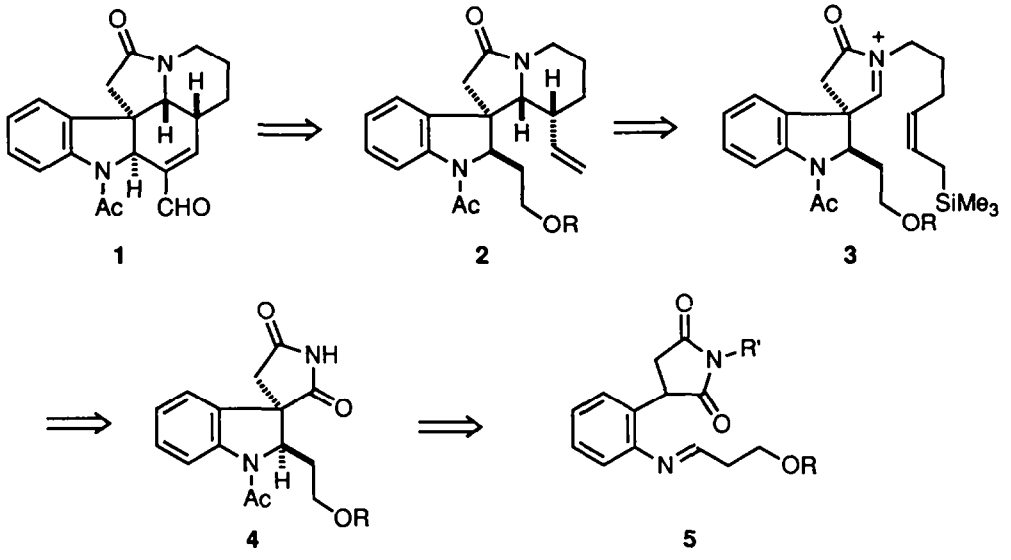
Several years ago, we have communicated a total synthesis of vindoline based on the sequential construction of rings AC → ABC → ABCD through a combination of a 1,5-electrocyclization and an *N*-acyliminium ring closure (Scheme I).[1,2] We then became also interested in a methodically similar but structurally alternative approach. Through slight variation of the reagents and techniques used earlier, the build-up of the Aspidosperma skeleton via an AC → ABC → ABCE sequence and subsequent closure of ring D was anticipated to be also feasible. Such a strategy would not only be highly dependent on the stereoselectivity of the formation of the ABC fragment (*cis*-orientation of R relative to the proximal imide carbonyl), but also hinge upon the stereocontrol experienced in the annulation of ring E (α-orientation of R'). Since the ABCE route could offer attractive possibilities for the synthesis of a number of modified ring D analogues through introduction of various groups R and R', it was deemed worthwhile to investigate such an approach.

Scheme I



Pentacyclic structure **1** represents an appropriate target molecule. Scheme II shows our retrosynthetic analysis, which first involves the aldol cyclization of the dialdehyde derived from **2**. The intramolecular attack of an allylsilane moiety onto an *N*-acyliminium intermediate (**3** → **2**) constitutes the key transformation of our strategy. The utility of this type of reaction for the synthesis of alkaloids has been shown in some recent publications.[3,4] Species **3** may be obtained from imide **4**, which in its turn could arise from electrocyclization of imine **5**.[5] The successful realization of this plan is the subject of this paper.

Scheme II

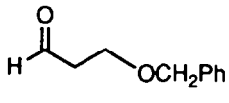


RESULTS AND DISCUSSION

Our first objective was a short synthesis of indoline **4**, which could be conveniently carried out on large scale. The unsubstituted nature of the cyclic imide nitrogen in **4** was strategically important, because various different nucleophilic substituents might be introduced at this point and subsequently tested in the *N*-acyliminium cyclization. After some experimentation we found that the *tert*-butyldimethylsilyl function served well as the imide protective group during the key electrocyclization step **5** → **4**. For the C-2 indoline substituent in **4** we first selected the 2,2-diethoxyethyl moiety. However, the interference of the acetal function of this substituent with the *N*-acyliminium intermediate during the intended ring closure **3** → **2** led to complex mixtures of reaction products. Therefore, a benzyl protected alcohol was considered, which in practice worked very well.

The necessary aldehyde **6**[6] was prepared via DIBAL-H reduction[7] of the acetal from 1,3-propanediol and benzaldehyde, followed by PCC oxidation[8] of the resulting alcohol. The required arylamine **7** was obtained from 3-(*ortho*-nitrophenyl)-pyrrolidine-2,5-dione[9] by reaction with *tert*-butyldimethylsilyl chloride in the presence of Et_3N and catalytic DMAP and subsequent hydrogenation of the nitro group. Condensation of **6** and **7** gave an imine, which was directly treated with lithium *tert*-butoxide in *t*-BuOH/THF at 5 °C for 30 min according to the general procedure for 1,5-electrocyclization.[5c] The crude product **8a** was immediately

subjected to *N*-acetylation and desilylation producing the crystalline imide **8b** in 74% overall yield from **7** as a single stereoisomer (mp 191-192 °C). The *cis*-indoline stereochemistry was not independently proven at this point, but was based on earlier experience.[5]



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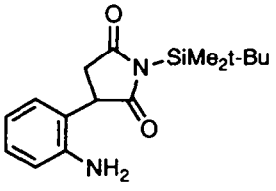

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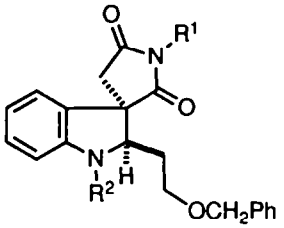
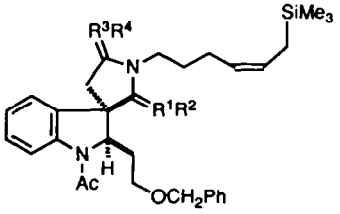
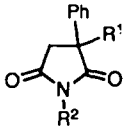


8a $R^1 = SiMe_2t\text{-}Bu$, $R^2 = H$
8b $R^1 = H$, $R^2 = Ac$
8c $R^1 = (CH_2)_3CH{=}CHCH_2SiMe_3$, $R^2 = Ac$

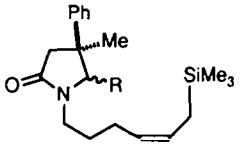
Mitsunobu coupling[10] of **8b** with (*Z*)-5-trimethylsilyl-3-penten-1-ol[3a] produced the allylsilane **8c** (mp 82-84 °C) in nearly quantitative yield. Acid-mediated $NaBH_4$ reduction of **8c** gave a high yield of a 55/45 mixture of regioisomeric hydroxylactams **9a** and **9b**. The disappointingly low excess of **9a** in this mixture[11] was somewhat compensated by the ready chromatographic separation of the isomers and the efficient recycling of the undesired **9b** through reoxidation (pyridine/CrO_3[12]) to **8c**. Application of two such cycles raised the isolated yield of **9a** to almost 75%. Ethoxy derivative **9c** was easily prepared from **9a** via mesylation and ethanolysis.



9a $R^1R^2 = H, OH$, $R^3R^4 = O$
9b $R^1R^2 = O$, $R^3R^4 = H, OH$
9c $R^1R^2 = H, OEt$, $R^3R^4 = O$



10a $R^1 = H$, $R^2 = H$
10b $R^1 = H$, $R^2 = (CH_2)_3CH{=}CHCH_2SiMe_3$
11 $R^1 = Me$, $R^2 = (CH_2)_3CH{=}CHCH_2SiMe_3$

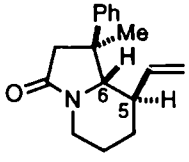


12a R = β-OH
12b R = α-OH
12c R = OEt

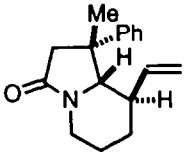
The crucial cyclization step was first probed with the model compounds **12a** and **12b**, which were prepared from imide **10a**[13] through Mitsunobu-coupling[10] to **10b**, followed by methylation to **11** and subsequent acid-mediated $NaBH_4$ reduction,[11] giving **12a** and **12b** exclusively as a 2:1 mixture of epimers. This regiochemical result is remarkable in the light of earlier findings[11] and emphasizes the important influence of the nitrogen substituent on the regioselectivity of the reduction. Either pure **12a**, obtained through chromatographic separation, or the epimer mixture of **12a** and **12b** could be transformed into a 1:1 mixture of epimeric ethoxylactams **12c** by treatment with triethylamine and methanesulfonyl chloride in THF and quenching the resulting mesylates with ethanol.

Formic acid-induced ring closure of either **12a** or the mixture of **12a** and **12b** produced an inseparable

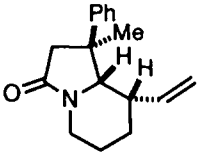
mixture of four cyclization products in an 80:8:8:4 ratio in virtually quantitative yield. Approximately the same mixture of isomers was obtained, when **12c** was cyclized under the influence of $SnCl_4$ for 18 h at 0 °C, although in this case 21% of protodesilylation product was formed as well. The three minor isomers **13b**, **13c**, and **13d** showed ^1H NMR absorptions for H-6 at δ 3.50 (J = 11 Hz), 3.64 (J = 3 Hz), and 3.92 (J = 3 Hz), respectively. The main product formed in 80% yield, as inferred from ^1H NMR analysis, possessed the stereochemistry given by **13a**. The H-6 doublet with J = 10.1 Hz (*trans* relationship between H-5 and H-6), coupled with its high-field shift of 3.21 ppm indicating a phenyl anisotropy effect, are corroborative for this structure which is also expected for mechanistic reasons. A chairlike π-complex conformation **14** in which the nucleophile approaches from the least hindered side in a manner discussed previously,[3a] satisfactorily explains the observed preference for the formation of **13a**. The quasi-equatorial orientation of the allylsilane moiety in **14** is crucial for this outcome.



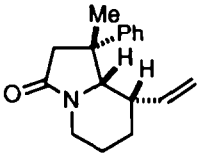
13a



13b

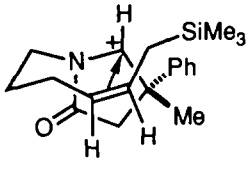


13c

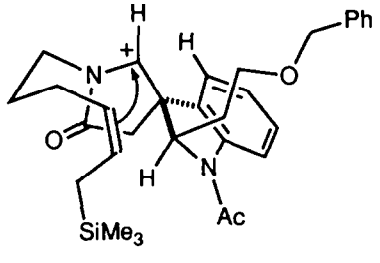


13d

A similar analysis for the π-complex **15** of the cyclization of hydroxylactam **9a** leads one to predict a preferred approach of the nucleophile from the less hindered indoline side of the *N*-acyliminium intermediate. The blockade by the *peri*-hydrogen atom of the aromatic ring forces the nucleophile to enter from the opposite direction in this rigid spirocyclic structure. Furthermore, the presence of the benzyloxyethyl substituent at C-2 of the indoline renders the quasi-equatorial orientation of the allylsilane moiety much less favorable as compared to the quasi-axial orientation, so that the geometry of the π-complex is best represented by **15**. Therefore, the preferred stereochemistry of the product was expected to be cis. Thus, the resultant relative stereochemistry would then correspond with that of the Aspidosperma skeleton.



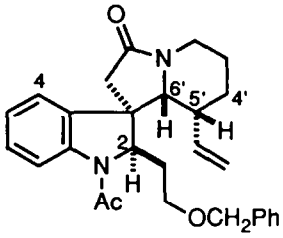
14



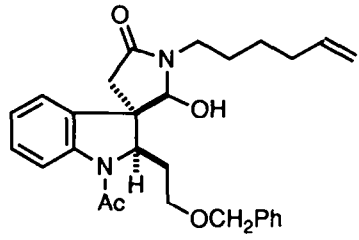
15

In practice, cyclization of **9a** or **9c** appeared to be a difficult process. Dissolution of **9a** in formic acid mainly led to protodesilylation and application of the almost neutral mesylate method[14] gave only starting material after aqueous work-up. After considerable experimentation it was found that cyclization of **9c** in dichloromethane in the presence of $BF_3 \cdot Et_2O$ gave reproducible results. In this way the cyclization product **16**

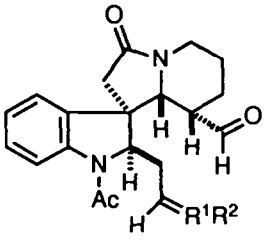
was obtained in 60-70% yield, always accompanied by the alkene **17** as a byproduct. Structural proof for **16** followed inter alia from NOE difference experiments which showed interaction between H-6' and H-4, H-6' and H-5', and H-2 and one of the C-4' protons.



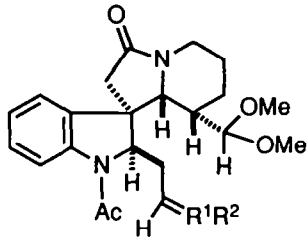
16



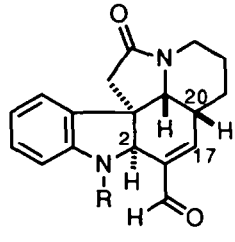
17



18 R^1R^2 = H, OCH_2Ph
22 R^1R^2 = O



19a R^1R^2 = H, OCH_2Ph
19b R^1R^2 = H, OCOPh
20 R^1R^2 = H, OH
21 R^1R^2 = O

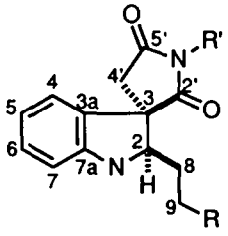


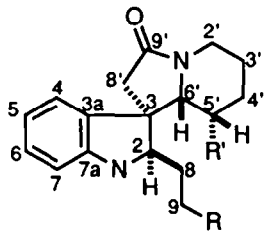
23 R = H
24 R = Ac

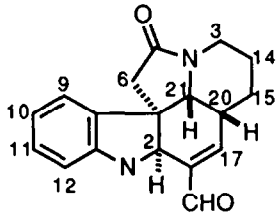
The remaining steps were straightforward and consisted of ozonolysis of **16** providing the aldehyde **18**, which was converted into the acetal **19a** in the usual manner. As an oxidative byproduct the benzoyl derivative **19b** was also obtained.[15] Hydrogenolysis of the benzyl ether to alcohol **20** was followed by oxidation[12] to aldehyde **21**. The latter compound proved unexpectedly stable towards mild deacetalization conditions.[16] Through treatment of **21** with 4 N aqueous HCl in acetonitrile at 60 °C for 30 min, a crude unstable mixture of dialdehydes **22** was obtained, which was immediately treated with piperidinium acetate in benzene[17] at 60 °C for 90 min to produce a 1:7:8 (^{1}H NMR) mixture of three aldehydes in ca. 80% yield. Chromatographic separation gave the pure pentacyclic enals **23** and **24** as major isomers, although the isolated yields were low (both in 15%), presumably as a consequence of instability on the column. The third isomer could not be characterized. The formation of **23** obviously resulted from an acid-catalyzed *N*-deacylation. The ^{1}H-NMR spectrum of **23** was resolved unambiguously by using the 2D-COSY technique. Most diagnostic were the signals of H-20 (2.77 ppm), H-2 (4.38 ppm), H-17 (6.60 ppm), and the aldehydic proton (9.52 ppm). The corresponding signals in **24** appeared at 2.70, 5.06, 6.64, and 9.60 ppm, respectively. These data exclude a possible double bond isomerization to the C-2,C-16 position.[2c] Moreover, NOE experiments proved that no epimerization at any asymmetric carbon had taken place. Thus, we have completed a novel method for the synthesis of the Aspidosperma skeleton.

EXPERIMENTAL

General information. Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer and are reported in cm^{-1}. ^1H NMR measurements were performed on a Varian A-60, HA-100, or XL-100, or a Bruker WM-250 or AC-200 instrument. ^{13}C NMR spectra were taken on a Bruker WM-250 or AC-200 instrument. Chemical shifts are given in ppm downfield from tetramethylsilane. Melting points were measured with a Leitz hot-stage microscope and are uncorrected, as are boiling points. Mass spectra (MS) were obtained on a AEI MS-902 or a Varian MAT-711 mass spectrometer. Chromatographic separations or purifications were carried out by means of flash chromatography on freshly filled silica gel (230-400 mesh) columns.[18] Unless otherwise indicated, a mixture of EtOAc and hexanes was used as the eluent, of which the polarity was adjusted in such a way that the R_f-value of the desired product or products on an analytical TLC plate was about 0.35. The NMR-data are assigned by using the numbering of the atoms of the appropriate skeletons as shown below.







3-(Phenylmethoxy)-1-propanol. To a stirred solution of 76.7 g (0.47 mol) of 2-phenyl-1,3-dioxane[6] in 450 mL of dry toluene at 0 °C under a nitrogen atmosphere was added dropwise 723 mL of a 1.5 M solution of DIBAL-H (1.08 mol) in toluene.[7] The reaction mixture was stirred at room temperature until all of the starting material had been converted, as indicated by TLC. The excess DIBAL-H was destroyed by careful addition of 140 mL of methanol. The resulting heavy suspension was treated with 500 mL of 6 N aqueous NaOH, so that most of the aluminum salts dissolved. The toluene layer was separated and the remaining mixture was extracted three times with ether. The combined ether and toluene solutions were washed with brine and dried over K_2CO_3. Removal of the solvent in vacuo and distillation of the residual oil gave 72.4 g (93%) of the alcohol as a colourless liquid (bp 129-131 °C, 5 mm Hg). ^1H NMR ($CDCl_3$) δ 7.31 (s, 5 H, Ph), 4.50 (s, 2 H, OCH_2Ph), 3.71 (t, 2 H, J = 6 Hz, CH_2OCH_2Ph), 3.61(t, 2 H, J = 6 Hz, CH_2OH), 2.73 (s, 1 H, OH), 1.82 (quint, 2 H, J = 6 Hz, CH_2CH_2OH).

3-(Phenylmethoxy)propanal (6). A solution of 5.0 g (30 mmol) of the above alcohol in 25 mL of dichloromethane was added to a vigorously stirred solution of 9.74 g (45 mmol) of PCC in 25 mL of dichloromethane.[8] The reaction was monitored with TLC. When no more starting material was detected, 50 mL of ether was added and the solution decanted from the insoluble dark residue. This residue was washed twice with 30 mL of ether. The combined organic fractions were filtered over florisil. The solvent was evaporated in vacuo. The crude product was best purified by flash chromatography to give 3.45 g (70%) of aldehyde **6**.[6] Purification by distillation was also possible, although the yield dropped to 45%. Alternatively, the aldehyde **6** was obtained in a yield of 82% (after flash chromatography), when the oxidation was performed with 6 equiv of the pyridine/CrO_3 complex.[12] ^1H NMR ($CDCl_3$) δ 9.82(t, 1 H, J = 2 Hz, CHO), 7.37 (s, 5 H, Ph), 4.55 (s, 2 H, OCH_2Ph), 3.82 (t, 2 H, J = 6 Hz, CH_2OCH_2Ph), 2.68 (dt, 2 H, J = 6, 2 Hz, CH_2CHO).

1-(*tert*-Butyldimethylsilyl)-3-(2'-aminophenyl)pyrrolidine-2,5-dione (7) To a stirred solution of 48.0 g (0.22 mol) of 3-(2'-nitrophenyl)pyrrolidine-2,5-dione[9] in 450 mL of dichloromethane was added at 0 °C under a nitrogen atmosphere 28.0 g (0.28 mol) of Et_3N, 35.0 g (0.23 mol) of *tert*-butyldimethylsilyl chloride and 690 mg (5.6 mmol) of DMAP, respectively. The mixture was allowed to warm to room temperature and was stirred overnight. After addition of 450 mL of hexane the mixture was washed with water and saturated aqueous sodium bicarbonate. The organic solution was dried over sodium sulfate and concentrated in

vacuo to give the crude product as a yellow solid, which was dissolved in 1 L of boiling diisopropyl ether. The hot bright yellow solution was treated with 3 g of norit for 5 min and was then filtered quickly over celite. The resulting pale yellow solution was allowed to slowly cool to room temperature, so that the product crystallized. After standing overnight in a refrigerator 54.7 g (75%) of protected imide was collected as yellowish crystals (mp 105-106 °C). Concentration of the mother liquor gave another 11.7 g (16%) of crystalline material. ^{1}H NMR ($CDCl_3$) δ 8.10 (dd, 1 H, J = 2, 8 Hz, H-3'), 7.65 (dt, 1 H, J = 2, 8 Hz, H-5'), 7.49 (dt, 1 H, J = 2, 8 Hz, H-4'), 7.34 (dd, 1 H, J = 2, 8 Hz, H-6'), 4.39 (dd, 1 H, J = 10, 7 Hz, H-3), 3.19 (dd, 1 H, J = 18, 10 Hz, H-4), 2.90 (dd, 1 H, J = 18, 7 Hz, H-4), 1.02 (s, 9 H, $SiCMe_3$), 0.48 (s, 3 H, SiMe), 0.46 (s, 3 H, SiMe). ^{13}C NMR ($CDCl_3$) δ 181.7 (s, C-2 or C-5), 180.4 (s, C-2 or C-5), 148.2 (s, C-2'), 133.9 (d, C-5'), 132.4 (sC-1'), 132.3 (d, C-6'), 129.0 (d, C-4'), 125.8 (d, C-3'), 47.4 (d, C-3), 39.1 (t, C-4), 26.3 (q, $C(CH_3)_3$), 18.9 (s, $SiCMe_3$), -4.4 (q, SiMe), -4.6 (q, SiMe). IR (KBr) 1762 (m, C=O imide), 1699 (s, C=O imide), 1517 (s, NO_2). MS, *m/z* (rel intensity) no M, 319 (M - CH_3, 2%), 304 (M - 2 CH_3, 0.5%), 277 (M - *t*-Bu, 100%), 100 (16%); field desorpsion MS, *m/z* 334 (M).

The above material (20 g, 59.8 mmol) was dissolved in 250 mL of toluene containing 1 mL of ethanol. The catalyst 10% Pd/C (500 mg) was added and the mixture was hydrogenated for 18 h under 1 atm of hydrogen pressure. The mixture was then filtered over celite to remove the catalyst. The solvent was removed in vacuo to give 17.3 g (95%) of compound **7** as an oil. ^{1}H NMR ($CDCl_3$) δ 7.4-6.7 (m, 4 H, Ar), 4.22 (dd, 1 H, J = 9, 6 Hz, H-3), 4.09 (br s, 2 H, NH_2), 3.07 (dd, 1 H, J = 18, 9 Hz, H-4), 2.84 (dd, 1 H, J = 18, 6 Hz, H-4), 0.94 (s, 9 H, $SiCMe_3$), 0.46 (s, 3 H, SiMe), 0.43 (s, 3 H, SiMe). IR ($CHCl_3$) 3440 (m, NH_2), 3350 (br m, NH_2), 1766 (m, C=O imide), 1698 (s, C=O imide).

Preparation of 8b by electrocyclization and acetylation. Aldehyde **6** (3.14 g, 19 mmol) and amine **7** (5.48 g, 18 mmol) were condensed to the imine by dissolution in 150 mL of toluene and evaporation of the volatiles in vacuo at room temperature. The reaction was monitored with TLC and the procedure repeated until the conversion was complete. In a separate flask, 5.4 mL of a 1.5 M solution of *n*-butyllithium (8.1 mmol) in hexane was added to a mixture of 135 mL of THF and 45 mL of *tert*-butanol at 0 °C. The imine dissolved in 20 mL of toluene was added all at once and the mixture stirred for 30 min at 5 °C. Work-up gave the crude indoline **8a** as a yellow oil, which was not purified. ^{1}H NMR ($CDCl_3$) δ 7.4-6.6 (m, 9 H), 4.54 (s, 2 H), 4.2-3.9 (br m, 2 H), 3.63 (t, 2 H, J = 6 Hz), 3.11 (d, 1 H, J = 19 Hz), 2.78 (d, 1 H, J = 19 Hz), 2.3-1.7 (m, 2 H), 0.95 (s, 9 H), 0.43 (s, 3 H), 0.40 (s, 3 H). IR ($CHCl_3$) 3400 (br, N-H), 1771 (m, C=O imide), 1699 (s, C=O imide).

This crude product was acetylated by stirring it overnight with 10 mL of acetic anhydride in 60 mL of toluene. The volatiles were removed in vacuo, the residue taken up in dichloromethane, and stirred vigorously with 5 mL of saturated aqueous $NaHCO_3$ for 1 h. The organic layer was washed with water and concentrated in vacuo to furnish the acetylated product as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.73 (br s, 1 H), 7.4-7.0 (m, 8 H), 4.64 (br t, 1 H, J = 6 Hz), 4.51 (d, 1 H, J = 12 Hz), 4.43 (d, 1 H, J = 12 Hz), 3.52 (dt, 1 H, J = 11, 6 Hz), 3.40 (dt, 1 H, J = 11, 6 Hz), 3.00 (d, 1 H, J = 18 Hz), 2.76 (d, 1 H, J = 18 Hz), 2.35 (s, 3 H), 2.28 (m, 1 H), 1.92 (m, 1 H), 1.04 (s, 9 H), 0.49 (s, 3 H), 0.44 (s, 3 H). IR ($CHCl_3$) 1773 (m, C=O imide), 1700 (s, C=O imide), 1655 (s, C=O amide).

The crude *N*-acetylindoline was dissolved in 60 mL of ethanol and treated at room temperature with 1.5 mL of a 20% aqueous HCl solution. The reaction mixture was stirred and after some time the product began to crystallize. When the conversion was complete, as indicated by TLC, the mixture was cooled in a refrigerator overnight. Upon filtration 4.64 g of compound **8b** was collected as fine almost white crystals (mp 191-192 °C). Concentration of the mother liquor and flash chromatography of the residue furnished another 0.35 g of the product so that the total yield was 5.04 g (74% in 4 steps from amine **7**). ^{1}H NMR (d_6-DMSO) δ 11.68 (br s, 1 H, NH, vanished after addition of D_2O), 7.84 (br d, 1 H, J = 7 Hz, H-7), 7.5-7.0 (m, 8 H, remaining aromatic H), 4.77 (dd, 1 H, J = 8, 6 Hz, H-2), 4.44 (s, 2 H, OCH_2Ph), 3.42 (t, 2 H, H-9, observed after addition of D_2O), 3.25 (d, 1 H, J = 18 Hz, H-4), 2.70 (d, 1 H, J = 18 Hz, H-4), 2.30 (s, 3 H, NAc), 2.23 (ddt, 1 H, J = 14, 8, 6 Hz, H-8), 1.83 (ddt, 1 H, J = 14, 6, 6 Hz, H-8). IR (KBr) 3460 (m, N-H imide), 3400 (br m, N-H imide), 1771 (m, C=O, imide), 1700 (s, C=O imide), 1657 (s, C=O, amide).

MS, *m/z* (rel intensity) 378 (M, 17%), 378 (M - CH_2=C=O, 9%), 291 (6%), 287 (M - benzyl, 21%), 277 (12%), 272 (22%), 245 (20%), 230 (32%), 220 (20%), 201 (37%), 130 (100%), 91 (benzyl, 92%); exact mass, *m/z* found 378.1589, calcd ($C_{22}H_{22}N_2O_4$) 378.1579.

Preparation of 8c by Mitsunobu coupling. A solution of 1.46 g (10 mmol) of dimethyl azodicarboxylate in 4 mL of THF was added slowly (ca. 30 min) to a mixture of 3.78 g (10 mmol) of **8b**, 1.73 g (10 mmol) of 6-trimethylsilyl-4-hexen-1-ol[3a] and 2.62 g (10 mmol) of triphenylphosphine in 16 mL of THF at 0 °C under a nitrogen atmosphere.[10] The cooling bath was removed and the mixture was stirred overnight at room temperature. Most of the solvent was removed in vacuo. The residue was taken up in 80 mL of chloroform and successively washed twice with 10 mL of 5% aqueous KOH and three times with 10 mL of water. The organic solution was dried over Na_2SO_4, filtered and concentrated in vacuo. The residual oil was dissolved in a small volume of ethyl acetate. Upon trituration with hexane most of the triphenylphosphine oxide crystallized and was removed by filtration. Concentration of the mother liquor and subsequent flash chromatography gave 5.2 g (98%) of **8c** as a colorless oil. Colorless crystals (mp 82-84 °C) could be obtained by recrystallization from a mixture of isopropanol and diisopropyl ether. ^{1}H NMR ($CDCl_3$) δ 8.0-7.4 (br s, 1 H, H-7), 7.4-7.2 (m, 6 H, Ph, H-6), 7.05 (dt, 1 H, *J* = 7.5, 1.0 Hz, H-5), 6.95 (dd, 1 H, *J* = 7.3, 0.6 Hz, H-4), 5.45 (dtt, 1 H, *J* = 10.7, 8.6, 1 Hz, CH=C*H*CH_2TMS), 5.25 (dtt, 1 H, *J* = 10.7, 6.9, 1 Hz, C*H*=CHCH_2TMS), 4.57 (br s, 1 H, H-2), 4.47 (d, 1 H, *J* = 11.9 Hz, OC*H*Ph), 4.34 (d, 1 H, *J* = 11.9 Hz, OC*H*Ph), 3.5-3.4 (m, 3 H, H-9, NC*H*H), 3.33 (br s, 1 H, NCH*H*), 2.96 (d, 1 H, *J* = 18.1 Hz, H-4'), 2.71 (d, 1 H, *J* = 18.1 Hz, H-4'), 2.40 (br m, 1 H, H-8), 2.33 (s, 3 H, NAc), 2.03 (br q, 2 H, *J* = ca. 7.4 Hz, CH_2CH_2CH=), 1.90 (br m, 1 H, H-8) 1.63 (quint, 2 H, CH_2CH_2CH=), 1.46 (dd, 2 H, *J* = 8.6, 1.1 Hz, CH_2TMS), -0.01 (s, 9 H, TMS). ^{13}C NMR ($CDCl_3$) δ 176.5 (s, C-2' or C-5'), 173.7 (s, C-2' or C-5'), 168.4 (s, NCOMe), 141.3 (s, C-7a), 137.8 (s, Ph), 134.0 (s, C-3a), 129.2 (d, C-4), 128.4 (d, Ph), 127.7 (d, Ph), 126.8 (d, *C*=CCTMS), 125.5 (d, C=*C*CTMS), 124.7 (d, C-6), 122.9 (d, C-5), 117.4 (d, C-7), 73.2 (t, OCPh), 69.2 (d, C-2), 66.7 (t, C-9), 55.1 (s, C-3), 45.8 (t, C-4'), 39.1 (t, NCH_2), 31.3 (t, C-8), 27.7 (t, *C*CC=C), 24.5 (t, *C*CC=C), 23.5 (q, $NCOCH_3$), 18.6 (t, CH_2TMS), -1.8 (q, TMS). IR ($CHCl_3$) 1770 (m, C=O imide), 1698 (s, C=O imide), 1657 (s, C=O amide), 1296 (s, TMS), 1118 (s, TMS). MS, *m/z* (rel intensity) 532 (M, 38%, 490 (M - CH_2=C=O, 8%), 441 (M - benzyl, 11%), 351 (24%), 130 (49%), 91 (benzyl, 100%); exact mass, *m/z* found 532.2743, calcd ($C_{31}H_{40}N_2O_4Si$) 532.2757.

Partial reduction of 8c. Imide **8c** (2.5 g, 4.7 mmol) was reduced with 2.0 g (52.9 mmol) of $NaBH_4$ in 100 mL of ethanol at 0 °C according to the procedure described for **11** (vide infra). Usual work-up and flash chromatography furnished 1.36 g (54%) of the desired **9a** and 1.10 g (44%) of the regioisomer **9b**. Data for **9a**: ^{1}H NMR ($CDCl_3$) δ 7.6 (br s, 1 H), 7.52 (d, 1 H, *J* = 7 Hz), 7.4-6.9 (m, 7 H), 5.51 (d, 1 H, *J* = 6 Hz), 5.5-5.1 (m, 2 H), 4.64 (d, 1 H, *J* = 6 Hz), 4.42 (br s, 1 H), 4.24 (d, 1 H, *J* =12 Hz), 4.15 (d, 1 H, *J* = 12 Hz), 3.7-3.0 (m, 4 H), 2.50 (s, 2 H), 2.33 (s, 3 H), 2.2-1.5 (m, 6 H), 1.44 (d, 2 H, *J* = 8 Hz), -0.02 (s, 9 H). IR ($CHCl_3$) 3390 (br m, O-H), 1697 (s, C=O lactam), 1642 (s, C=O amide), 1293 (s, TMS), 1120 (s, TMS). Data for **9b**: ^{1}H NMR ($CDCl_3$) δ 7.65 (br s, 1 H), 7.5-7.0(m, 8 H), 5.6-5.0 (m, 3 H), ca. 4.5 (br s, 1 H), 4.47 (d, 1 H, *J* = 12 Hz), 4.33 (d, 1 H, *J* = 12 Hz), 4.19 (d, 1 H, *J* = 7 Hz), 3.7-3.0 (m, 4 H), 2.52 (dd, 1 H, *J* = 14, 6 Hz), 2.30 (s, 3 H), 1.79 (dd, 1 H, *J* = 14, 5 Hz), 2.7-1.3 (m, 6 H), 1.45 (d, 2 H, *J* = 8 Hz), -0.01 (s, 9 H). IR ($CHCl_3$) 3400 (br m, O-H), 1692 (s, C=O lactam), 1649 (s, C=O amide), 1295 (s, TMS), 1122 (s, TMS).

Reoxidation of hydroxylactam 9b to imide 8c. A solution of 2.67 g (5.0 mmol) of **9b** in 5 mL of dichloromethane was added to a stirred solution of 30 mmol of the pyridine/CrO_3 complex in 70 mL of dichloromethane.[12] The reaction was monitored with TLC. When all of the starting material had been converted, the solution was decanted from the dark residue. The latter was washed twice with 50 mL of chloroform. The combined organic solutions were washed three times with 1 N aqueous NaOH and once with brine, dried over Na_2SO_4, and concentrated in vacuo to give the crude imide as a yellowish oil. Flash chromatography provided 2.25 g (82%) of pure **8c**.

Ethoxylactam 9c. To a solution of 267 mg (0.5 mmol) of hydroxylactam **9a** in 5 mL of THF at -30 °C was added 0.1 mL

(0.72 mmol) of Et_3N and 0.05 mL (0.65 mmol) of methanesulfonyl chloride, respectively. The temperature of the reaction mixture was allowed to raise to room temperature in 15 min. Then 1 mL (ca. 50 equiv) of dry ethanol was added. After stirring for an additional 90 min, 5 mL of saturated aqueous $NaHCO_3$ was added and the mixture was extracted twice with chloroform. The combined organic layers were washed with brine, dried over K_2CO_3, and concentrated in vacuo to furnish 267 mg (95%) of the almost pure ethoxylactam **9c** as an oil. The crude product was pure enough for further synthesis but could easily be purified by flash chromatography. ^1H NMR ($CDCl_3$) δ 8.02 (br s, 1 H, H-7), 7.4-6.9 (m, 8 H, Ph, H-4, H-5, H-6), 5.47 (dt, 1 H, J = 11, 8 Hz, CH=C*H*CH_2TMS), 5.28 (dt, 1 H, J = 11, 6 Hz, C*H*=CHCH_2TMS), 5.07 (s, 1 H, H-2'), 4.4 (br s, 1 H, H-2), 4.32 (d, 1 H, J = 12 Hz, OC*H*HPh), 4.16 (d, 1 H, J = 12 Hz, OCH*H*Ph), 3.9-3.0 (m, 6 H, H-9, NCH_2, OCH_2Me), 2.97 (d, 1 H, J = 14 Hz, H-4'), 2.71 (d, 1 H, J = 14 Hz, H-4'), 2.26 (s, 3 H, NAc), 2.2-1.6 (m, 6 H, CH_2CH_2CH=, H-8), 1.46 (d, 2 H, J = 8 Hz, CH_2TMS), 1.20 (t, 3 H, J = 7 Hz, OCH_2CH_3), -0.02 (s, 9 H, TMS). IR ($CHCl_3$) 1698 (s, C=O lactam), 1653 (s, C=O amide).

1-(6-Trimethylsilyl-4-hexenyl)-3-phenylpyrrolidine-2,5-dione (10b). A solution of 877 mg (60 mmol) of dimethyl azodicarboxylate was added slowly (ca. 30 min) to a stirred mixture of 1.051 g (6.0 mmol) of 3-phenylsuccinimide (**10a**),[13] 1.034 g (6.0 mmol) of 6-trimethylsilyl-4-hexen-1-ol,[3a] and 1.574 g (6.0 mmol) of triphenylphosphine in 25 mL of THF at 0 °C under a nitrogen atmosphere. The reaction was monitored with TLC. Work-up according to the procedure as described for **8c** and subsequent flash chromatography furnished 1.547 g (75%) of **10b** as a colorless oil. ^1H NMR ($CDCl_3$) δ 7.5-7.1 (m, 5 H, Ph), 5.44 (dt, 1 H, J = 11, 8 Hz, CH=C*H*CH_2TMS), 5.25 (dt, 1 H, J = 11, 6 Hz, C*H*=CHCH_2TMS), 3.99 (dd, 1 H, J = 5, 10 Hz, H-3), 3.58 (dd, 2 H, J = 8, 7 Hz, NCH_2), 3.16 (dd, 1 H, J = 18.5, 10 Hz, H-4), 2.78 (dd, 1 H, J = 18.5, 5 Hz, H-4), 2.01 (q, 2 H, J = ca. 6 Hz, CH_2CH_2CH=), 1.68 (m, 2 H, CH_2CH_2CH=), 1.44 (d, 2 H, J = 8 Hz, CH_2TMS), -0.02 (s, 9 H, TMS). IR ($CDCl_3$) 1772 (w, C=O imide), 1699 (s, C=O imide), 1245 (s, TMS).

1-(6-Trimethylsilyl-4-hexenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione (11). To a solution of 1.5 g (4.6 mmol) of imide **10b** in 10 mL of THF, under a nitrogen atmosphere, was added 4.5 g of K_2CO_3 and 2.3 g (16 mmol) of methyl iodide, respectively. The mixture was stirred for 3 days at room temperature and was then poured out into 100 mL water. The resulting mixture was extracted twice with ether. The combined ether fractions were washed with water and dried over K_2CO_3. Removal of the solvent in vacuo and subsequent flash chromatography gave 950 mg (61%) of **11** as a colorless oil. ^1H NMR ($CDCl_3$) δ 7.5-7.3 (m, 5 H, Ph), 5.44 (dt, 1 H, J = 10, 8 Hz, CH=C*H*CH_2TMS), 5.25 (dt, 1 H, J = 10, 6 Hz, C*H*=CHCH_2TMS), 3.58 (t, 2 H, J = ca. 7 Hz, NCH_2), 3.08 (d, 1 H, J = 18 Hz, H-4), 2.82 (d, 1 H, J = 18 Hz, H-4), 2.01 (dt, 2 H, J = 7, 6 Hz, CH_2CH_2CH=), 1.70 (s, 3 H, CMe), 1.70 (m, 2 H, CH_2CH_2CH=), 1.43 (d, 2 H, J = 8 Hz, CH_2TMS), -0.02 (s, 9 H, TMS). IR ($CHCl_3$) 1770 (w, C=O imide), 1700 (s, C=O imide), 1247 (s, TMS)

Partial reduction of imide 11. The imide (950 mg, 2.8 mmol) was dissolved in 100 mL of ethanol and cooled to 0 °C. After addition of 1.11 g of solid $NaBH_4$, 1-3 drops of a 2 N solution of sulfuric acid in ethanol were added every 15 min for a period of 2-5 h. The reaction was monitored with TLC until the starting imide had disappeared. The mixture was poured into brine, diluted with water to a volume of ca. 500 mL and extracted three times with chloroform. Evaporation of the solvent and flash chromatography furnished two fractions. The first fraction (293 mg, 39%) consisted of a 1:2 mixture of the **12a** and **12b**. The second fraction (388 mg, 51%) contained only pure **12a**. Data for **12a**: ^1H NMR ($CDCl_3$) δ 7.4-7.2 (m, 5 H), 5.55-5.00 (m, 2 H), 5.12 (d, 1 H, J = 8 Hz), 4.54 (d, 1 H, J = 8 Hz), 3.49 (dt, 1 H, J = 14, 7 Hz), 3.13 (dt, 1 H, J = 14, 7 Hz), 2.77 (d, 1 H, J = 18 Hz), 2.61 (d, 1 H, J = 18 Hz), 1.86 (q, 2 H, J = 7 Hz), 1.49 (quint, 2 H, J = 7 Hz), 1.46 (s, 3 H), 1.34 (d, 2 H, J = 8 Hz), -0.06 (s, 9 H). IR ($CHCl_3$) 1697 (s, C=O lactam), 1245 (s, TMS). MS, *m/z* (rel intensity) 345 (M, 23%), 330 (M - CH_3, 13%), 327 (M - H_2O, 6%), 290 (12%), 276 (19%), 145 (13%), 131 (12%), 118 (51%), 73 (100%). Exact mass, *m/z* found 345.2114, calcd ($C_{20}H_{31}NO_2Si$) 345.2124. Some ^1H NMR signals of the other epimer, derived from the spectrum of the mixture, are: δ 5.07 (d, 1 H, J = 6 Hz), 3.04 (d, 1 H, J = 16 Hz), 2.84 (d, 1 H, J = 6 Hz), 2.32 (d, 1 H, J = 16 Hz), 1.38 (s, 3 H), -0.02 (s, 9 H).

1-(6-Trimethylsilyl-4-hexenyl)-5-ethoxy-4-methyl-4-phenyl-2-pyrrolidinone (12c). To a stirred solution of 90

mg (0.26 mmol) of pure **12a** in THF was added at -30 °C under a nitrogen atmosphere, 0.047 mL (0.34 mmol) of Et_3N and 0.024 mL (0.32 mmol) of methanesulfonyl chloride, respectively. The temperature was allowed to rise to -10 °C during 1 h. Then, 1 mL (96 equiv) of dry ethanol was added. After stirring for 30 min at room temperature, 10 mL of saturated aqueous $NaHCO_3$ was added and the mixture was extracted twice with dichloromethane. The combined organic layers were dried over K_2CO_3. Evaporation of the solvent in vacuo gave 90 mg (92%) of a 1:1 epimer mixture of ethoxylactams **12c**. ^1H NMR ($CDCl_3$) δ 7.4-7.2 (m, 5 H), 5.6-5.0 (m, 2 H), 4.69 (s, 0.5 H), 4.63 (s, 0.5 H), 3.8-3.3 (m, 2 H), 3.2-2.8 (m, 2 H), 3.06 (d, 0.5 H, J = 17 Hz), 2.70 (d, 0.5 H, J = 17 Hz), 2.52 (d, 0.5 H, J = 17 Hz), 2.30 (d, 0.5 H, J = 17 Hz), 2.1-1.4 (m, 4 H), 1.44 (s, 1.5 H), 1.37 (s, 1.5 H), 1.30 (d, 2 H, J = 8 Hz), 1.17 (t, 1.5 H, J = 7 Hz), 0.73 (t, 1.5 H, J = 7 Hz), -0.06 (s, 4.5 H), -0.09 (s, 4.5 H). IR ($CHCl_3$) 1702 (s, C=O lactam), 1245 (s, TMS).

Cyclization of hydroxylactams 12a and 12b in formic acid. Either pure **12a** or a 1:2 mixture of **12a** and **12b** (60 mg) was stirred in 2.5 mL of formic acid at room temperature for 2 h. Concentration in vacuo gave a residue which was dissolved in dichloromethane. The solution was shaken with saturated aqueous $NaHCO_3$ to remove the last traces of acid and dried over Na_2SO_4. Removal of the solvent in vacuo furnished 44 mg (ca. 100%) of a 10:4:4:1 mixture of the diastereomeric 5-ethenyl-7-methyl-7-phenyl-1-azabicyclo[4.3.0]nonan-9-ones **13a-13d**, which could not be separated by flash chromatography. Data for **13a**: ^1H NMR (derived from the spectrum of the mixture, $CDCl_3$) δ 7.4-7.2 (m, 5 H, Ph), 5.53 (ddd, 1 H, J = 8.3, 10.4, 17.2 Hz, C*H*=CH_2), 4.92 (dd, 1 H, J = 1.5, 10.4 Hz, CH=C*H*H), 4.60 (d, 1 H, J = 17.2 Hz, CH=CH*H*), 4.21 (br d, 1 H, J = ca. 13 Hz, H-2), 3.21 (d, 1 H, J = 10.1 Hz, H-6), 2.75 (d, 1 H, J = 17.2 Hz, H-8), 2.61 (m, 1 H, H-2), 2.55 (d, 1 H, J = 17.2 Hz, H-8), 1.66 (s, 3 H, CMe), 1.8-1.4 (m, 3 H, H-3, H-4, H-5), 1.3-1.1 (m, 2 H, H-3, H-4). Chemical shifts of the C-6 protons of the other isomers are given in the text. ^{13}C NMR ($CDCl_3$) δ 174.1 (s, C-9), 144.4 (s, Ph), 138.8 (d, *C*H=CH_2), 127.8 (t, Ph), 127.0 (t, Ph), 126.6 (t, Ph), 116.1 (t, CH=*C*H_2), 70.6 (d, C-6), 48.7 (t, C-8), 42.8 (s, C-7), 42.4 (d, C-5), 40.3 (t, C-2), 31.5 (t, C-4), 26.9 (q, Me), 23.3 (t, C-3). MS of the mixture, *m/z* (rel intensity) 255 (M, 50%), 227 (6%), 188 (100%), 118 (80%), 110 (57%); exact mass, *m/z* found 255.1618, calcd ($C_{17}H_{21}NO$) 255.1623.

Cyclization of ethoxylactam 12c with $SnCl_4$. A 1 M solution of $SnCl_4$ (0.30 mL, 0.3 mmol) in dichloromethane was added at 0 °C under a nitrogen atmosphere to a stirred solution of 90 mg (0.24 mmol) of ethoxylactams **12c** (1:1 epimer mixture) in 2.5 mL of dichloromethane. The solution was stirred overnight and then treated with 5 mL of saturated aqueous $NaHCO_3$. The mixture was extracted three times with dichloromethane and the combined organic layers were dried over K_2CO_3. Removal of the solvent in vacuo and flash chromatography of the residue gave 44 mg (72%) of a mixture of the bicyclic compounds **13a-13d** in a similar ratio as above and 15 mg (21%) of the protodesilylation product.

Synthesis of 16 via cyclization of ethoxylactam 9c with $BF_3{\cdot}Et_2O$. Ethoxylactam **9c** (844 mg, 1.5 mmol) was stirred for 1 h at room temperature with 42 mg (1 mmol) of CaH_2 in 5 mL of dichloromethane. Likewise, 0.47 mL (3.8 mmol) of freshly distilled $BF_3{\cdot}Et_2O$ (from CaH_2) was stirred for 1 h with 42 mg (1 mmol) of CaH_2 in 5 mL of dichloromethane. The $BF_3{\cdot}Et_2O$ solution was then added to the ethoxylactam mixture. After stirring for 60 h the solution was decanted and the remaining CaH_2 was washed with 10 mL of dichloromethane. The combined organic solutions were washed twice with saturated aqueous $NaHCO_3$ and dried over Na_2SO_4. Evaporation of the solvent and flash chromatography of the residual oil furnished 460 mg (69%) of tetracyclic compound **16** as a colorless oil and 180 mg (26%) of the protodesilylation product **17**. Crystals of **16** (mp 144.5-146 °C) could be obtained from a hot mixture of ethanol and diisopropyl ether. The ^1H and ^{13}C NMR spectra of **16** showed signals of two rotamers (ratio ca. 1:1). ^1H NMR ($CDCl_3$) δ 7.87 (d, 0.5 H, J = 8 Hz, H-7), 7.3-7.0 (m, 6 H, Ph, H-6), 6.97 (d, 0.5 H, J = 8 Hz, H-7), 6.91 (m, 2 H, H-4, H-5), 6.04 (dt, 0.5 H, J = 17, 10 Hz, C*H*=CH_2), 5.98 (dt, 0.5 H, J = 17, 10 Hz, C*H*=CH_2), 5.30 (d, 0.5 H, J = 17 Hz, CH=C*H*H), 5.23 (d, 0.5 H, J = 17 Hz, CH=C*H*H), 5.10 (d, 1 H, J = 10 Hz, CH=CH*H*), 4.96 (dd, 0.5 H, J = 3, 8 Hz, H-2), 4.51 (dd, 0.5 H, J = 2.5, 8 Hz, H-2), 4.30 (d, 0.5 H, J = 12 Hz, OC*H*HPh), ca. 4.25 (m, 1 H, H-2'), 4.25 (d, 0.5 H, J = 12 Hz, OC*H*HPh), 4.20 (d, 0.5 H, J = 12 Hz, OCH*H*Ph), 4.09 (d, 0.5 H, J = 12 Hz, OCH*H*Ph),

3.82 (d, 0.5 H, J = 2.5 Hz, H-6'), 3.78 (d, 0.5 H, J = 2.5 Hz, H-6'), 3.5-3.2 (m, 2 H, H-9), 2.87 (m, 1 H, H-5'), ca. 2.77 (m, 1 H, H-2'), 2.70 (d, 0.5 H, J = 17 Hz, H-8'), 2.67 (d, 0.5 H, J = 17 Hz, H-8'), 2.23 (s, 1.5 H, NAc), 2.12 (s, 1.5 H, NAc), 2.1-2.0 (m, 1 H, H-8), 2.01 (d, 0.5 H, J = 17 Hz, H-8'), 1.95 (d, 0.5 H, J = 17 Hz, H-8'), 1.86-1.55 (m, 4 H, H-3', 2x H-4', H-8), 1.41 (m, 1 H, H-3'). ^{13}C NMR ($CDCl_3$) δ 170.2 and 170.1 (s, C-9'), 168.1 and 168.0 (s, NCOMe), 142.4-116.4 (27 signals, remaining sp^2 carbons), 73.1 and 73.0 (t, OCPh), 67.2 and 65.5 (t, C-9), 65.5 and 65.1 (d, C-6'), 65.4 and 64.9 (d, C-2), 51.5 and 50.5 (s, C-3), 45.9 and 45.8 (t, C-8'), 42.0 and 41.7 (d, C-5'), 40.4 (t, C-2'), 31.6 and 30.9 (t, C-8), 31.6 and 31.2 (t, C-4'), 23.1 and 22.7 (q, Me), 19.6 (t, C-3'). IR ($CHCl_3$) 1672 (s, C=O lactam), 1656 (s, C=O amide), 995 (m, vinyl), 920 (m, vinyl). MS, m/z (rel intensity) 444 (M, 100%), 428 (21%), 426 (12%), 413 (12%), 402 (M - CH_2=C=O, 11%), 353 (M - benzyl, 74%), 338 (31%), 336 (40%), 311 (19%), 309 (25%), 294 (27%), 267 (36%), 265 (24%), 156 (47%), 151 (36%), 144 (31%), 130 (81%), 110 (40%), 99 (54%), 91 (benzyl, 71%), 84 (43%), 71 (44%); exact mass, m/z found 444.2411, calcd ($C_{28}H_{32}N_2O_3$) 444.2413. Data for **17**: ^{1}H NMR ($CDCl_3$) δ 7.82 (br d, 1 H, J = ca. 8 Hz, H-7), 7.5-7.0 (m, 8 H, Ph, H-4, H-5, H-6), 5.95 (ddt, 1 H, J = 10, 16, 7 Hz, C*H*=CH_2), 5.49 (s, 1 H, H-2'), 5.07 (dm, 1 H, J = 16 Hz, CH=C*H*H), 5.01 (dm, 1 H, J = 10 Hz, CH=CH*H*), 4.60 (s, 1 H, OH), 4.34 (m, 2 H, OCH_2Ph), 3.94 (dd, 1 H, J = 4, 7 Hz, H-2), 3.8-3.4 (m, 3 H, H-9, NC*H*H), 3.3-3.0 (m, 1 H, NCH*H*), 2.76 (d, 1 H, J = 17 Hz, H-4'), 2.34 (s, 3 H, NAc), 2.33 (d, 1 H, J = 17 Hz, H-4'), 2.14 (ca. q, 2 H, J = 6 Hz, CH_2CH=), 2.0-1.2 (m, 6 H, $NCH_2CH_2CH_2$, H-8). IR ($CHCl_3$) 3400 (br m, O-H), 1697 (s, C=O lactam), 1655 (s, C=O amide).

Preparation of aldehyde 18 by ozonolysis of 16. A 50 mL flask, containing a solution of 300 mg of **16** in 10 mL of dichloromethane was cooled to -78 °C. Ozone (5% in oxygen) was bubbled through the mixture until a blue color persisted. Then, nitrogen was passed through the solution at -78 °C until the blue color disappeared. Dimethyl sulfide (1 mL) was added and the temperature was allowed to rise slowly to room temperature (ca. 2 h). The solvent was quickly removed in vacuo. The resulting oil was stirred overnight in 2 mL of dimethyl sulfide at room temperature. Evaporation of the volatiles and flash chromatography of the residue yielded 143 mg (47%) of pure **18**. Some recognizable signals in the ^{1}H NMR spectrum ($CDCl_3$) of **18** are: δ 9.82 (br s, 1 H, CHO), 8.2-7.8 (m, 1 H, H-7), 7.6-6.8 (m, 8 H, remaining aromatic protons), 5.03 (br s, 1 H, H-2). IR ($CHCl_3$) 1720 (m, C=O aldehyde), 1675 (s, C=O lactam), 1653 (s, C=O amide). MS, m/z (rel intensity) 446 (M, 13%), 444 (M - H_2, 19%), 355 (M - benzyl, 13%), 353 (444 - benzyl, 15%), 338 (12%), 311 (13%), 309 (11%), 267 (17%), 265 (16%), 199 (12%), 174 (31%), 173 (24%), 156 (45%), 144 (33%), 130 (93%), 122 (24%), 105 (37%), 91 (benzyl, 100%), 77 (44%), 65 (20%). Exact mass, m/z found 446.2199, calcd ($C_{27}H_{30}N_2O_4$) 446.2205.

Preparation of dimethoxyacetal 19a from 18. A mixture of 150 mg (0.34 mmol) of aldehyde **18**, 100 mg (1.0 mmol) of methyl orthoformate, and one crystal of *p*-toluenesulfonic acid monohydrate was stirred in 2 mL of refluxing methanol for 3 h. After cooling to room temperature, 10 mL of saturated aqueous $NaHCO_3$ was added and the mixture was extracted three times with chloroform. The combined organic layers were dried over K_2CO_3 and the solvent removed in vacuo. Flash chromatography of the residue gave 130 mg (79%) of the acetal **19a** as an oil. The ^{1}H NMR spectrum showed signals of two rotamers (ratio ca. 1:1), due to hindered rotation of the acetyl group. ^{1}H NMR ($CDCl_3$) δ 8.04 (br d, 0.5 H, J = 8 Hz), 7.11 (br d, 0.5 H, J = 8 Hz), 7.6-6.9 (m, 8 H), 5.22 (dd, 0.5 H, J = 4, 8 Hz), 4.80 (dd, 0.5 H, J = 4, 8 Hz), 4.7-4.0 (m, 4 H), 3.97 (d, 0.5 H, J = ca. 3 Hz), 3.93 (d, 0.5 H, J = ca. 3 Hz), 3.40 (s, 3 H), 3.35 (s, 3 H), 3.8-3.1 (m, 2 H), 2.95 (m, 1 H), 2.68 (d, 1 H, J = 17 Hz), 2.36 (s, 1.5 H), 2.32 (s, 1.5 H), 2.10 (d, 0.5 H, J = 17 Hz), 2.06 (d, 0.5 H, J = 17 Hz), 2.8-1.2 (m, 7 H). IR ($CHCl_3$) 1677 (s, C=O lactam), 1650 (s, C=O amide).

Deprotection of benzyl ether 19a to alcohol 20. Benzyl ether **19a** (130 mg, 0.26 mmol) was dissolved in 5 mL of ethanol. Then, 50 mg of 10% Pd/C and 1 drop of water were added and the mixture was subjected to hydrogenolysis until TLC showed total conversion of the starting material (after ca. 5 h). The mixture was filtered over celite and concentrated in vacuo. Flash chromatography (acetone/dichloromethane = 3:2) of the residue gave 98 mg (92%) of the alcohol **20** as an oil which slowly solidified upon standing in a refrigerator. When this reaction was performed in a methanol solution, the product was obtained in only

60% yield. Due to hindered rotation of the acetyl group, the 250 MHz ^{1}H NMR spectrum exhibited signals of two rotamers. The remarkable 9:1 ratio of the rotamers might be explained by assuming a hydrogen bond interaction between the OH group and the acetyl function. ^{1}H NMR ($CDCl_3$) δ 7.92 (d, 0.1 H, J = 7.8 Hz, H-7), 7.07 (d, 0.9 H, J = 7.8 Hz, H-7), 7.3-6.9 (m, 3 H, H-4, H-5, H-6), 5.15 (dd, 0.9 H, J = 11.5, 3.1 Hz, H-2), 4.72 (dd, 0.1 H, J =11.5, 3.1 Hz, H-2), 4.51 (d, 1 H, J = 7.5 Hz, C*H*(OMe)$_2$), 4.33 (dd, 1 H, J = 12.9, 4.6 Hz, H-2'), 4.05 (dd, 1 H, J = 10, 4.6 Hz, OH), 3.91 (d, 0.1 H, J = ca. 3 Hz, H-6'), 3.85 (d, 0.9 H, J = 2.9 Hz, H-6'), 3.44 (m, 2 H, H-9), 3.39 (s, 3 H, OMe), 3.31 (s, 3 H, OMe), 2.91 (dt, 1 H, J = 12.5, 3.5 Hz, H-2'), 2.69 (d, 0.9 H, J = 15.8 Hz, H-8'), 2.43 (m, 1 H, H-5'), 2.38 (s, 2.7 H, NAc), 2.31 (s, 0.3 H, NAc), 2.2-2.0 (m, 2 H, H-8, H-3'), 2.03 (d, 0.9 H, J = 15.8 Hz, H-8'), 1.8-1.4 (m, 3 H, H-3', H-4', H-8), 1.26 (br t, 1 H, J = ca. 11.7 Hz, H-4'). IR ($CHCl_3$) 3410 (br m, O-H), 1677 (s, C=O lactam), 1650 (s, C=O amide). Exact mass, *m/z* found 402.2153, calcd ($C_{22}H_{30}N_2O_5$) 402.2154.

Alternative route to alcohol 20 from 16. Olefin **16** (500 mg, 1.12 mmol) was ozonized at -78 °C in a mixture of 3 mL of dichloromethane and 3 mL of methanol, according to the procedure described for the synthesis of aldehyde **18**. The formed methoxyhydroperoxides were reduced with 3 mL of dimethyl sulfide at room temperature for 18 h. After evaporation of the solvent, the resulting crude aldehyde mixture was dissolved in 6 mL of methanol. After addition of 2 mL of methyl orthoformate and one crystal of *para*-toluenesulfonic acid monohydrate, the mixture was refluxed for 3 h. Work-up, as described for the synthesis of acetal **19a**, and subsequent flash chromatography furnished a mixture of the acetals **19a** and **19b**. This crude mixture was hydrogenolysed in 10 mL of ethanol (containing 1 drop of water) over 100 mg of 10% Pd/C for 5 h. The reaction mixture was filtered over celite and the solvent was removed in vacuo. Flash chromatography of the residue gave 212 mg (53% from **16**) of alcohol **20** and 125 mg (22% from **16**) of the benzoyl ester **19b**. Data for **19b**: ^{1}H NMR (4:6 mixture of rotamers, $CDCl_3$) δ 8.05-7.95 (m, 2.4 H), 7.07 (d, 0.6 H, J = 7.9 Hz), 7.6-6.9 (m, 6 H), 5.32 (dd, 0.6 H, J = 10.0, 2.6 Hz), 4.79 (dd, 0.4 H, J = 9.2, 1.9 Hz), 4.53 (d, 1 H, J = 8.1 Hz), 4.38 (m, 1 H), 4.5-3.9 (m, 2 H), 3.97 (d, 0.4 H, J = 2.4 Hz), 3.91 (d, 0.6 H, J = 2.6 Hz), 3.29 (s, 1.8 H), 3.23 (s, 1.8 H), 3.18 (s, 1.2 H), 3.16 (s, 1.2 H), 2.93 (m, 1 H), 2.65 (d, 0.6 H, J = 16.1 Hz), 2.60 (d, 0.4 H, J = 15.6 Hz), 2.49 (m, 1 H), 2.38 (s, 1.2 H), 2.36 (s, 1.8 H), 2.04 (d, 1 H, J = ca. 16 Hz), 2.4-1.5 (m, 6 H). IR ($CHCl_3$) 1718 (s, C=O ester), 1677 (s, C=O lactam), 1652 (s, C=O amide). Exact mass, *m/z* found 506.2407, calcd ($C_{29}H_{34}N_2O_6$) 506.2417.

Oxidation of alcohol 20 to aldehyde 21. A solution of 3.3 mmol pyridine/CrO_3 complex was prepared by stirring 522 mg (6.6 mmol) of pyridine and 330 mg (3.3 mmol) of CrO_3 in 8.5 mL of dichloromethane at room temperature for 30 min.[12] To this mixture was added at once, 197 mg (0.55 mmol) of alcohol **20** in 0.5 mL of dichloromethane. After stirring for an additional 20 min the solution was decanted from the dark tarry residue and the latter was washed twice with 10 mL of chloroform. The combined solutions were washed three times with 1 N aqueous NaOH, once with 1 N aqueous HCl, and once with saturated aqueous $NaHCO_3$, respectively. Drying over Na_2SO_4 and concentration in vacuo gave a yellowish oil. Crystallization from benzene furnished 174 mg (89%) of **21** as a white solid (mp 190-195 °C (dec)). Due to hindered rotation of the acetyl group, the NMR spectra showed signals of two rotamers. ^{1}H NMR (1:4 mixture of rotamers, $CDCl_3$) δ 9.62 (dd, 0.8 H, J = 4.5, 1.7 Hz, CHO), 9.46 (br s, 0.2 H, CHO), 7.99 (d, 0.2 H, J = 7.4 Hz, H-7), 7.09 (d, 0.8 H, J = 8.1 Hz, H-7), 7.3-6.9 (m, 3 H, H-4, H-5, H-6), 5.42 (dd, 0.8 H, J = 8.2, 3.8 Hz, H-2), 4.96 (br m, 0.2 H, H-2), 4.57 (d, 1 H, J = 8.4 Hz, C*H*(OMe)$_2$), 4.38 (dd, 1 H, J = 12.9, 4.5 Hz, H-2'), 3.91 (br s, 0.2 H, H-6'), 3.87 (d, 0.8 H, J = 2.7 Hz, H-6'), 3.45 (s, 3 H, OMe), 3.31 (s, 3 H, OMe), 2.95 (br t, 1 H, J = ca. 12.2 Hz, H-2'), 2.87 (ddd, 0.8 H, J = 14.6, 3.7, 1.8 Hz, H-8), 2.80 (m, 0.2 H, H-8), 2.67 (d, 0.8 H, J = 16.0 Hz, H-8'), 2.64 (d, 0.2 H, J = 16.0 Hz, H-8'), 2.5-2.3 (m, 2 H, H-5', H-8), 2.38 (s, 3 H, NAc), ca. 2.13 (m, 1 H, H-3'), 2.10 (d, 1 H, J = 16.0 Hz, H-8'), 1.8-1.5 (m, 3 H, H-3', H-4'). ^{13}C NMR (main rotamer, $CDCl_3$) δ 220.5 (d, CHO), 169.6 (s, C-9'), 168.2 (s, NCOMe), 141.3 (s, C-7a), 138.2 (s, C-3a), 128.7 (d, C-4), 124.8 (d, C-6), 122.1 (d, C-5), 115.8 (d, C-7), 101.3 (d, *C*H(OMe)$_2$), 65.1 (d, C-6'), 63.5 (d, C-2), 55.2 (q, OMe), 50.9 (q, OMe), 50.9 (s, C-3), 45.1 (t, C-8), 44.3 (t, C-8'), 40.1 (t, C-2'), 38.6 (d, C-5'), 27.1 (t, C-3'), 23.4 (q, NCO*C*H$_3$), 19.6 (t, C-4'). IR ($CHCl_3$) 1720 (m, C=O aldehyde), 1769 (s, C=O lactam), 1650 (s, C=O amide). MS, *m/z* (rel intensity) 400 (M, 7%),

297 (10%), 144 (7%), 130 (16%), 75 (100%); exact mass, *m/z* found 400.2001, calcd ($C_{22}H_{28}N_2O_5$) 400.1998.

20-Desethyl-17-formyl-5-oxo-16,17-dehydroaspidospermidine (23) and *N*-acetyl-20-desethyl-17-formyl-5-oxo-16,17-dehydroaspidospermidine (24). Aldehyde **21** (200 mg, 0.5 mmol) was stirred in a mixture of 12 mL of acetonitrile and 4 mL of 4 N aqueous HCl at 60 °C for 30 min. The mixture was then cooled to room temperature and was extracted twice with chloroform. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and dried over Na_2SO_4. Evaporation of the solvent gave an oil, of which the ^1H NMR spectrum showed ca. seven aldehyde signals. To this crude mixture was added 10 mL of a benzene solution of piperidinium acetate, which was prepared by adding 2 drops of piperidine and 3 drops of acetic acid to 30 mL of dry benzene. After heating at 60 °C for 90 min, the solution was cooled to room temperature and poured into 10 mL of saturated aqueous $NaHCO_3$. The mixture was extracted three times with chloroform and the combined organic layers were dried over Na_2SO_4. Evaporation of the solvent furnished 135 mg (ca. 80%) of a crude mixture of three aldehydes in a ratio of 1:7:8 (^1H NMR). Flash chromatography of this mixture gave 22 mg (15%) of **23** and 25 mg (15%) of **24** as oils, which slowly solidified upon standing in a refrigerator. **23**: ^1H NMR ($CDCl_3$) δ 9.52 (s, 1 H, CHO), 7.08 (d, 1 H, J = 7.7 Hz, H-9), 7.06 (t, 1 H, J = 7.6 Hz, H-11), 6.74 (dt, 1 H, J = 7.4, 0.8 Hz, H-10), 6.60 (dd, 1 H, J = 2.1, 1.3 Hz, H-17), 6.55 (d, 1 H, J = 7.7 Hz, H-12), 4.38 (s, 2 H, H-2, NH), 4.06 (dd, 1 H, J = 13.3, 4.4 Hz, H-3), 3.90 (d, 1 H, J = 4.6 Hz, H-21), 2.77 (m, 1 H, H-20), 2.70 (s, 2 H, H-6), 2.70 (dt, 1 H, J = 13.3, 3.5 Hz, H-3), 2.10 (br d, 1 H, J = 13.9 Hz, H-15), 1.80 (tt, 1 H, J = 13.9, 3.9 Hz, H-15), 1.70 (br d, 1 H, J = ca. 13 Hz, H-14), 1.40 (tt, 1 H, J = ca. 13, 4 Hz, H-14). IR ($CHCl_3$) 3420 (br m, N-H), 1680 (br s, C=O aldehyde + C=O lactam). **24**: ^1H NMR ($CDCl_3$) δ 9.60 (s, 1 H, CHO), 7.44 (br s, 1 H, H-12), 7.4-7.1 (m, 3 H, H-9, H-10, H-11), 6.64 (d, 1 H, J = 1.5 Hz, H-17), 5.06 (s, 1 H, H-2), 4.07 (dd, 1 H, J = 13.3, 4.6 Hz, H-3), 3.81 (d, 1 H, J = 4.3 Hz, H-21), 2.82 (d, 1 H, J = 17.5 Hz, H-6), 2.70 (br s, 1 H, H-20), 2.67 (br t, 1 H, J = 13.5 Hz, H-3), 2.56 (d, 1 H, J = 17.5 Hz, H-6), 2.37 (s, 3 H, NAc), 2.10 (br d, 1 H, J = ca. 13 Hz, H-15), 1.76 (tt, 1 H, J = ca. 13, 4 Hz, H-15), ca. 1.67 (br d, 1 H, J = ca. 13 Hz, H-14), 1.44 (tt, 1 H, J = 13.4, 3.7 Hz, H-14). IR ($CHCl_3$) 1680 (br s, C = O aldehyde + C = O lactam), 1650 (s, C=O amide). MS, *m/z* (rel intensity) 336 (M, 39%), 294 (M - H_2C=C=O, 100%), 130 (65%), 69 (54%); exact mass, *m/z* found 336.1472, calcd ($C_{20}H_{20}N_2O_3$) 336.1474.

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