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STEREOSPECIFIC SYNTHESIS OF (+)- AND (-)-SESBANIMIDE A

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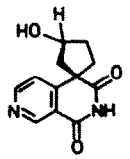
Abstract - Starting from L-xylose and D-xylose derivatives, (-)-sesbanimide A and (+)-sesbanimide A, respectively, have been synthesized. The carbohydrate templates constitute ring B of the alkaloid on which the remaining two rings are constructed in the sequence B → AB → ABC.

The antileukemic principle of the seeds of sesbania drummondii has had an interesting history. An initial report in 1979 ascribing structure 1[1] (sesbanine) to the active component triggered off studies directed to the synthesis of the molecule in a number of laboratories[2]. Sesbanine itself was, however, shown to be inactive. A further examination of the extracts of the seeds led to the isolation of a number of compounds[3a] of which sesbanimide A (2a) has been demonstrated to be the most active product in a number of cancer screening systems[3a,c].

The structure of sesbanimide A was derived from X-ray crystallographic data[3b], which, albeit did not define absolute configurations of the asymmetric centres. The total synthesis of (-)-sesbanimide A (2b), the antipode of the natural compound, communicated by us recently[4], establishes the configuration of natural sesbanimide A as the 7S,8R,9S,10R,11R-compound. Since the publication of this communication two other groups have reported[5a,b] the synthesis of the alkaloid. In the present paper we present details of our work on the synthesis of both enantiomers of sesbanimide A.



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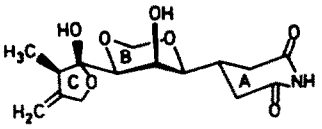
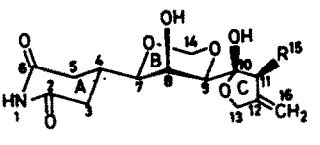
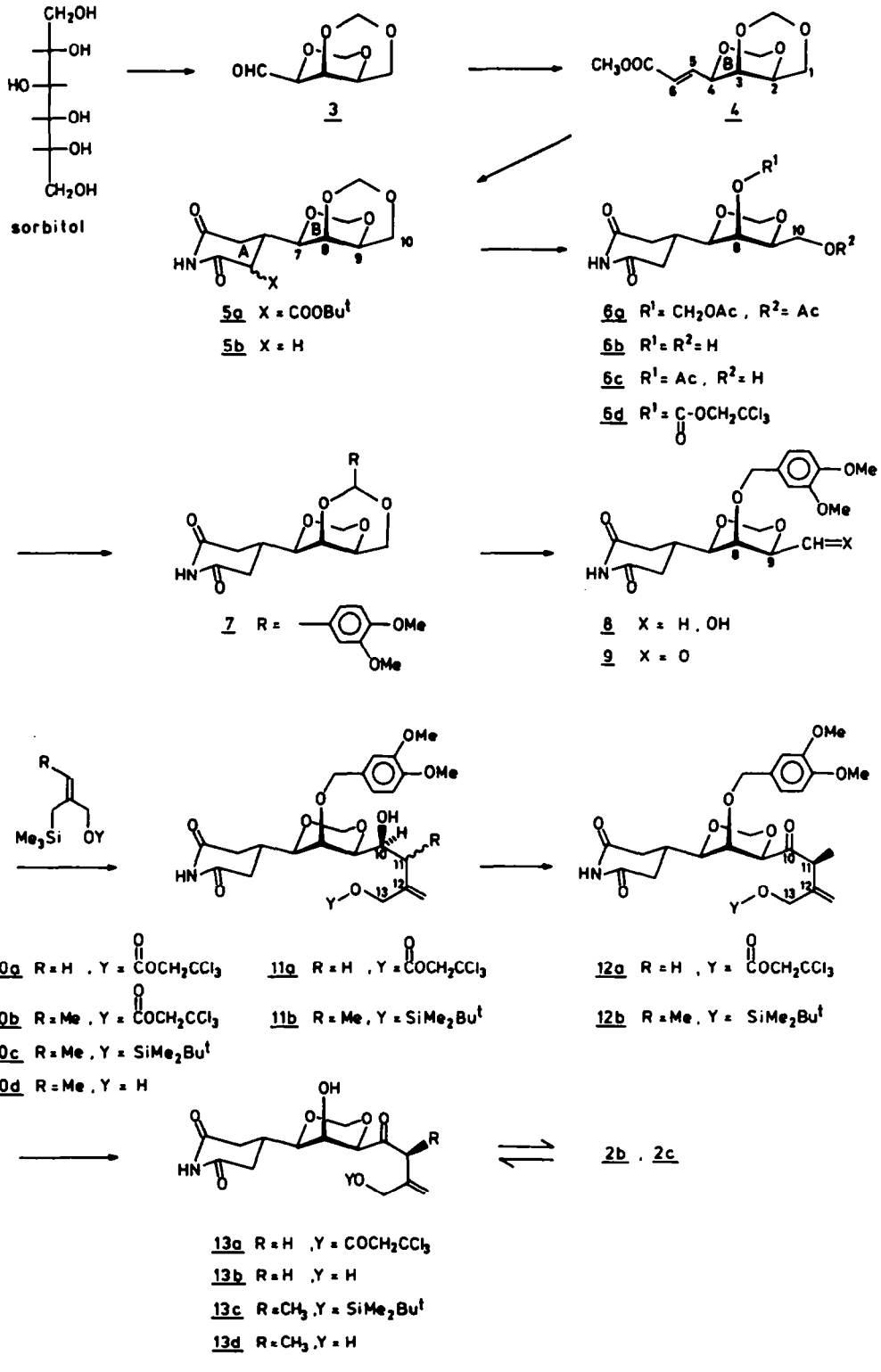


2a



2b R = CH_3
2c R = H


sorbitol
3
4
5a X = COOBu^t
5b X = H
6a R^1 = CH_2OAc, R^2 = Ac
6b R^1 = R^2 = H
6c R^1 = Ac, R^2 = H
6d R^1 = $C(=O)-OCH_2CCl_3$
7 R = 3,4-dimethoxyphenyl
8 X = H, OH
9 X = O
10a R = H, Y = $COCH_2CCl_3$
10b R = Me, Y = $COCH_2CCl_3$
10c R = Me, Y = $SiMe_2Bu^t$
10d R = Me, Y = H
11a R = H, Y = $COCH_2CCl_3$
11b R = Me, Y = $SiMe_2Bu^t$
12a R = H, Y = $COCH_2CCl_3$
12b R = Me, Y = $SiMe_2Bu^t$
13a R = H, Y = $COCH_2CCl_3$
13b R = H, Y = H
13c R = CH_3, Y = $SiMe_2Bu^t$
13d R = CH_3, Y = H
2b, 2c

Scheme A

In planning the synthesis of sesbanimide A we decided in favour of a strategy which visualized ring B as the starting synthon to be derived from the appropriate carbohydrate. It was envisioned that the remaining two rings be constructed in the sequence B → AB → ABC. In this scheme the labile ring C was to be elaborated in the last steps of the synthesis. Inspection of ring B and consideration of potential functional groups which can be elaborated to rings A and C leads to the identification of xylose as the required carbohydrate synthon. Since at the commencement of our work the absolute configuration of sesbanimide was not known, the choice of the specific xylose was essentially arbitrary. In deciding to opt for L-xylose we were influenced by its ready availability in a suitable derivatized form (3)[6] from the inexpensive starting material sorbitol (D-glucitol) (Scheme A).

Initiating the synthesis with aldehyde 3 as the ring B synthon, the glutarimide ring (A) was constructed in three practical steps. Extension of the aldehyde by two carbons, to give unsaturated ester 4, was achieved by a Wittig reaction. The product consisted primarily of one isomer, namely, that with the E-geometry. Reaction of 4 with $CH_2(CONH_2)COOtBu$ in the presence of base resulted in a Michael addition followed by a cyclization reaction to give a mixture of diastereomers of ester 5a, in high yield. This mixture was treated with trifluoroacetic acid, followed by heating in DMF, to affect the removal of the t-butoxycarbonyl function and thereby resulting in the conversion of 5a to 5b.

Construction of ring C required the specific opening of the C(10)-bearing acetal ring in the biacetal product 5b and adjustment of the oxidation state of that carbon, viz. C(10) (sesbanimide numbering) for further elaboration. The desired ring-opening of the acetal group in 5b was readily carried out by its reaction with acetic anhydride-acetic acid-sulphuric acid mixture, whereupon the product 6a was formed exclusively. This selectivity is associated with steric accessibility to the reagents of that acetal ring which contains the ether oxygen derived from the primary hydroxyl group. The diacetate 6a smoothly hydrolyzed to diol 6b upon treatment with sodium methoxide in methanol/chloroform at -15°C.

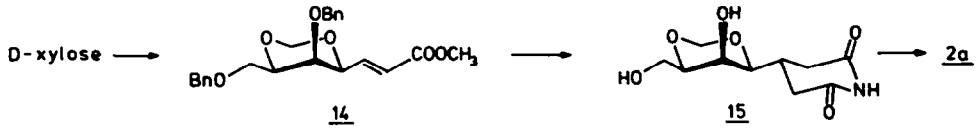
The projected synthetic sequence required the oxidation of C(10) in 6b to the aldehyde level. For this conversion the selective protection of the secondary C(8)-hydroxyl group is a prerequisite. Attempts to oxidize the primary hydroxy group in derivatives in which the C(8)-OH was protected by an acyl function, as in 6c and 6d, were unsuccessful. In all these cases a facile trans elimination reaction involving the axial C(9)-H and the C(8)-OC(=O)R group appeared to be the predominant process. It became obvious that the C(8)-OH would have to be protected by a group devoid of electron-demand and incapable of elimination as an OR moiety. Based upon this rationale, diol 6b was converted into acetal 7 and the latter selectively opened under reductive conditions (Et_2AlCl-CH_2Cl_2, Et_3SiH, - 55°C) to alcohol 8. As expected, 8 could be oxidized to aldehyde 9 by chromium trioxide-pyridine, at room temperature.

The elaboration of ring C was first examined in a model study. Condensation of aldehyde 9 with allylsilane derivative 10a[7] was most effectively achieved under the influence of BF_3. Although the reaction can in principle lead to two diastereomers, only one product was isolated. The structure assigned to this product, viz. 11a, is based upon mechanistic considerations. According to these it is assumed that the silyl reagent approaches the carbonyl carbon from the least hindered side of the molecule in an aldehyde 9-$(BF_3)_n$ complex in which the -CH=O...BF_3 ligand is farthest removed from the C(9)-O...BF_3 moiety[8]. The hydroxyl group in 11a was oxidized (CrO_3-pyridine) to yield ketone 12a, which upon removal of the protecting groups of the hydroxyls at C(8) (DDQ, CH_2Cl_2, H_2O) and C(13) (Zn/THF-Na_2HPO_4 (buffer)[9] led to the formation of product 13b. The NMR spectrum of 13b showed it to be an solvent-dependent equilibrium[10] mixture of three compounds, namely, the hydroxy ketone 13b and the corresponding two hemiacetals, one of which is represented by 11-demethylsesbanimide 2c.

For the preparation of sesbanimide A, coupling of aldehyde 9 was initially attempted with allylsilane 10b (BF_3). In this case the presence of the methyl group in the silane necessitates the application of higher temperatures (above -60°C). Under these conditions, however, the substrate molecule (9) was not stable. The reactivity of the allylsilane for the coupling could be

enhanced by the use of derivative 10c. The condensation of 10c with 9 let to the formation of two diastereomers (in the ratio 1.7 : 1) corresponding to structure 11b. Once again, the stereochemistry of the C(10)-OH in 11b is assigned on the basis of the mechanism discussed earlier. The diastereomers were separated chromatographically and the major alcohol oxidized (CrO_3--pyridine) to ketone 12b. Assignment of configuration of the C(11)-methyl group in this ketone is derived from the reactions described in the sequel. When the C(8)-OH and the C(13)-OH in 12b are liberated by sequential reactions with DDQ/CH_2Cl_2/H_2O and AcOH/THF/H_2O, respectively, the hydroxy ketone 13d is formed which forms crystalline hemiacetal 2b, m.p. 154°-156°C. The NMR spectrum of this product, in $CDCl_3$ is identical to that of natural sesbanimide A[3a,10]. The optical rotation ($[\alpha]_D^{20}$) of 2c has a value of -52° (c 0.32, $CHCl_3$) which is opposite to that observed for natural sesbanimide A[10]. These results lead to the conclusion that 2b, whose 7R,8S, 9R,10S,11S-configuration is known from its synthesis, is the antipode of natural sesbanimide A. It therefore follows that the absolute stereochemistry of the natural alkaloid is established as 7S,8R,9S,10R,11R.

Having developed the synthetic scheme for 7R,8S,9R,10S,11S-sesbanimide (2b) the synthesis of the natural alkaloid was undertaken. The 7S,8R,9S-diol 15 (Scheme B) required for this purpose was prepared from D-xylose by a modification of the literature procedure[11] employing construction of the glutarimide ring following the method used for the synthesis of 5b (D-xylose → 14 → 15). Since 15 is the antipode of diol 6b, a sequence of chemical transformations as described in Scheme A led to (the synthesis of) (+)-7S,8R,9S,10R,11R sesbanimide A (2a) which was identical in all respects to the natural alkaloid.



Scheme B

In view of the fact that the evaluation of antitumour activity of sesbanimide A has been hampered due to its limited availability from natural sources, the development of a chemical synthesis opens the way for such evaluation and, in addition, provides potential access to modified sesbanimides for structure-activity relationship studies. Application of the generalized version of scheme A to the synthesis of sesbanimide analogues, especially those involving modifications in the B and C regions is being actively pursued in our laboratory.

EXPERIMENTAL

All m.ps. are uncorrected. IR spectra were recorded on a Perkin Elmer 1310 spectrophotometer. The absorptions are given in cm^{-1}. NMR spectra were run on Bruker WM 250 and AC 200 instruments. Unless stated otherwise, IR and NMR spectra were taken in $CHCl_3$ and $CDCl_3$, respectively. Mass spectra were obtained with a Varian Matt-711 spectrometer. Optical rotations were measured on a Perkin Elmer 241 polarimeter.

Unsaturated ester 4.
A suspension of aldehyde 3[6] (monohydrate, 17.28 g, 90 mmol) and methyl triphenylphosphoranylidene

acetate (31.8 g, 95 mmol) in toluene (600 ml) was refluxed with removal of water for 3 hours. Evaporation of the solvent and crystallisation of the residue from methanol produced 4 (E-isomer) as colourless needles (14.28 g, 69%). Removal of the $Ø_3PO$ from the filtrate (EtOAc) and chromatography yielded the Z-isomer (1.66 g, oil). 4 (E-isomer): m.p. 164-164.5°. IR: 1725, 1670. ^{1}H NMR: 3.85 (s, broad, H_2), 3.75 (m, OCH_3, H_3), 3.83 (d x d, J = 11.5, 2.0, H_{1a}), 4.20 (d x d x d, J = 11.5, 2.0, 1.2, H_{1b}), 4.34 (d x d, J = 4.5, 1.9, H_8), 4.77, 4.85, 5.15 and 5.28 (4 acetal protons, J = 6.3), 6.20 (d x d, J = 16.0, 1.9, H_6), 6.92 (d x d, J = 16.0, 4.5, H_5). MS: Found: 230.0773. Calc. for $C_{10}H_{14}O_6$: 230.0756. $[\alpha]_D$: -12.5° (c 2.02, $CHCl_3$). Found: C, 51.9; H, 5.0; $C_{10}H_{14}O_6$ requires: C, 52.17; H, 6.13. 4 (Z-isomer): IR: 1715, 1655. ^{1}H NMR: 3.42 (s, H_2), 3.64 (s, OCH_3), 3.80 (d x d, Y = 12.6, 1.7, H_{1b}), 3.95 (s, H_3), 4.15 (d, J = 12.6, H_{1b}), 4.68, 4.84, 5.11 and 5.22 (4 acetal protons, J = 6.3), 5.25 (m, H_4), 5.92 (d x d, J = 11.7, 1.4, H_6), 6.38 (d x d, J = 11.7, 6.9, H_5).

t-Butyl carbamoylacetate

A mixture of t-butyl cyanoacetate (100 g), MnO_2 (200 g) (freshly prepared from $MnCl_2$ and $KMnO_4$[12]) and water (24 ml) in p.dioxane (1 l) was stirred and refluxed during 7 hours. The catalyst was removed by filtration (Celite) and washed twice with p-dioxane. Evaporating the solvent and crystallisation from EtOAc/hexane yielded t-butyl carbamoylacetate as colourless needles (26.2 g). 45 g of starting material was recovered from the filtrate by distillation. Yield: 23% (42% based upon recovered t-butyl cyanoacetate). M.p.: 88-88.5°. IR: 3500, 3400, 3350, 1720, 1680 and 1580. ^{1}H NMR: δ 1.45 (s, 9H), 3.23 (s, 2H), 6-7.5 (br. 2H). Found: C, 52.8; H, 8.2; N, 8.8; $C_7H_{13}NO_3$ requires: C, 52.82; H, 8.23; N, 8.80.

Glutarimides 5a and 5b

Potassium-t-butoxide (5.6 g, 50 mmol) was added to a solution of t-butyl carbamoylacetate (9.54 g, 60 mmol) in THF (250 ml) at 0° and the mixture was stirred until the butoxide had dissolved. Powdered 4 (12.65 g, 55 mmol) was added and the mixture was stirred at 0° during 4 hours. Additional butoxide (0.56 g, 5 mmol) was added, followed after 1 hour, by another 5 mmol portion. To suppress elimination reactions in starting ester 4, excess butoxide should be avoided. After a total reaction time of 6 hours acetic acid (3.6 gr, 60 mmol) was added. Extractive work-up (H_2O, EtOAc) yielded 5a as a syrup (ca 2 : 1 mixture of isomers), which was hydrolysed, without further purification, by treatment with trifluoroacetic acid (80 ml) during 1.5 hour at room temperature. The dark solution was evaporated and the residue dissolved in methanol, the solvent removed under reduced pressure and the resulting residue heated in DMF (80 ml). At this stage evolution of CO_2 was observed. Cooling and addition of ether gave 78% 5b as a white solid (11.0 g). M.p. 254-255° (H_2O). IR (KBr): 3260, 1730, 1705. ^{1}H NMR: δ 2.37 (d x d, H_{3ax}, J = 18.0, 11.3), 2.49 (d x d, H_{5ax}, J = 17.0, 9.5), 2.6 (m, H_4 + H_{3eq}), 2.96 (m, H_{3eq}), 3.38 (d x d, J = 8.0, 1.7, H_7), 3.53 (s, $H_{8/9}$), 3-59 (s, $H_{9/8}$), 3.81 (d x d, J = 12.7, 1.8, H_{10a}), 4.18 (d, J = 12.7, H_{10b}), 4.71 (m, 2 x O-CH-O), 5.15 (d, J = 6.3, O-CH-O), 5.22 (d, J = 6.4, O-CH-O). 7.92 (broad, N-H). MS: Found: 257.0893. Calc. for $C_{11}H_{15}NO_6$: 257.0887. $[\alpha]_D$: -10.1° (c 1.01, DMSO). Found: C, 51.4; H, 6.0; N, 5.6; $C_{11}H_{15}NO_6$ requires: C, 51.36; H, 5.88; N, 5.44.
5a In a small-scale reaction one of the isomeric t-butyl esters 5a was obtained as a crystalline compound. M.p. 192-197° (MeOH). IR (KBr): 3200, 1735, 1700. ^{1}H NMR: δ 2.48 (d x d, J = 17.8, 4.1, H_{5eq}), 2.72 (d x d, J = 17.8, 5.4, H_{5ax}), 3.00 (m, H_4), 3.43 (d, J = 9.4, H_7), 3.51 (s, $H_{8/9}$), 3.63 (s, $H_{9/8}$), 3.8 (m, H_3 + H_{10a}), 4.15 (d, J = 12.6, H_{10b}), 4.7 (d + d, J ≈ 6, 2 x O-CH-O), 5.17 (d + d, J ≈ 6, 2 x O-CH-O), 8.34 (N-H). MS: Found: 357.1446. Calc. for $C_{16}H_{23}NO_8$: 357.1469.

Acetal ring opening of 5b

Acetal 5b (10.28 g, 40 mmol) was added to an ice-cold mixture of acetic acid (18 ml, acetic anhydride (20 ml) and sulfuric acid (0.3 ml, 95%) and the resulting solution stirred during 2 hours at 0°C. The reaction mixture was diluted with cold water and extracted three times with $CHCl_3$. The solid residue obtained after drying and evaporating the solvent, was recrystallized from methanol to provide 6a (13.16 g, 91.5%). M.p. 132-134°. IR : 3380, 1740, 1710. ^{1}H NMR: δ 2.1 (s, CH_3C=O), 2.2-3.05 (glutarimide protons), 3.37 (d, J = 7.9, H_7), 3.71 (s, H_8), 3.86 (d x d, J = 6.7, 6.4, H_9), 4.13 (d x d, J = 11.4, 6.3, H_{10a}), 4.28 (d x d, J = 11.4, 6.8, H_{10b}), 4.74 (d, J = 6.3, O-CH-O), 5.15 (d, J = 6.3, O-CH-O), 5.28 (d, J = 6.4, $-CH_2O$-Ac), 5.45 (d, J = 6.4, $-CH_2O$Ac), 7.96 (N-H). $[\alpha]_D$: -21.7° (c 2.0, $CHCl_3$). Found: C, 50.0; H, 6.0; N, 4.1; $C_{15}H_{21}NO_9$ requires: C, 50.14; H, 5.89; N, 3.90.

Glutarimide diol 6b

A solution of sodium (0.9 g, 39.1 mmol) in abs. methanol (100 ml) was diluted with $CHCl_3$ (150 ml) and cooled in an ice-salt mixture. Di-acetate 6a (10.77 g, 30 mmol) was added, and the mixture stirred during 90 min at -18 to -10°. Addition of acetic acid (2.4 g, 40 mmol), concentration and stirring with methanol gave diol 6b (6.33 g, 86%). M.p. 207-208° (H_2O). IR (KBr): 3300-3400, 3180, 3080, 1700. ^{1}H NMR (d_6-DMSO): δ 2.0-2.7 (glutarimide protons) 3.36 (d, J = 6.6, H_7), 3.4-3.6 (m, $H_{8,9,10}$), 4.67 (d, J = 6.0, O-CH-O), 4.7 (broad, OH), 4.78 (d, J = 7.9, OH), 4.99 (d, J = 6.0, O-CH-O), 10.77 (N-H). $[\alpha]_D$: +3.6° (c 0.50, DMSO). Found: C, 49.1; H, 6.2; N, 5.9; $C_{10}H_{15}NO_6$ requires: C, 48.98; H, 6. 7; N, 5.71.

3,4-Dimethoxybenzylideneacetal 7

A mixture of powdered diol 6b (2,45 g, 10 mmol), 3,4-dimethoxybenzaldehyde (4.98 g, 30 mmol) and p.TsOH (monohydrate, 0.14 g) in toluene (300 ml) was stirred and refluxed with azeotropical removal of water, during 5 hours. The suspension was cooled and filtered, yielding 3.90 g acetal 7 (98.7%) as a white solid. M.p. 229-232°. IR: 3380, 1710. ^{1}H NMR: δ 2.3-3.0 (glutarimide protons), 3.47 (d x d, J = 7.6, 1.6, H_7), 3.57 (d, J = 1.2, H_8), 3.83 (m, H_9), 3.88 (s, OCH_3), 3.91 (s, OCH_3), 4.06 (d x d, J = 12.8, 1.9, H_{10a}), 4.33 (d x d, J = 12.8, 1.2, H_{10b}), 4.77 (d, J = 6.4, O-CH-O), 5.23 (d, J = 6.4, O-CH-O), 5.50 (s, CH-Ar), 6.83 (d, J = 8.1, Ar-H), 6.97 (d, J = 8.1, Ar-H), 6.99 (s, Ar-H), 7.82 (N-H). Found: N, 3.7; $C_{19}H_{23}NO_8$ requires N, 3.65.

3,4-Dimethoxybenzylether 8

Diethylaluminium chloride (20 ml of a 1 M solution in toluene) was added dropwise to a stirred suspension of 7[11] (1.572 g, 4 mmol) in a mixture of CH_2Cl_2 (120 ml) and triethylsilane (4 ml) at -60°. The reaction mixture turned yellow, and after stirring for 90 min. at -55° all the solid material went into solution. The reaction was quenched with Et_3N (6 ml), followed by ethanol (5.5 ml). Stirring was continued during 2 hours. At 0° the mixture was diluted with hexanes (75 ml) and filtered over Celite. The filtrate was applied to a column (silicagel 60, packed with 1% ethanol in CH_2Cl_2). Eluting with consecutively 1%, 3%, 6% and 10% ethanol in CH_2Cl_2 gave starting material 7 (0.130 g) and dimethoxybenzylether 8 (1.022 g, 64.5%), m.p. 205-206° (etnanol). IR: 3370, 1730 (sh), 1710. ^{1}H NMR: δ 1.80 (broad, OH), 2.1-3.0 (glutarimide protons), 3.31 (d, J = 6.5, H_7), 3.50 (s, H_8), 3.7-4.0 (m, H_9, J_{10a}, H_{10b}), 3.87 (s, OCH), 3.89 (s, OCH_3), 4.45 (d, J = 11.7, OCH_3Ar), 4.75 (d, J = 6.3, H_{14a}), 4.76 (d, J = 11.5, OCH_bAr), 5.20 (d, J = 6.3, H_{14b}), 6.8-6.9 (m, 3H-Ar), 7.75 (N-H). MS: Found: 395.1580. Calc. for $C_{19}H_{25}NO_8$: 395.1524. $[\alpha]_D$: -35.8° (c 1.0, DMSO). Found: C, 57.6; H, 6.5; N, 3.7. $C_{19}H_{25}NO_8$ requires: C, 57.71; H, 6.37; N, 3.54.

Oxidation of 8[13]

Pyridine (1.29 ml, 16 mmol) was added dropwise to a suspension of CrO_3 (0.8 g, 8 mmol) in a mixture of CH_2Cl_2 (8 ml) and DMF (2 ml) and stirred for 15 min. at room temperature. A solution of alcohol 8 (0.79 g, 2 mmol) in hot DMF (4 ml) was cooled to room temperature, diluted with 20 ml CH_2Cl_2 and added to the chromium reagent. Acetic anhydride (0.75 ml, 8 mmol) was added and after stirring for 8 min. the reaction was quenched with ethanol (1 ml). The reaction mixture was poured into ethyl acetate (150 ml), and filtered over a short silica column to remove the chromium salts (elution with 200 ml 6% ethanol in ethylacetate). Removal of the solvents (0.1 mm, < 40°) and flash chromatography (silica, 1%, 2% and 3% ethanol in ethyl acetate) gave 9 as a colourless glass (0.51 g, 64,5%). IR: 3370, 1730, 1710. ^{1}H NMR: δ 2.0-3.0 (glutarimide protons), 3.34 (d, J = 7.0, H_7), 3.86 (s, OCH_3), 3.88 (s, OCH_3), 3.6-4.0 (m, H_8, H_{10}), 4.09 (s, H_9), 4.32 (d, J = 11.5, O-CH-Ar), 4.63 (d, J = 11.5, O-CH-Ar), 4.81 (d, J = 6.3, H_{14a}), 5.32 (d, J = 6.3, H_{14b}), 6.83 (m, 3H-Ar), 8.01 (N-H), 9.74 (s, H_{10}). MS: Found: 393.1423. Calc. for $C_{19}H_{23}NO_8$: 393.1423.

Allylsilane 10a

2,2,2-Trichloroethyl chloroformate (2,54 g, 12 mmol) was added dropwise to a solution of 2-hydroxymethyl allylsilane[14] (1.44 g, 10 mmol) and pyridine (2 ml) in CH_2Cl_2 (15 ml) at 15°. After 1 hour at room temperature the reaction mixture was diluted with ether and extracted with water and with a $CuSO_4$ solution. The residue obtained after drying and removal of the solvents was purified by flash chromatography (silica, 0.5-2% ethylacetate in hexanes) yielding 3.45 g 10a as an oil (96%). IR: 1760, 1640. ^{1}H NMR: δ 0.05 (s, 9H), 1.55 (s, $-CH_2$-Si), 4.55 (d, J = 1, CH_2-O), 4.75 (s, CH_2CCl_3), 4.80 (m, $=CH_2$), 4.95 (m, $=CH_2$).

BF_3 catalyzed coupling of 9 with 10a

BF_3 etherate (0.38 ml, 3.0 mmol) was added dropwise to a stirred solution of aldehyde 9 (0.23 g, 0.82 mmol) in CH_2Cl_2 (6 ml) at -78°. After 15 min., allylsilane 10a (0.288 g, 0.8 mmol) was added and the mixture was stirred at -78° for 4 hours. The reaction was quenched with 1.5 ml Et_3N, followed after 5 min. by 0.5 ml ethanol. Extractive work up (pH 7) and flash chromatography (silica, ethylacetate) yielded alcohol 11a (glass, 0.232 g, 58.4%) as a single isomer. IR: 3365, 1760, 1705. ^{1}H NMR: δ 2.0-3.0 (glutarimide protons), 2.13 (d x d, J = 13.8, 9.3, H_{11a}), 2.25 (d, J = 3.6, OH), 2.70 (d, J = 13.8, H_{11b}), 3.22 (d, J = 7.3, H_7), 3.32 (d, J = 9.0, H_9), 3.72 (s, H_8), 3.83 and 2,86 (2 x s, OCH_3), 4.02 (d x d, J = 9.3, 9.0 (after D_2O-exchange, H_{10}), 4.60 (d, J = 11.8, -CH-Ar), 4.68 (m, H_{13}, H_{14a}), 4.76 (s, CH_2-CCl_3), 4.81 (d, J = 11.8, CHAr), 5.13 (d, J = 6.2, H_{14b}), 5.15 (s, H_{16a}), 5.31 (s, H_{16b}), 6.7-6.9 (m, 3H-Ar), 7.93 (N-H).

Oxidation of alcohol 11a

Compound 11a (0.232 g, 0.36 mmol) was oxidized with CrO_3 (1.5 mmol) as described for the synthesis of aldehyde 9. Flash chromatography (silica) with ethylacetate/hexanes gave ketone 12a (glass, 0.164 g, 71.3%). IR: 3370, 1760, 1710. H NMR: δ 2.0-2.9 (glutarimide protons), 3.27 (d, J = 7.4, H_7), 3.47 (d, J = 18.4, H_{11a}), 3.70 (d, J = 18.4, H_{11b}), 3.84 and 3.87 (2s, OCH_3), 3.92 (s, H_8), 4.10 (s, H_9), 4.22 (d, J =11.6, CH_aAr), 4.62 (d, J = 11.6, CH_bAr), 4.72 (d, J = 6.3, H_{14a}), 4.73 (s, CH_2CCl_3), 4.76 (s, 2H_{13}), 5.08 (s, H_{16a}), 5.27 (d, J = 6.3, H_{14b}), 5.36 (s, H_{16b}), 6.8 (m, 3H Ar), 7.76 (N-H).

Debenzylation of 12a

Compound 12a (0.159 g, 0.248 mmol) and DDQ (0.114 g, 5 mmol) were stirred in a mixture of CH_2Cl_2 (3 ml) and water (0.1 ml) during 2 hr at room temperature. Removal of the water and flash chromatography (silica, CH_2Cl_2/ethanol) yielded 13a (glass, 0.081 g, 66.8%). IR: 3370, 1660, 1725 (sh), 1708. ^{1}H NMR: δ 2.17 (s, OH), 2.3-3.0 (glutarimide protons), 3.4 (m, H_7 + 2H_{11}), 3.98 and 4.10 (2s, H8 + H9), 4.8 (m, 2H_{13}, H_{14a}, CH_2CCl_3), 5.14 (s, H_{16a}), 5.21 (d, J = 6.3, H_{14b}), 5.36 (s, H_{16b}), 7.93 (N-H).

11-Demethyl sesbanimide 13b

2,2,2-Trichloroethyl ester 13a (81 mg, 0.166 mmol) was stirred with a mixture of zinc dust (0.4 g) in THF (2.5 ml) and KH_2PO_4 (0.5 ml, 1H, pH6) for 3 hours at room temperature. The reaction mixture was diluted with CH_2Cl_2 and dried over Na_2SO_4. Flash chromatography (silica, 2%-10% ethanol in CH_2Cl_2) yielded 13b (glass, 0.037 g, 72%). This product is completely insoluble in $CDCl_3$. In d_6-DMSO only the ring opened form 13b is present. In $CDCl_3$, containing 10% CD_3OD, 2c and 13b appeared in the ratio 5 : 3. (2c as a mixture of c-10 isomers). IR (KBr): 3200-3600, 1725-1690. ^{1}H NMR (d_6-DMSO): δ 2.2-2.8 (glutarimide protons), 3.3-3.4 (m, H_7, 2H_{11}), 3.85 (m, H_8, 2H_{13}), 4.26 (s, H_9), 4.72 (d, J = 6.4, H_{14a}), 4.83 (d x d, J = 0.7, 0.9, H_{16a}), 4.85 (m, OH), 5.11 (d, J = 6.4, H_{14b}), 5.12 (d x d x d, J = 0.7, 0.7, 0.8, H_{16b}), 5.27 (d, J = 8.4, C-8 OH), 9.5 (N-H).

^{1}H NMR ($CDCl_3$ + 10% CD_3OD): characteristic for 2c is the AB-system for the C-13 protons: δ 4.27 and 4.75 (J ≅ 12.9). ^{13}C NMR: δ 198 (s, C 10). MS: Found: 295.1040 (M-18). Calc. for $C_{14}H_{17}NO_6$: 295.1056, $[\alpha]_D$ = 0° in $CHCl_3$/5% methanol; +10.5° in $CHCl_3$/10% methanol; and +22.5° in methanol.

Allylsilane 10b
2-Trimethylsilylmethyl-2-buten-1-ol (10d) was prepared[16] from ethyl 3-(trimethylsilyl) propionate[15] and acetaldehyde. 10d (1.58 g, 10 mmol) was allowed to react with 2,2,2-trichloroethyl chloroformate as described for 10a. Chromatography (silica, EtOAc/hexanes 1:50) gave 95% 10b as an oil. IR: 1760, 1660. ^{1}H NMR: δ 0.05 (s, 9H), 1.50 (d, J = 6.5, CH_3), 1.52 (s, CH_2Si), 4.50 (broad, OCH_2C=C), 4.69 (s, CH_2CCl_3), 5.48 (q, J = 6.5, C=CH).

Allylsilane 10c
A solution of alcohol 10d[15] (1.58 g, 10 mmol), tert. butylmethylsilyl chloride (1.81 g, 12 mmol), di-isopropylethyl amine (1.2 ml) and DMAP (5 mg) in CH_2Cl_2 (15 ml) was stirred overnight at room temperature. Concentrating, hexanes/water extraction and chromatography (silica, 0.5 → 3% ethylacetate in hexanes) gave 2.53 g 10c as a colourless liquid (93%). IR: 1640. ^{1}H NMR: δ 0.06 (s, 9H), 0.96 (s, 9H), 1.55 (s, CH_2Si), 1.63 (d, J = 7, CH_3), 4.02 (m, CH_2O), 5.44 (broad quartet, J = 7).

Coupling of allylsilane 10c with aldehyde 9
$BF_3.Et_2O$ (0.317 ml, 2.5 mmol) was added dropwise to a solution of 9 (0.197 g, 0.5 mmol) in CH_2Cl_2 (5 ml) at -90°. After stirring for 10 minutes allylsilane 10c (0.179 g, 0.7 mmol) was added and stirring was continued for 1 hour (bath temperature -90 to -80°). The reaction was quenched with Et_3N (1.4 ml) and diluted with CH_2Cl_2 and water. Extractive work up (pH 7, HOAc) and flash chromatography (consecutively, silica, EtOAc/hexanes → 1:1, 1:2) yielded two diastereomeric alcohols 11b.
11S-11b, oil, 0.095 g, (32%). IR: 3360, 1720 (sh), 1705. ^{1}H NMR: δ 0.13 (s, $SiCH_3$), 0.15 (s, $SiCH_3$), 0.92 (s, 9H), 1.24 (d, 3H, H_{15}), 1.8-2.8 (glutarimide protons), 3.01 (m, H_{11}), 3.09 (d, J = 7.3, H_7), 3.29 (d, J = 9.7, H_9), 3.68 (s, H_8), 3.82 and 3.87 (OCH_3), 3.9 (m, H_{10}), 3.93 (d, J = 11.3, H_{13a}), 4.21 (d, J = 11.3, H_{13b}), 4.44 (d, J = 10.1, OH), 4.56 (d, J = 6.0, H_{14a}), 4.63 (d, J = 11.8, CH_aAr), 4.86 (d, J = 11.8, CH_bAr), 5.00 (s, broad, H_{16a}), 5.09 (s, broad, H_{16b}), 5.12 (d, J = 6, H_{14b}), 6.78 (d, J = 8.6, HAr), 6.9 (m, 2 HAr), 7.69 (N-H).
11R-11b, oil, 0.055 g (18.5%). IR: 3360, 1725 (sh), 1705. ^{1}H NMR: δ 0.11 (s, $SiCH_3$), 0.13 (s, $SiCH_3$), 0.91 (s, 9H), 1.03 (d, 3H, J = 7.1, H_{15}), 1.8-2.9 (glutarimide protons), 2.8 (m, H_{11}), 3.20 (d, J = 7.2, H_7), 3.44 (d, J = 9.3, H_9), 3.71 (s, H_8), 3.82 and 3.87 (OCH_3), 3.9 (m, H_{10}), 4.05 (d, J = 12.1, H_{13a}), 4.18 (s, OH), 4.22 (d, J = 12.0, H_{13b}), 4.59 (d, J = 11.8, CH_aAr), 4.67 (d, J = 6.1, H_{14a}), 4.85 (d, J = 11.7, CH_bAr), 5.06 (s, H_{16b}), 5.11 (s, H_{16b}), 5.16 (d, J = 6.1, H_{14b}). 6.79 (d, J = 8.6, HAr), 6.88 (m, 2 HAr), 7.69 (N-H).

Ketone 12b
Alcohol 11b (11S-isomer, 50 mg, 0.085 mmol) was oxidized with CrO_3 (0.5 mmol) as described for the synthesis of aldehyde 9. Flash chromatography (silica, ethylacetate/hexanes) gave ketone 12b (glass, 0.030 g, 59%). IR: 3370, 1710. ^{1}H NMR: δ 0.05 (s, 6H), 0.90 (s, 9H), 1.20 (d, J = 6.9, H_{15}), 2.0-2.9 (glutarimide protons), 3.23 (d, J = 6.9, H_7), 3.62 (q, J = 6.9, H_{11}), 3.83 (s, H_8), 3.84 and 3.87 (OCH_3), 3.94 (d, J = 9.5 H_{13a}), 4.13 (d, J = 1.3, H_9), 4.20 (d, J = 9.5, H_{13b}), 4.25 (d, J = 11.6, CH_aAr), 4.59 (d, J = 11.4, CH_bAr), 4.65 (d, J = 6.3, H_{14a}), 4.75 (s, H_{16a}), 5.15 (s, H_{16b}), 5.21 (d, J = 6.3, H_{14b}), 6.85 (m, 3 HAr), 7.78 (N-H). MS: Found: 591.2847. Calc. for $C_{30}H_{55}NO_9Si$: 591.2864.

Debenzylation of 12b
A mixture of 12b (30 mg, 0.051 mmol) and DDQ (50 mg) in CH_2Cl_2 (1 ml), THF (0.5 ml) and water (0.1 ml) was stirred at room temperature for 2 hours. Chromatography (CH_2Cl_2/ethanol) gave 13c as a glass (0.013 g, 58%). IR: 3360, 1730 (sh), 1705. ^{1}H NMR: δ 0.05 (s, 6H), 0.89 (s, 9H), 1.17 (d, J = 6.9, H_{15}), 2.3-3.0 (glutarimide protons), 2.62 (d, J = 9.2, OH), 3.36 (d, J = 8.1, H_7), 3.51 (q, J = 6.9, H_{11}), 3.99 (d, J = 9.1, H_8), 4.15 (s, H_{13}, H_9), 4.69 (d, J = 6.3, H_{14a}), 4.82 (s, H_{16a}), 5.15 (s, H_{16b}), 5.16 (d, J = 6.3, H_{14b}), 8.04 (N-H).

(-)-Sesbanimide A (2b)
13c (0.026 g, 0.058 mmol) was stirred over night in a mixture of acetic acid (1 ml), THF (0.5 ml) and water (0.5 ml). The solvents were removed in vacuo and the residue was coevaporated three times with ethylacetate. The residue was crystallized from CH_2Cl_2/ether, yielding 0.016 g 2b (86%). M.p.: 154-156°. IR: 3540, 3370, 2770, 1730 (sh), 1710. ^{1}H NMR: δ 1.19 (d, J = 6.7, H_{16}), 2.37 (d x d, J = 16.2, 9.1, H_{3a}), 2.47 (d x d, J = 17.0, 9.2, H_{5a}), 2.60 (m, H_4), 2.75 (d x d x d, J = 17.0, 4.4, 1.5), 2.90 (d x d x d, J = 16.8, 4.0, 1.4), 3.34 (d, J = 8.4, H_7), 3.55 (d, J = 7.2, 8-OH), 3.58 (s, H_9), 3.99 (d, J = 7.2, H_8), 4.21 (S, 10-OH), 4.46 (d x d, J = 13.0, 1.6), 4.55 (d x d, J = 13.0, 2.0), 4.77 (d, J = 6.2, H_{14a}), 4.95 (d, J = 2.4, H_{16a}), 5.00 (d, J = 2.5, H_{16b}), 5.21 (d, J = 6.2, H_{14b}), 7.99 (NH). MS: Found: 309.1214. Calc. for $C_{15}H_{19}NO_6$ (M-18): 309.1212. $[\alpha]_D$: -52° (c 0.32, $CHCl_3$).

Glutarimide diol 15
Potassium t-butoxide (2.01 g, 18 mmol) was added to a solution of t-butyl carbamoyl acetate (3.2 g, 20 mmol) in THF (100 ml) at 0° and the mixture was stirred until the butoxide had dissolved. Compound 14[11] (7.164 g, 18 mmol) was added and stirring was continued for 3 hours. Additional butoxide (0.2 g, 1.8 mmol) was added, followed after 1 hour by a second portion (0.2 g, 1.8 mmol). After a total reaction time of 5 hours acetic acid (1.32 g, 22 mmol) was added. Extractive work up (water/ether) and removal of the solvents yielded a syrup, which was hydrolyzed with trifluoroacetic acid (30 ml) at room temperature (1.5 hour). Removal of the TFA, coevaporation with methanol and decarboxylation in DMF (30 ml) at 160° (5 min) gave 10 g of the crude dibenzyl ether of 15. Hydrogenation with Pd/C (0.30 g) in methanol (150 ml) for 4 hours, and removal of the catalyst (hot methanol) gave crystalline 15 (3.82 g, 86.5%), m.p. 208-209° (H_2O). Except for the sign of the rotation ($[\alpha]_D$ = -3.5°, c 0.37, DMSO) 15 was identical to 6b.

(+)-Sesbanimide A (2a)
Conversion of 15 to 2a was carried out via a sequence of reactions identical to the one employed for converting 6b to 2b, m.p. 154-156.5° $[\alpha]_D^{20}$ = + 56° (c 0.21). MS: Found: 309.1214, calc. for $C_{15}H_{19}NO_6$ (M-18): 309.1212.

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