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Synthesis of γ-Lactones from intermediate 2-(γ-Hydroxyacyl)-imidazoles by N-Methylation and Base-catalyzed C - C Bond Cleavage. Application to the Synthesis of (±)- Cavernosine.

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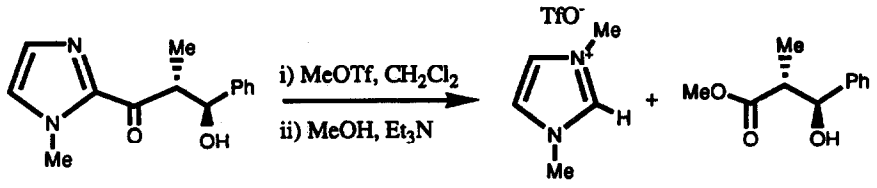
Abstract: Reaction of the allyl anions of *O*-trialkylsilyl-*N*-alkyl-2-(1'-hydroxyprop-2'-enyl)imidazoles with aldehydes and ketones gives products of α- and γ-attack. Greater steric hindrance in the anion (triisopropylsilyl vs t-butyldimethylsilyl) and in the aldehyde or ketone favours the γ-products. Sequential desilylation, *N*-methylation and treatment with base resulted in cleavage of these products to γ-lactones. The method was applied to the synthesis of (±)-cavernosine.

That the reactions of the carbonyl group in 2-acylimidazoles and their corresponding *N*-alkyl imidazolium salts are very different has been known since 1984.[1] The former behave as typical aromatic ketones whereas their salts are acylating agents i.e. they act like carboxylic acid derivatives. We have recently demonstrated the application of this dichotomous behaviour to the stereospecific synthesis of 3-hydroxy-3-phenylpropionic esters(Scheme 1).[2] In that study we showed that the β-hydroxy group does not compete with the external nucleophile (methanol) for attack on the carbonyl group of the salt, probably because of strain in the β-lactone that would result. Nevertheless, intramolecular acylation represented an attractive goal and we felt that success might be had with the γ-hydroxy analogues which should lead to less strained lactones.

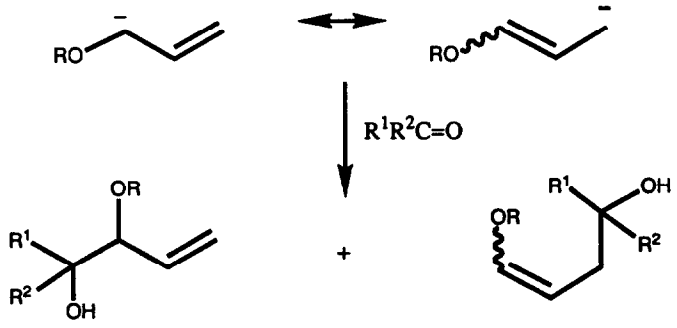


Scheme 1

Here we detail the synthesis of the desired γ-hydroxy *N*-alkyl-2-acylimidazoles and their conversion into γ-lactones[3] together with an application of the method to the synthesis of racemic cavernosine, a terpenoid γ-lactone responsible in part for the toxicity of the marine sponge, *Fasciospongia cavernosa*, to freshwater fish.[4]

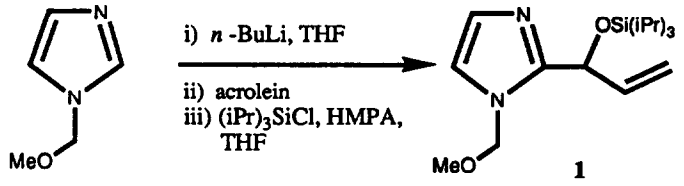
Results and Discussion

Since a route to γ-hydroxy ketones by the reaction of enolate anions with epoxides, formally analogous to the aldol reaction, seemed to have little precedent[5], the alternative approach of trapping the ambident anion of an allyl ether[6] with an aldehyde or ketone at the γ-position (Scheme 2) was adopted.



Scheme 2

Allyl silyl ethers were chosen as starting materials (a) because of the anticipated ready removal of the silyl group in the enol silyl ether product and (b) because the use of bulky groups on silicon should allow the normally favoured α-attack[7] to be countered by steric hindrance. Preliminary studies established that the *tert*-butyldimethylsilyl group was not big enough to overcome this bias but that the triisopropylsilyl group provided the necessary bulk.



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Scheme 3

Reaction of 2-lithio-*N*-methoxymethyl imidazole in THF with acrolein and then triisopropylsilyl chloride in a mixture of hexamethylphosphoramide (HMPA) and THF (1 : 20) at low temperatures gave the starting allyl silyl ether, **1**(Scheme 3).

Sec-butyllithium is the standard base for the deprotonation of allyl ethers[6] but for the bulky silyl ether **1** this proved too big so that ring deprotonation became competitive. Fortunately, **1** succumbed to the proton abstracting power of a combination of *n*-butyllithium and tetramethylethylenediamine (TMEDA). Generation and reaction of the resultant allyl anion at low temperature (-90 °C) was necessary in order to avoid 1,4 O -> C silyl shift.[7,8] Quenching the anion at - 90 °C with aldehydes and ketones gave good total yields of products (**2**,**3**) with generally the γ-product **2** predominating (Table 1) (Scheme 4). Cyclohexanones gave exclusively the γ - products in high yields. In nearly every case the γ : α ratio was better using the bulkier triisopropylsilyl derivative rather than the *tert*-butyldimethylsilyl one. Thus, the principal of using steric encumbrance to disfavour the normal α-attack seemed to be successful.

Conversion of the γ - products into their corresponding lactones **4** was carried out without purification of the intermediates (Scheme 5). Desilylation by tetrabutylammonium fluoride (TBAF)[9] in aqueous THF at room temperature was followed by tlc and when the reactions were complete (15 - 30min)

Table 1. Reaction of the Anion of **1** with Aldehydes and Ketones

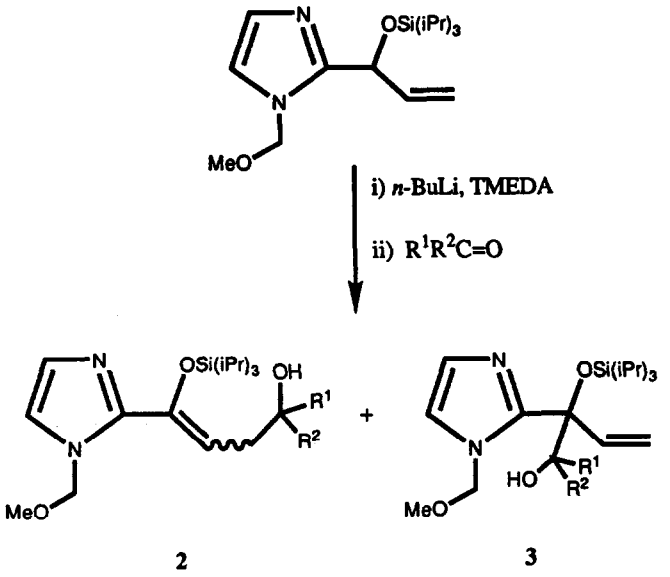
Carbonyl	R^1	R^2	Yieldof **2** (%)[a]	Yield of **3** (%)[a]
isobutyraldehyde	iPr	H	35 (42)	53 (32)
benzaldehyde	Ph	H	62 (57)	0 (0)
3-cyclohexene-1-carboxaldehyde	C_6H_9	H	40	37
acetone	Me	Me	42 (24)	24 (53)
isobutyl methyl ketone	iBu	Me	47 (17)	17 (49)
diethyl ketone	Et	Et	68	13
cyclohexanone	-$(CH_2)_5$-		70 (63)	0 (29)
2,6-dimethyl-cyclohexanone[b]	-$(C_5H_8Me_2)$-		85[c]	0
2,2,6-trimethyl-cyclohexanone	-$(C_5H_7Me_3)$-		89[c]	0

a: figures in brackets represent the yields from the corresponding TBDMS allyl ethers

b: mixture of *cis* - and *trans* -isomers

c: mixture of diastereoisomers

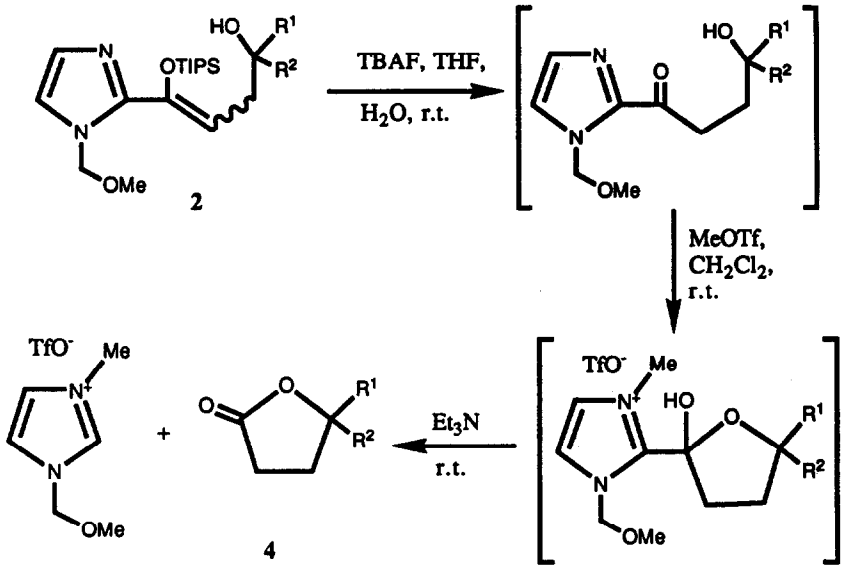
the ketones were freed from the residual reagent by filtration through a pad of silica gel. *N*-Methylation proceeded without difficulty using methyl triflate[10] (1 equivalent) in dichloromethane at room temperature and was deemed complete on total disappearance of the carbonyl absorption from the ir spectrum of the reaction mixture since the quaternised ketones existed entirely as the lactols. One equivalent of triethylamine was immediately added, instantly releasing the butyrolactones, which were isolated in high yields [> 90% except for the volatile 4,4-dimethyl (33%) and 4,4-diethyl (58%) congeners] after chromatography (silica gel). Known lactones had spectroscopic data in agreement with those reported in the literature.



Scheme 4

A interesting test of this new method of preparing butyrolactones lay in making the natural product, cavernosine **5**.[4] Dihydro- β -ionone **6**[11] was our starting point (Scheme 6). Addition of trimethylsilyl cyanide catalysed by zinc iodide[12] gave the silylated cyanohydrin **7** in 97% yield. Reduction of the cyano group with diisobutylaluminium hydride (DIBAL) required careful attention to reaction and work up conditions. Use of 4 equivalents of the reducing agent in toluene at 6 °C as described[13] led to overreduction to the amine **8** (47%); with 2 equivalents under milder conditions (- 60 °C followed by slow warming to room temperature overnight) the desired aldehyde **9** was obtained after hydrolysis of the intermediate imine with oxalic acid in 63% yield. With the superior work up described recently[14] the yield of **9** in this step rose to 71%.

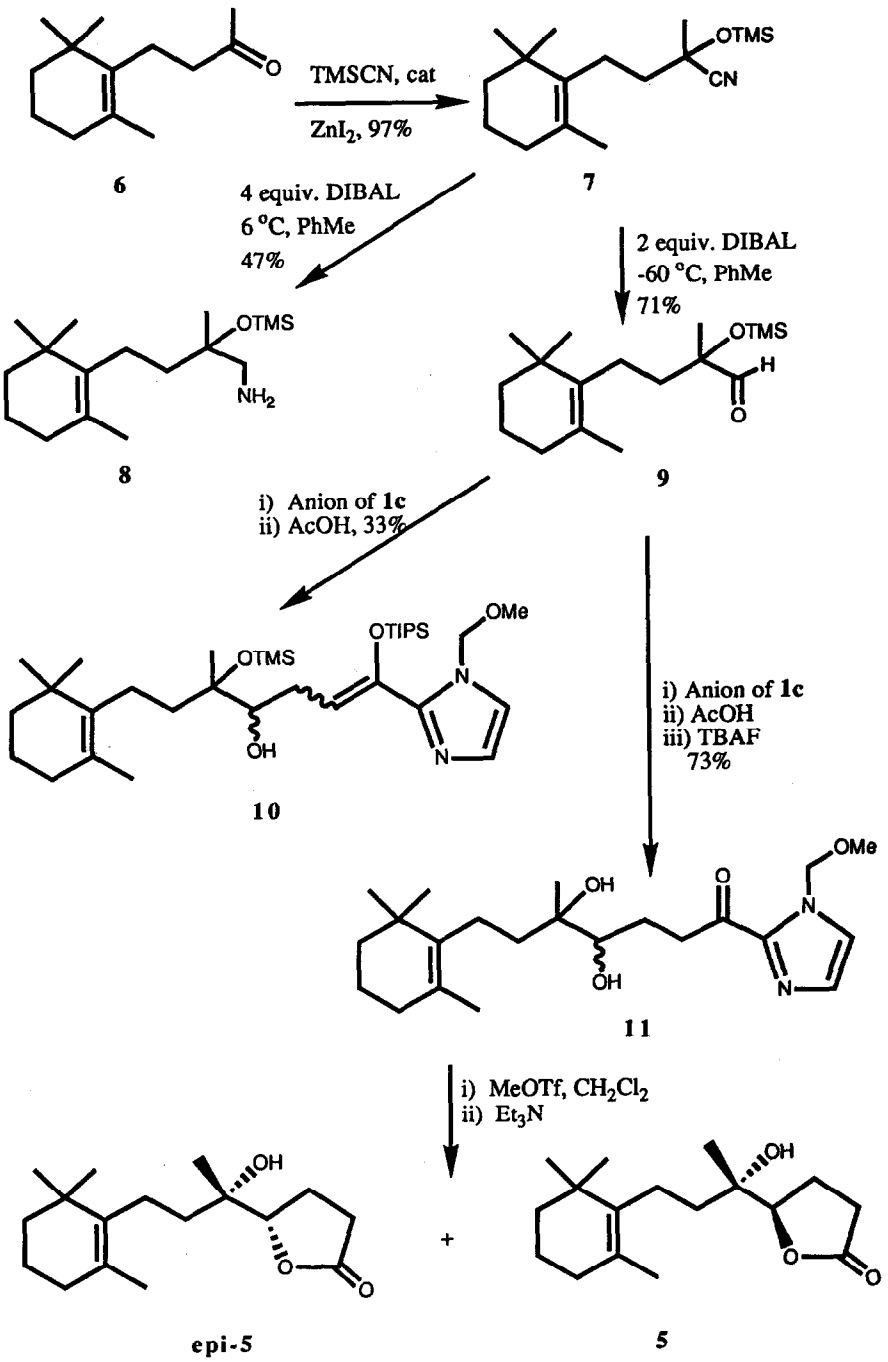
On addition of this aldehyde (1.5 - 2 equivalents) to the yellow solution of the anion of **1** the colour was discharged rapidly and tlc of the reaction mixture showed only one product spot together with excess



Scheme 5

aldehyde and some silyl enol ether derived by protonation. The γ-product could be isolated as a mixture of the two diastereoisomers of the bis-silyl derivatives (33%; 1.3 : 1) **10**. However, a better yield was obtained by desilylation immediately after work up to give the dihydroxyketones (73%; 1.5 : 1) **11**. None of the alternative α-product could be detected and this high regioselectivity was attributed again to steric bulk, this time at the tertiary α-centre of aldehyde **9**. The diastereoselectivity of the reaction was clearly not so satisfactory in spite of expectations.[15] The two diastereoisomers of dihydroxyketone **11** were not separated at this stage because cavernosine can be readily separated from its epimer.[4b]

Ketone **11** offered the possibility of producing two sizes of lactone after methylation and base treatment and therein lay one reason for its choice as a target molecule. However, only compounds with the smaller five-membered ring were detected in the IR spectrum of the reaction mixture (1777 cm^{-1}). The epimeric lactones were separated on silica gel and the 1.4 : 1 ratio was found to favour the *erythro*-product,


TMSCN, cat
ZnI2, 97%
OTMS
CN
6
7
4 equiv. DIBAL
6 °C, PhMe
47%
2 equiv. DIBAL
-60 °C, PhMe
71%
OTMS
NH2
OTMS
H
O
8
9
i) Anion of 1c
ii) AcOH, 33%
OTIPS
OMe
OTMS
OH
N
N
10
i) Anion of 1c
ii) AcOH
iii) TBAF
73%
OMe
OH
O
OH
N
N
11
i) MeOTf, CH2Cl2
ii) Et3N
OH
O
O
+
OH
O
O
epi-5
5

Scheme 6

cavernosine. The chemical shifts in the ^{1}H- and ^{13}C-NMR spectra of the racemic, *erythro* lactone agreed well with those reported by the Swiss group.[4b] Small but clear differences in the 500 MHz ^{1}H NMR spectra of the two epimers allowed differentiation between cavernosine and epicavernosine. Thus, the *gem*-dimethyl group singlets are separated in the spectrum of cavernosine (0.98 and 0.99ppm) but overlap (1.00 ppm) in that of its epimer; the lactone CH peak is at higher field in the former (4.35 *versus* 4.41 ppm) whereas the reverse is true for the methyl group on the tertiary alcohol (1.34 *versus* 1.18 ppm).

Experimental

Melting points were determined on a Kofler hot-stage or Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 881 spectrophotometer as thin films or as solutions in CH_2Cl_2. ^{1}H and ^{13}C NMR spectra were recorded on Jeol FX90Q, Jeol GSX 270, or Bruker WM 500 instruments, using tetramethylsilane or chloroform as internal standards in $CDCl_3$ unless otherwise stated. Signals are quoted as singlet (s), doublet (d), triplet (t), quartet (q), sextet (sex), septet (sep), multiplet (m) and broad (br). Mass spectra were recorded on a VG Micromass 7070B machine by the EI method.

Preparative gravity column chromatography was performed on Crosfield Sorbsil C60 silica gel. Petroleum refers to light petroleum of b.p. 40 - 60 °C. Ether refers to diethyl ether. Ether and THF were distilled from sodium and potassium metal respectively under argon immediately prior to use. Triethylamine and TMEDA were distilled from calcium hydride and stored under an argon atmosphere. Dichloromethane was distilled from phosphorus pentoxide under argon just prior to use. *n*-Butyllithium and *sec*-butyllithium were purchased from Aldrich Chemicals as solutions in hexanes and cyclohexane respectively. All other solvents and chemicals were purified by standard methods.

1-Methoxymethyl-2-(1'-triisopropylsilyloxyprop-2'-enyl)imidazole (1)

To a solution of *N*-methoxymethylimidazole (1.17 g, 10.43 mmol) in dry THF (30 ml) at -78 °C under argon was added *n*-butyllithium (1.6M in hexanes, 7.2 ml, 11.52 mmol) dropwise. The reaction mixture was stirred at this temperature for 1 h and then a solution of acrolein (1.1 ml, 922.9 mg, 16,5 mmol) in THF (2 ml) was added slowly. After 2 h at the same temperature a solution of triisopropylsilyl chloride (2.6 ml, 2.34 g, 12.18 mmol) in a mixture of HMPA (2 ml) and THF (9 ml) was added. The reaction was allowed to warm to room temperature and then stirred overnight. The solvent was removed under vacuum, the residue was suspended in ether and the suspension was filtered through a short silica gel pad using ether as eluent to

give the product as an oil (2.13 g, 65%) (Found: C, 62.67; H, 10.24; N, 8.24. $C_{17}H_{32}N_2O_2Si$ requires C, 63.02; H, 9.96; N, 8.65%); δ_H (270 MHz) 0.9 - 1.2 (21H, m, 3 x *i*-Pr), 3.3 (3H, s, OMe), 5.2 (1H, ddd, *J* 2Hz, *J'* 2Hz, *J"* 10Hz, CH_{cis}=), 5.3 (1/2 ABq, *J* 10Hz, 1/2 CH_2OMe), 5.5 (1H, ddd, *J* 2Hz, *J'* 2Hz, *J"* 17Hz, CH_{trans}=), 5.5 (1/2 ABq, *J* 10Hz, 1/2 CH_2OMe), 5.7 (1H, m, CHOSi), 6.1 (1H, ddd, *J* 4Hz, *J'* 10Hz, *J"* 17Hz, CH=), 6.9 (1H, s, ArH), 7.0 (1H, s, ArH); δ_C (67.5 MHz) 12 (CHSi), 18 (Me_2CH), 53 (OMe), 61 (NCH_2O), 112 (CH_2=), 120 (NCH), 128 (NCH), 138 (CH=), 148 (NCN); *m/z* 324 (M^+), 281 (M^+ - *i*Pr).

General Procedure for the Reaction of Aldehydes and Ketones with the Anion of 1

To a solution of **1** and TMEDA (both 0.03 M) in THF under argon at -78 °C was added *n*-butyllithium (1.6 M in hexanes, 1 equivalent) dropwise. The resultant yellow solution was stirred for at this temperature for 30 min before the temperature was lowered to -90°C and a cooled (to -78 °C) solution (0.2M) of the carbonyl compound(2 equiv.) in THF was added dropwise ensuring that the temperature of the reaction did not rise above -80 °C. The reaction was quenched after approximately 3 min with acetic acid and the mixture was allowed to warm to room temperature. The solvent was removed under vacuum and the resultant slurry was treated with dichloromethane and water. The aqueous layer was separated and the organic layer was washed with water (2 x) and dried. After filtration of the drying agent the solvent was evaporated and the oil was chromatographed on silica gel with the solvent designated.

2-(4'-Hydroxy-5'-methyl-1'-triisopropylsilyloxyhex-1'-enyl)-1-methoxymethylimidazole (**2a**)

The product was isolated from the reaction with isobutyraldehyde after elution from silica gel using ether as an oil (35%) (Found: M^+: 396.2802. $C_{21}H_{40}N_2O_3Si$ requires 396.2808); δ_H (90 MHz) 0.9 - 1.3 (27H, m, iPr_3Si + Me_2CH), 1.8 (1H, sex, C*H*Me_2), 2.2 (1H, br, OH), 2.5 (2H, t, *J* 7Hz, CH_2C=), 3.3 (3H, s, OMe), 3.45 (1H, m, C*H*OH), 5.2 (1H, t, *J* 7Hz, CH=), 5.3 (2H, ABq, 10Hz, NCH_2O), 7.0 (2H, ABq, *J* <1Hz, 2 x ArH); *m/z* 396 (M^+), 353 (M^+ - *i*Pr); earlier fractions contained the α-product **3a** as mainly one diastereoisomer as an oil (53%); δ_H (270 MHz) 0.8 - 1.3 (27H, m, iPr_3Si + Me_2CH), 1.9 (1H, m, C*H*Me_2), 3.3 (3H, s, OMe), 5.1 - 5.8 (5H, m, C*H*OH, CH_2OMe and $=CH_2$), 6.3 (1H, dd, *J* 10Hz, *J'* 17Hz, CH=), 6.9 (2H, s, 2 x ArH).

2-(4'-Hydroxy-4'-phenyl-1'-triisopropylsilyloxybut-1'-enyl)-1-methoxymethylimidazole (**2b**)

The product was isolated from the reaction with benzaldehyde after elution from silica gel using ether as an oil (62%); δ_H (270 MHz), 0.9 - 1.2 (21H, m, iPr_3Si), 2.0 (1H, br, OH), 2.7 - 2.85 (2H, m, CH_2C=), 3.1 (1H, s, OMe), 4.8 (1H, t, *J* 8Hz, C*H*OH), 5.14 (1H, t, *J* 8Hz, CH=), 5.16 (2H, ABq, *J* 11Hz,

NCH_2O), 6.95 (2H, ABq, *J* <1Hz, 2 x ArH), 7.2 - 7.4 (5H, m, Ph). This product was characterised as the ketone from desilylation obtained as an oil (93%) (Found: M^+: 274.1321. $C_{15}H_{18}N_2O_3$ requires 274.1317); ν_{max} (CH_2Cl_2) 1680 cm^{-1}; δ_H (270 MHz) 2.2 (2H, m, C*H*$_2$CHOH), 3.2 (1H, m, CHC=O), 3.4 (3H, s, OMe), 3.4 (1H, m, CHC=O), 3.6 (1H, br.s, OH), 4.8 (1H, m, C*H*OH), 5.7 (2H, s, NCH_2O), 7.2 - 7.4 (7H, m, 2 x ArH + Ph); *m/z* 274 (M^+), 168.

2-[4'-(Cyclohex-3"-enyl)-4'-hydroxy-1'-triisopropylsilyloxybut-1'-enyl]-1-methoxymethylimidazole (**2c**)
The product was isolated as a mixture of diastereoisomers from the reaction with 3-cyclohexene-1-carboxaldehyde after elution from silica gel using ether as an oil (40%) (Found: M^+: 434.2956. $C_{24}H_{42}N_2O_3Si$ requires 434.2965); δ_H (270 MHz) 0.9 - 1.1 (21H, m, *i*Pr$_3$Si), 1.6 - 2.3 (7H, m, cycloalkyl), 2.45 (2H, m, CH_2C=), 3.2 (3H, s, OMe), 3.4 - 3.6 (1H, C*H*OH), 5.2 (1H, m, CH=), 5.25 (2H, ABq, *J* 10Hz, NCH_2O), 5.65 (2H, slightly broad s, CH=CH), 7.0 (2H, 2 x s, 2 x ArH); δ_C (67.5 MHz) 13, 18, 24, 26, 26, 27, 29, 31, 40, 41, 53, 75, 75, 77, 112, 113, 120, 127, 127, 128, 129, 142, 148; *m/z* 434 (M^+), 391 (M^+ - *i*Pr), 324.

2-(4'-Hydroxy-4'-methyl-1'-triisopropylsilyloxypent-1'-enyl)-1-methoxymethylimidazole (**2d**)
The product was isolated from the reaction with acetone after elution from silica gel using ether as an oil (42%) (Found: M^+ - *i*Pr: 339.2109. $C_{17}H_{31}N_2O_3Si$ requires 339.2104); δ_H (270 MHz) 0.9 - 1.1 (21H, m, *i*Pr$_3$Si), 1.2 (6H, s, 2 x Me), 1.9 (1H, br, OH), 2.4 (2H, d, *J* 8Hz, CH_2), 3.2 (3H, s, OMe), 5.2 (1H, t, *J* 8Hz, CH=), 5.25 (2H, s, NCH_2O), 7.0 (2H, 2 x s, 2 x ArH); δ_C (67.5 MHz) 13 (Me_2CH), 18 (*Me*$_2$CH), 30 (2 x Me), 40 (CH_2), 56 (OMe), 71 (COH), 77 (NCH_2O), 113 (CH=), 120 (NCH), 128 (NCH), 142 (NCN), 147 (=COSi); *m/z* 382 (M^+), 339 (M^+ - *i*Pr); earlier fractions contained the α-product **3d** as an oil (24%); δ_H (270 MHz) 0.9 - 1.2 (21H, m, *i*Pr$_3$Si), 1.2 (3H, s, Me), 1.6 (3H, s, Me), 3.3 (3H, s, OMe), 3.8 (1H, s, OH), 5.1 - 5.3 (2H, m, CH_2=), 5.5 (1H, 1/2 ABq, *J* 10Hz, C*H*HOMe), 5.7 (1H, 1/2 ABq, *J* 10Hz, CH*H*OMe), 6.5 (1H, dd, *J* 10Hz, *J'* 18Hz), 6.9 - 7.0 (2H, m, 2 x ArH).

2-(4',6'-Dimethyl-4'-hydroxy-1'-triisopropylsilyloxyhept-1'-enyl)-1-methoxymethylimidazole (**2e**)
The product was isolated from the reaction with isobutyl methyl ketone after elution from silica gel using ether as an oil (47%) (Found: M^+: 424.3127. $C_{23}H_{44}N_2O_3Si$ requires 424.3121); δ_H (270 MHz) 0.9 - 1.1 (27H, m, *i*Pr$_3$Si + *Me*$_2$CH), 1.2 (3H, s, Me), 1.4 (2H, d, *J* 7Hz, C*H*$_2$*i*Pr), 1.7 (1H, br.s, OH), 1.8 (1H, sept, *J* 7Hz, C*H*Me$_2$), 2.4 (2H, d, *J* 9Hz, CH_2C=), 3.25 (3H, s, OMe), 5.2 (1H, t, *J* 9Hz,

CH=), 5.25 (2H, s, NCH_2O), 7.0 (2H, ABq, *J* <1Hz, 2 x ArH); *m/z* 424 (M^+), 381 (M^+ - *i*Pr), 324.

2-(4'-Ethyl-4'-hydroxy-1'-triisopropylsilyloxyhex-1'-enyl)-1-methoxymethylimidazole (**2f**)

The product was isolated from the reaction with diethyl ketone after elution from silica gel using ether as an oil (68%) (Found: M^+: 410.2958. $C_{22}H_{42}N_2O_3Si$ requires 410.2965); δ_H (270 MHz) 0.9 (6H, t, *J* 9Hz, 2 x Me), 1.0 - 1.1 (21H, m, *i*Pr_3Si), 1.5 (4H, q, *J* 9Hz, 2 x CH_2), 1.6 (1H, br.s, OH), 2.4 (2H, d, *J* 8Hz, CH_2C=), 3.2 (3H, s, OMe), 5.2 (1H, t, *J* 8Hz, CH=), 5.3 (2H, s, NCH_2O), 7.0 (2H, ABq, *J* <1Hz, 2 x ArH); δ_C (67.5 MHz) 8 (2 x Me), 13 (Me_2CHSi), 18 (Me_2CHSi), 31 (2 x CH_2), 35 (CH_2C=), 56 (OMe), 75 (COH), 77 (NCH_2O), 113 (CH=), 120 (NCH), 128 (NCH), 142 (NCN), 147 (=COSi); *m/z* 410 (M^+), 367 (M^+ - *i*Pr), 324 (M^+ - 2 x *i*Pr); earlier fractions contained the α-product **3f** as an oil (13%); δ_H (270 MHz) 0.8 (6H, t, *J* 8Hz, 2 x Me), 0.9 - 1.1 (21H, m, *i*Pr_3Si), 1.2 - 1.6 (4H, m, 2 x CH_2), 3.3 (3H, s, OMe), 4.8 (1H, 1/2 ABq, *J* 10Hz, C*H*HOMe), 5.4 (1H, m, C*H*H=), 5.7 (1H, m, CH*H*=), 5.8 (1H, 1/2 ABq, *J* 10Hz, CH*H*OMe), 6.4 (1H, dd, *J* 11Hz, *J'* 17Hz, CH=), 7.0 (2H, m, 2 x ArH).

2-[3'-(1"-Hydroxy-1"-cyclohexyl)-1'-triisopropylsilyloxyprop-1'-enyl)-1-methoxymethylimidazole (**2g**)

The product was isolated from the reaction with cyclohexanone after elution from silica gel using 2% methanol in ether as an oil (70%) (Found: M^+: 422.2954. $C_{23}H_{42}N_2O_3Si$ requires 422.2965); δ_H (270 MHz) 1.0 - 1.15 (21H, m, *i*Pr_3Si), 1.4 - 1.9 (10H, m, cyclohexyl), 2,4 (2H, d, *J* 7Hz, CH_2C=), 3.2 (3H, s, OMe), 5.2 (1H, t, *J* 7Hz, CH=), 5.25 (2H, s, NCH_2O), 7.0 (2H, ABq, *J* <1Hz, 2 x ArH); *m/z* 422 (M^+), 379 (M^+ - *i*Pr).

2-[3'-(2",6"-Dimethyl-1"-hydroxy-1"-cyclohexyl)-1'-triisopropylsilyloxyprop-1'-enyl]-1-methoxymethyl-imidazole (**2h**)

The product was isolated as two separate stereoisomers from the reaction with a mixture of the two stereoisomers of 2,6-dimethylcyclohexanone (Aldrich) after elution from silica gel using ether as oils (74 and 11%); major *cis*-isomer: (Found: M^+: 450.3277. $C_{25}H_{46}N_2O_3Si$ requires 450.3278); δ_H (270MHz) 0.95 - 1.8 (35H, m, *i*Pr_3Si + cyclohexyl + 2 x Me), 2.6 (2H, d, *J* 9Hz, CH_2C=), 3.2 (3H, s, OMe), 5.1 (1H, t, *J* 9Hz, CH=), 5.3 (2H, s, NCH_2O), 7.0 (2H, 2 x s, 2 x ArH); *m/z* 450 (M^+), 407 (M^+ - *i*Pr), 324; minor *trans*-isomer: δ_H (270MHz) 0.9 - 1.1 (27H, m, *i*Pr_3Si + 2 x Me), 1.1 - 1.9 (8H, m, cyclohexyl), 2.3 (1H, 1/2 dABq, *J* 9Hz, *J'* 14Hz, CH*H*C=), 2.7 (1H, 1/2 dABq, *J* 9Hz, *J'* 14Hz, C*H*HC=), 3.2 (3H, s, OMe), 5.25 - 5.35 (3H, m, NCH_2O + CH=), 7.0 (2H, ABq, *J* <1Hz, 2 x ArH).

2-[3'-(1"-Hydroxy-2",2",6"-trimethyl-1"-cyclohexyl)-1'-triisopropylsilyloxyprop-1'-enyl]-1-methoxymethylimidazole (**2i**)

The product was isolated as two separate stereoisomers from the reaction with 2,2,6-trimethylcyclohexanone (Aldrich) after elution from silica gel using ether as oils (69 and 20%): major isomer: (Found: M^+: 464.3423. $C_{26}H_{48}N_2O_3Si$ requires 464.3434); δ_H (270 MHz) 0.9 - 1.2 (30H, m, *i*Pr_3Si + 3 x Me), 1.3 - 1.9 (7H, m, cyclohexyl), 2.45 (1H, 1/2 dABq, *J* 6Hz, *J'* 15Hz, CH*H*C=), 2.75 (1H, 1/2 dABq, *J* 9Hz, *J'* 15Hz, C*H*HC=), 3.25 (3H, s, OMe), 5.2 - 5.3 (3H, m, NCH_2O + CH=), 7.0 (2H, ABq, *J* <1Hz, 2 x ArH); *m/z* 464 (M^+), 421 (M^+ - *i*Pr), 324; minor isomer: δ_H (270 MHz) 0.9 - 1.1 (30H, m, *i*Pr_3Si + 3 x Me), 1.15 - 1.65(6H, m, cyclohexyl), 1.9 (1H, m, C*H*Me), 2.55 (2H, d, *J* 8Hz, CH_2C=), 3.2 (3H, s, OMe), 5.25 (2H, s, NCH_2O), 5.3 (1H, t, *J* 8Hz, CH=), 6.95 (2H, ABq, *J* 1Hz, 2 x ArH).

General Procedure for the Conversion of γ-Products into γ- Lactones

To a solution of the γ-product in THF (0.03M) was added water (3 - 4 equiv.) followed by a solution of TBAF in THF (Aldrich, 1.0M, 1 equiv.). The reaction was followed by tlc and was usually complete in 15 - 30min. The solvent was removed under vacuum, the resultant oil was taken up in ether and the ethereal solution was filtered through a silica gel pad. The filtrate was evaporated to leave the crude ketone. This was dissolved in dichloromethane (0.05M) and the solution was treated with methyl triflate (1 equiv.) dropwise. The progress of the reaction was followed by solution cell IR spectroscopy, monitoring disappearance of the carbonyl absorption. After the time indicated neat triethylamine (1 equiv.) was added, the solvent was removed and the residue was suspended in ether. The suspension was applied to a silica gel column and the lactone was eluted with ether.

4-Isopropylbutyrolactone **4a**[16]

From γ-product **2a**; reaction with methyl triflate took overnight and the lactone was isolated as an oil (99%); ν_{max} (CH_2Cl_2) 1769 cm^{-1}; δ_H (270 MHz) 0.95 (3H, d, *J* 8Hz, Me), 1.0 (3H, d, *J* 8Hz, Me), 1.8 - 2.0 (2H, m, CH_2), 2.25 (1H, m, C*H*Me_2), 2.5 (2H, m, CH_2CO), 4.2 (1H, m, CHOCO); δ_C (67.5 MHz) 18 (Me), 19 (Me), 28 (CH_2), 30 (CH_2), 33 (*C*HMe_2), 86 (*C*HOCO), 178 (CO); *m/z* 128 (M^+), 100 (M^+ - CO), 85 (M^+ - *i*Pr).

4-Phenylbutyrolactone **4b**[17]

From γ-product **2b**; reaction with methyl triflate took overnight and the lactone was isolated as an oil (90%):

ν_{max} (CH_2Cl_2) 1778 cm^{-1}; δ_H (270 MHz) 2.2 (1H, m, C*H*CHPh), 2.65 (3H, m, C*H*CHPh + CH_2CO), 5.5 (1H, dd, *J* 7Hz, *J'* 7Hz, C*H*Ph), 7.2 (5H, m, Ph).

4-(Cyclohex-3'-enyl)-butyrolactone **4c**[18]

From γ-product **2c**; reaction with methyl triflate took overnight and the lactone was isolated as a mixture of diastereoisomers an oil (90%) (Found: M^+ 166.0990. $C_{10}H_{14}O_2$ requires M^+ 166.0994); ν_{max} (CH_2Cl_2) 1775 cm^{-1}; δ_H (270MHz) 1.2 - 2.2 (7H, m, cyclohexyl), 2.25 (2H, m, CH_2CHOCO), 2.55 (2H, m, CH_2CO), 4.3 (1H, m, CHOCO), 5.7 (2H, m, CH=CH); δ_C (67.5 MHz) 24 - 25 (4 carbons), 26 -27 (3 carbons), 28, 29, 39, 84 (2 x *C*HOCO), 125 (alkene C), 126 (alkene C), 127 (alkene C), 128 (alkene C), 177 (CO); *m/z* 166 (M^+), 85 (M^+ - cyclohexenyl).

4,4-Dimethylbutyrolactone **4d**[19]

From γ-product **2d**; reaction with methyl triflate took 3h and the lactone was isolated as an oil (33%); ν_{max} (CH_2Cl_2) 1769 cm^{-1}; δ_H (270 MHz) 1.4 (6H, s, 2 x Me), 2.0 (2H, t, *J* 9Hz, CH_2CH_2CO), 2.6 (2H, t, *J* 9Hz, CH_2CO).

4-Isobutyl-4-methylbutyrolactone **4e**[20]

From γ-product **2e**; reaction with methyl triflate took 1.5h and the lactone was isolated as an oil (95%); ν_{max} (CH_2Cl_2) 1760 cm^{-1}; δ_H (270 MHz) 0.95 (3H, d, *J* 6Hz, Me), 1.0 (3H, d, *J* 6Hz, Me), 1.4 (3H, s, Me), 1.6 (2H, dd, *J* 2Hz, *J'* 6Hz, side chain CH_2), 1.8 (1H, hept. *J* 6Hz, CH), 2.05 (2H, m, CH_2CH_2CO), 2.6 (2H, m, CH_2CO); δ_C (67.5 MHz) 18 (Me), 25 (Me), 25 (Me), 26 (CH_2), 29 (CH_2), 34 (CH_2), 50 (CH), 87 (*C*HOCO), 177 (CO); *m/z* 156 (M^+), 141 (M^+ - Me), 99 (M^+ - *i*Bu).

4,4-Diethylbutyrolactone **4f**[21]

From γ-product **2f**; reaction with methyl triflate took 5h and the lactone was isolated as an oil (58%); ν_{max} (CH_2Cl_2) 1764 cm^{-1}; δ_H (270 MHz) 0.9 (6H, t, *J* 8Hz, 2 x Me), 1.7 (4H, q, *J* 8Hz, 2 x CH_2), 2.0 (2H, t, *J* 9Hz, CH_2CH_2CO), 2.6 (2H, t, *J* 9Hz, CH_2CO); δ_C (67.5 MHz) 8 (2 x Me), 29 (CH_2), 30 (CH_2), 31 (CH_2), 90 (C-O), 177 (C=O).

1-Oxa-spiro[4.5]decan-2-one **4g**[22]

From γ-product **2g**; reaction with methyl triflate took 2h and the lactone was isolated as an oil (96%); ν_{max} (CH_2Cl_2) 1765 cm^{-1}; δ_H (270 MHz) 1.2 - 1.8 (10H, m, cyclohexyl), 2.0 (2H, t, *J* 9Hz, CH_2CH_2CO),

2.6 (2H, t, *J* 9Hz, CH_2CO); δ_C (67.5 MHz) 23 (CH_2), 25 (CH_2), 29 (CH_2), 33 (CH_2), 37 (CH_2), 86 (C-O), 177 (C=O); *m/z* 154 (M^+), 111, 99, 98 (M^+ - CH_2CH_2CO).

5,9-Dimethyl-1-oxa-spiro[4.5]decan-2-one **4h**

From the major diastereoisomer of the γ-product **2h**; reaction with methyl triflate took **4h** and the lactone was isolated as an oil (90%) (Found: M^+: 182.1309. $C_{11}H_{18}O_2$ requires 182.1307); ν_{max} (CH_2Cl_2) 1759 cm^{-1}; δ_H (270 MHz) 0.9 (6H, d, *J* 6Hz, 2 x Me), 1.3 - 1.7 (8H, m, cyclohexyl), 2.05 (2H, m, CH_2CH_2CO), 2.55 (2H, m, CH_2CO); δ_C (67.5 MHz) 15 (2 x Me), 25 (CH_2), 28 (CH_2), 29 (CH_2), 31(CH_2), 41 (2 x CH), 90 (C-O), 177 (C=O); *m/z* 182 (M^+), 153, 139.

2-Methyl-4-(2',2',6'-trimethylcyclohex-1'-enyl)-2-trimethylsilyloxy-butyronitrile (**7**)

To a stirred solution of dihydro-β-ionone (1.6 g, 8.21 mmol) and zinc iodide (2 mg) in dry dichloromethane (25 ml) was slowly added trimethylsilyl cyanide (1.05 ml, 781 mg, 7.9 mmol) by
syringe. The flask was wrapped in aluminium foil and the mixture was left to stir overnight. The solution was concentrated to about 6 ml on a rotary evaporator and then the concentrate was filtered through a short silica gel pad. The remaining solvent was evaporated to leave the product as an oil (2.22 g, 92%) (Found: M^+: 293.2177. $C_{17}H_{31}NOSi$ requires 293.2175); ν_{max} (neat) 1540 cm^{-1}; δ_H (270 MHz) 0.4 (9H, s, Me_3Si), 1.1 (6H, s, 2 x Me), 1.55 (2H, m, CH_2), 1.7 (2H, m, CH_2), 1.7 (3H, s, Me), 1.73 (3H, s, Me), 1.9 (2H, dd, *J* 7Hz, *J'* 10Hz, CH_2), 2.05 (2H, t, *J* 7Hz, CH_2), 2.2 - 2.45 (2H, m, CH_2); *m/z* 293 (M^+), 278 (M^+ - Me).

2-Methyl-4-(2',2',6'-trimethylcyclohex-1'-enyl)-2-trimethylsilyloxy-butylamine (**8**)

To a stirred solution of silylated cyanohydrin **7** (157 mg, 0.535 mmol) in dry toluene (3 ml) under argon at 6 °C was added DIBAL (Aldrich: 1.5M in toluene, 1.45 ml, 2.18 mmol) by syringe. The reaction mixture was stirred for a further 2h at this temperature and then quenched with saturated aqueous ammonium chloride (5 ml). The two layers were separated and the aqueous phase was extracted with ether (2 x 5 ml). The combined organic layers were dried, the drying agent was filtered off and the solvent was removed to leave a colourless oil. This was purified by passage through a short silica gel pad eluting with ether to give after evaporation of the solvent the product as an oil (74 mg, 47%) (Found: M^+: 297.2485. $C_{17}H_{33}NOSi$ requires 297.2488); ν_{max} (neat) 3400, 3300 cm^{-1}; δ_H (270 MHz) 0.1 (9H, s, Me_3Si), 1.0 (6H, s, 2 x Me), 1.2 (3H, s, Me), 1.4 (2H, m, CH_2), 1.5 - 1.6 (8H, m, 3 x CH_2 + NH_2), 1.6 (3H, s, Me), 1.9 (4H, m, 2 x CH_2), 2.6 (2H, s, CH_2N); δ_C (67.5 MHz) 20 (Me), 20 (Me), 22 (Me_3Si), 23 (CH_2), 24 (Me), 28

(Me), 29, 32, 35 (CMe_2), 39, 40, 52 (CH_2N), 77 (COSi), 127 (C=C), 137 (C=C); *m/z* 297 (M^+), 282 (M^+ - Me).

2-Methyl-4-(2',2',6'-trimethylcyclohex-1'-enyl)-2-trimethylsilyloxy-butyraldehyde (**9**)

To a stirred solution of silylated cyanohydrin **7** (50 mg, 0.169 mmol) in dry toluene (0.5 ml) under argon at -45 °C was added DIBAL (1.5M in toluene, 0.23 ml, 0.35 mmol) by syringe. The reaction mixture was allowed to warm to 0 °C over 0.5h and then stirred at this temperature for 1h further. The mixture was then poured into a mixture of ether (1.3 ml), saturated aqueous ammonium chloride solution (1.3 ml) and 1.6N sulphuric acid (2.5 ml). This two-phase suspension was stirred vigorously at room temperature for 12h, then the organic layer was separated and the aqueous layer was extracted with ether (3 x 2 ml). The combined organic layers were washed with water (2 ml), dried, filtered and concentrated to a yellow oil. This oil was chromatographed on silica gel to give the aldehyde as a colourless oil (35.3 mg, 71%) (Found: M^+: 296.2178. $C_{17}H_{32}O_2Si$ requires 296.2172); ν_{max} (CH_2Cl_2) 1736 cm^{-1}; δ_H (270 MHz) 0.3 (9H, s, Me_3Si), 1.1 (3H, s, Me), 1.1 (3H, s, Me), 1.5 (3H, s, Me), 1.5 - 1.9 (6H, m, CH_2), 1.7 (3H, s, Me), 2.0 (2H, m, CH_2), 2.1 - 2.3 (2H, m, CH_2), 9.7 (1H, s, CHO); δ_C (67.5 MHz) 2 (Me_3Si), 20, 20, 22, 22, 29, 32, 35, 40, 81 (COSi), 128 (C=C), 136 (C=C), 205 (CO).

2-[4'-Hydroxy-5'-methyl-1'-triisopropylsilyloxy-7'-(2",2",6"-trimethylcyclohex-1"-enyl)-5'-trimethylsilyloxy-hept-1'-enyl]-1-methoxymethylimidazole (**10**)

To a solution of **1** (275 mg, 0.85 mmol) and TMEDA (100 mg, 0.85 mmol) in THF (25 ml) under argon at -80 °C was added *n*-butyllithium (1.6 M in hexanes, 1 equivalent) dropwise. The resultant yellow solution was stirred at this temperature for 30 min before a cooled (to -70 °C) solution of the aldehyde **9** (377 mg, 1.27 mmol) in THF (5 ml) was added dropwise. After the addition the temperature was allowed to rise to -60 °C and the reaction to stir for 5 min. The reaction was worked up as usual to give the product as a mixture of diastereoisomers after chromatography on silica gel using light petroleum : ether (3 : 2) as eluent (oil: 174 mg, 33%) (Found: M^+: 620.4412. $C_{34}H_{64}N_2O_4Si_2$ requires 620.4405); δ_H (270 MHz) 1.0 - 1.1 (36H, m, iPr_3Si + Me_3Si + 2 x Me), 1.15 (3H, 2 x s, MeCOSi on each diastereoisomer), 1.4 (2H, m, cyclohexyl CH_2), 1.5 - 1.6 (6H, m, 3 x CH_2), 1.6 (3H, 2 x s, allylic Me on each diastereoisomer), 1.9 (2H, br.t, *J* 6Hz, allylic CH_2), 2.0 - 2.4 (3H, m, allylic CH_2 + allylic CH), 2.6 - 2.7 (1H, m, allylic CH), 3.25 (3H, 2 x s, OMe on each diastereoisomer), 3.55 (1H, m, CHOH), 5.25 (3H, m, NCH_2O + CH=), 7.0 (2H, ABq, *J* <1Hz, ArH); δ_C (67.5 MHz) 1, 13, 18, 19, 20, 21, 22, 22, 23, 29, 29, 29, 30, 33, 35, 36, 39, 40, 51, 75, 75, 77, 78, 80, 114, 114, 120, 127, 128, 137, 140, 140, 147; *m/z* 620 (M^+), 577 (M^+ - *i*Pr).

2-[4',5'-Dihydroxy-5'-methyl-7'-(2",2",6"-trimethylcyclohex-1"-enyl)-heptanoyl]-1-methoxymethylimidazole (**11**)

To a solution of **1** (121 mg, 0.373 mmol) and TMEDA (44 mg, 0.373 mmol) in THF (12 ml) under argon at -88 °C was added *n*-butyllithium (1.6 M in hexanes, 1 equivalent) dropwise. The resultant yellow solution was stirred at this temperature for 30 min before a scooled (to -78 °C) solution of the aldehyde **9** (211 mg, 0.71 mmol) in THF (5 ml) was added dropwise at such a rate that the temperature did not rise above -85 °C. The reaction was stirred for 5min and then quenched with acetic acid. A solution of TBAF in THF (1.0 M, 1.2 ml) was added and the mixture was stirred for a further 1h and then worked up in the usual manner to give the product as a mixture of diastereoisomers after chromatography on silica gel using 5% methanol in ether as eluent (oil: 107 mg, 73%); ν_{max} (CH_2Cl_2) 3380, 1680 cm^{-1}; δ_H (270 MHz) 1.0 (3H, s, Me in one diastereoisomer), 1.1 (3H, s, Me in one diastereoisomer), 1.12 (3H, s, Me in one diastereoisomer), 1.2 (3H, s, Me in one diastereoisomer), 1.4 - 2.2 (12H, m, 6 x CH_2), 1.6 (3H, 2 x s, Me in each diastereoisomer), 2.1 (3H, 2 x s, Me in each diastereoisomer), 3.0 - 3.2 (2H, m, CH_2CO), 3.35 (3H, s, OMe in each diastereoisomer), 3.45 (1H, m, C*H*OH), 5.75 (2H, ABq, *J* 9Hz, NCH_2O), 7.2 (1H, d, *J* <1Hz, ArH), 7.3 (1H, d, *J* <1Hz, ArH).

Cavernosine and Epicavernosine

Cyclisation of the dihydroxyketone **11** (72 mg, 0.183 mmol) to the lactol and subsequent cleavage was carried out according to the general procedure above. The solvent was removed by evaporation and the resultant oil was triturated with ether (4 x 5 ml). The combined triturates were filtered through Celite and the filtrate was concentrated to an oil (44 mg). This was chromatographed on silica gel using ether : petroleum ether as eluent to give cavernosine **5** in the early fractions as an oil (26 mg, 50%); ν_{max} (CH_2Cl_2) 1777 cm^{-1}; δ_H (500 MHz)(assignments made with the help of a ^1H - ^1H COSY spectrum) 1.0 (6H, 2 x s, Me_2C), 1.34 (3H, s, MeCOH), 1.4 (2H, m, C*H*$_2$CMe$_2$), 1.5 (2H, m, C*H*$_2$C(Me)OH), 1.55 (2H, m, central CH_2 of the cyclohexene ring), 1.6 (3H, s, allylic Me), 1.7 (1H, br.s, OH), 1.9 (2H, t, *J* 6Hz, endocyclic allylic CH_2), 2.0 (1H, dt, *J* 6Hz, *J'* 13Hz, exocyclic allylic C*H*H), 2.15 (1H, dt, *J* 4.5Hz, *J'* 13Hz exocyclic allylic CH*H*), 2.15 (1H, m, C*H*H.CH2CO), 2.25 (1H, m, CH*H*.CH_2CO), 2.55 (2H, m, CH_2CO), 4.35 (1H, t, *J* 8Hz, CHOCO); δ_C (125.8 MHz) (assignments made with the help of a DEPT spectrum and a ^1H - ^{13}C 2D correlation map) 19.5 (central CH_2 of the cyclohexene ring), 19.7 (allylic Me), 21.8 (exocyclic allylic CH_2), 22.0 (*C*H$_2$CH$_2$CO), 23.2 (*Me*COH), 28.5 (C*Me*Me), 28.5 (CMe*Me*), 29.0 (*C*H$_2$CO), 32.6 (endocyclic allylic CH_2), 35.0 (*C*Me$_2$), 37.0 (*C*H$_2$CMeOH), 39.8 (*C*H$_2$CMe$_2$),

73.0 (COH), 85.6 (CHOCO), 127.5 (alkenic C), 136.0 (alkenic C), 177.2 (CO); *m/z* 280 (M^+), 265 (M^+ - Me), 262 (M^+ - H_2O), 247 (M^+ - Me - H_2O), 224 (M^+ - CH_2CH_2CO), 206 (224 - H_2O), 195 (M^+ - $C_4H_5O_2$ lactone), 123 (trimethylcyclohexenyl species), 99, 56, 28 (CO); later fractions yielded epicavernosine **epi-5** as an oil (18 mg, 36%) contaminated with a trace of cavernosine: δ_H (270 MHz) 1.0 (6H, s, 2 x CMe_2), 1.2 (3H, s, MeCOH), 1.4 (2H, m, CH_2), 1.55 - 1.70 (6H, m, 3 x CH_2), 1.6 (3H, s, Me), 1.9 (2H, t, *J* 6Hz, CH_2), 2.1 - 2.35 (4H, m, 2 x CH_2), 2.55 (2H, m, CH_2), 4.4 (1H, dd, *J* 7.5Hz, *J'* 8.5Hz).

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