Studies on Pyrrolidinones. Synthesis and Cyclization of *N*-[α-Naphthyl-(3,4,5-trimethoxyphenyl)-methyl]pyroglutamic Acid

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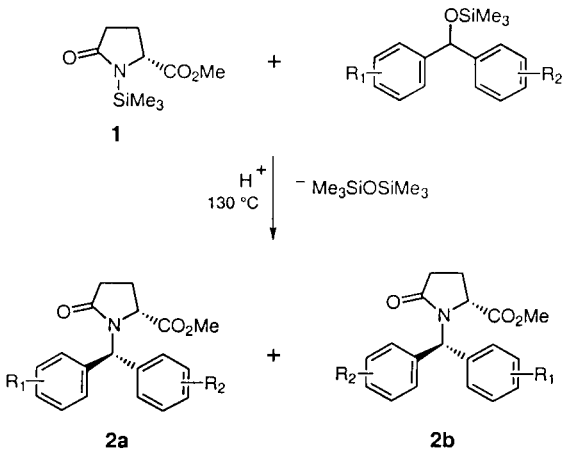
Received December 24, 1998

Condensation of trimethoxyphenyl naphthylcarbinol trimethylsilyl ether with methyl *N*-trimethylsilyl-pyroglutamate yields two separable esters. The Friedel-Crafts cyclization of the acids obtained after saponification gives analogs of azapodophylloxin. Reduction and treatment of the obtained products with hydrobromic acid yields analogs of azatoxin.

J. Heterocyclic Chem., **37**, 215 (2000).

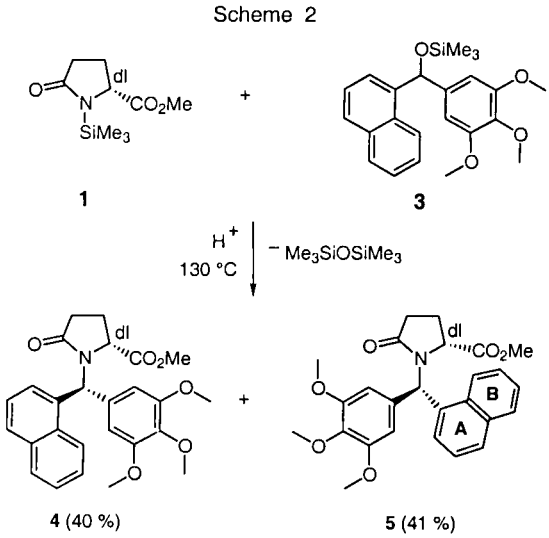
We recently described an easy synthesis of *N*-(diarylmethyl)pyroglutamic esters **2**, obtained as a non-separable mixture of diastereomeric compounds **2a** and **2b** [1] (Scheme 1).

Scheme 1



When the same reaction was performed with the silyl ether **3** [2], the crystallization in ethyl acetate of the crude reaction mixture allowed for easy separation of each isomer in very good yield. In the ^{1}H nmr spectrum of product **4**, the methyl ester group reveals a peak at the expected value of 3.39 ppm, but for compound **5**, the same group reveals a singlet at 2.45 ppm. This very strong shielding effect shows that, in deuteriochloroform, the methyl ester group of **5** is placed near the B ring of the naphthyl substituent, while in ester **4**, this methyl group is not in the shielding cone of an aromatic ring. An X-ray study [3] performed on ester **5** confirmed this observation (Figure 1) and the results allowed us to assign the stereochemistry of **4** and **5** as shown in Scheme **2**.

Scheme 2



Because the cyclization of compounds **4** and **5** can give products whose structure shows some similarities with anticancer agents azatoxin **6a** [4] and podophyllotoxin **6b** [5] (Scheme 3), it was interesting to realize such a cyclization.

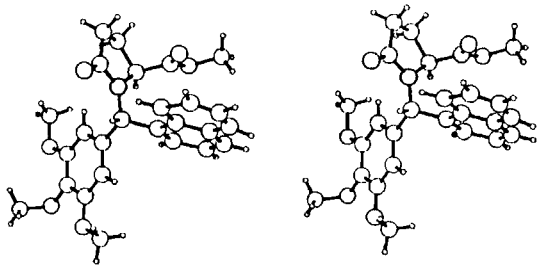
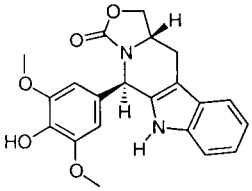
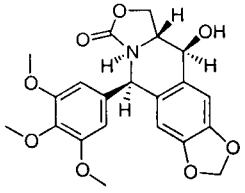


Figure 1. ORTEP diagram of Compound **5**.

Scheme 3

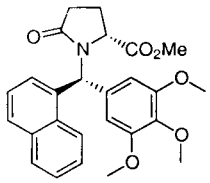


6a azatoxin



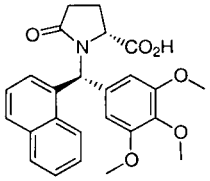
6b podophyllotoxin

Scheme 4



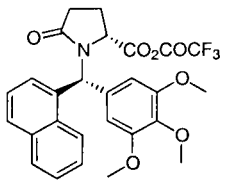
4

1) NaOH
2) HCl

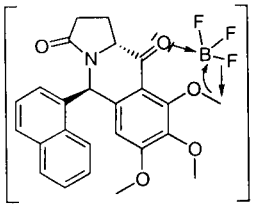


7

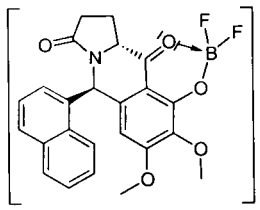
$(CF_3CO)_2O$



BF_3/ether

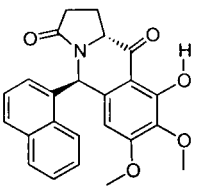


9



10

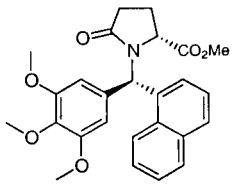
H_2O



8 70%

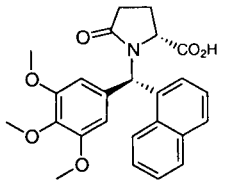
Thus ester **4** was saponified giving acid **7** that was cyclized by using trifluoroacetic anhydride, followed by boron trifluoride in ether [6], giving ketone **8** in 70% yield. Interestingly, in intermediate **9**, the proximity of a ketone and of a methoxy group leads to the formation of a phenol [7] (Scheme 4). It is noteworthy that the ^1H nmr spectrum of the oil obtained after filtration of complex **10** and washing with water, shows only the presence of aromatic cleavage products and the absence of another cyclization compound.

Scheme 5



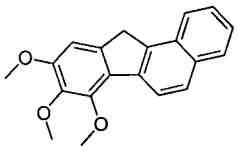
5

1) NaOH
2) HCl



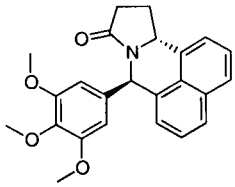
11

1) $(CF_3CO)_2O$
2) BF_3/ether
3) H_2O



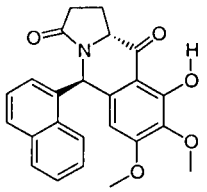
14 2%

+



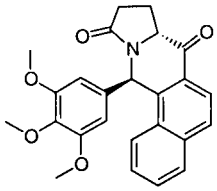
13 15%

+



8 30%

+



12 15%

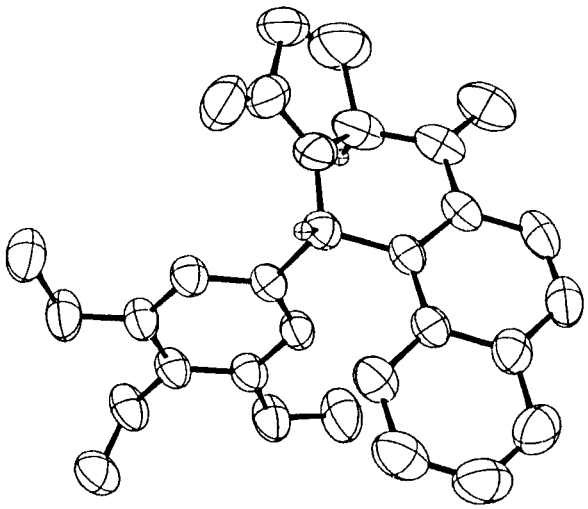


Figure 2. ORTEP diagram of Compound **12**.

In the same manner as for lactam **7**, the acid **11** produced by saponification of ester **5** was submitted to the action of trifluoroacetic anhydride and boron trifluoride. A complex mixture of products was obtained whose separation gave the target ketone **12**, as well as ketone **8**, the aryllactam **13** and the polyaromatic product **14**. The ^1H nmr spectrum of the residues also shows the presence of some other aromatic compounds (Scheme 5).

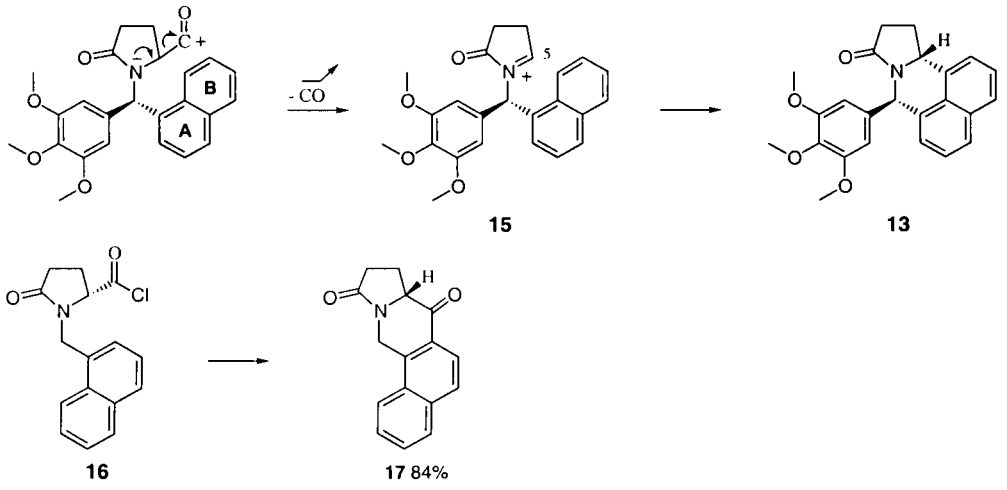
As for other decarboxylations of pyroglutamic acids observed during Friedel-Crafts acylation [8], there is formation of an acyliminium salt **15** which yields product **13**. Because cyclization of acid **16** gives only ketone **17** [9] (Scheme 6), it is possible that this type of decarboxylating cyclization is kinetically favored by the proximity of the C_5 carbon of the pyrrolidinone ring with the B ring of the naphthalene nucleus (see the X-ray structure of ester **5** in Figure 1).

The formation of the benzofluorene **14** is interesting because it explains why ketone **8** was obtained during the cyclization of acid **11**: breaking the benzhydryl bond of **18a** could give cation **19**; recapture of the pyrrolidinone moiety would then yield the racemic mixture **18a,b**. On the other hand, evolution of cation **19**, followed by cyclization would give product **14** (Scheme 7).

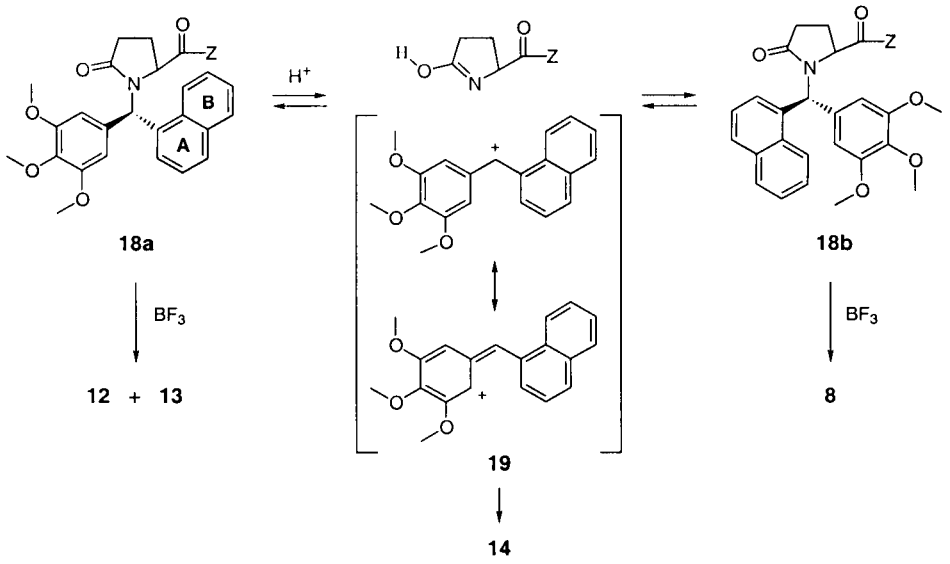
Reduction of **8**:

The reduction of a carbonyl to a methylene group by triethylsilane in trifluoroacetic acid [10a,b] did not succeed with a rather similar compound **20** [11] therefore the ketone **8** was instead treated with sodium borohydride. The triethylsilane reduction [12] of alcohol **21** in trifluoroacetic acid gave a good yield of product **22** (Scheme 8); the same approach has been used by A. Kubo in a similar case [10c].

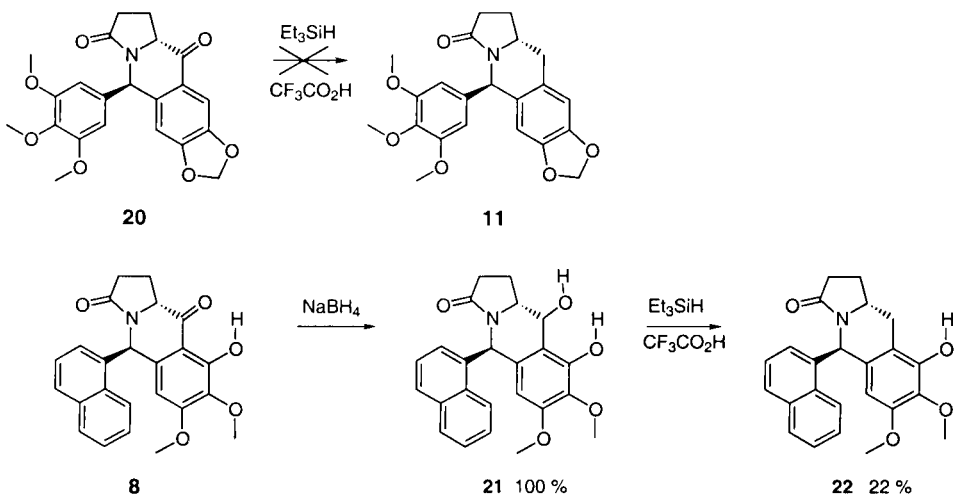
Scheme 6



Scheme 7



Scheme 8

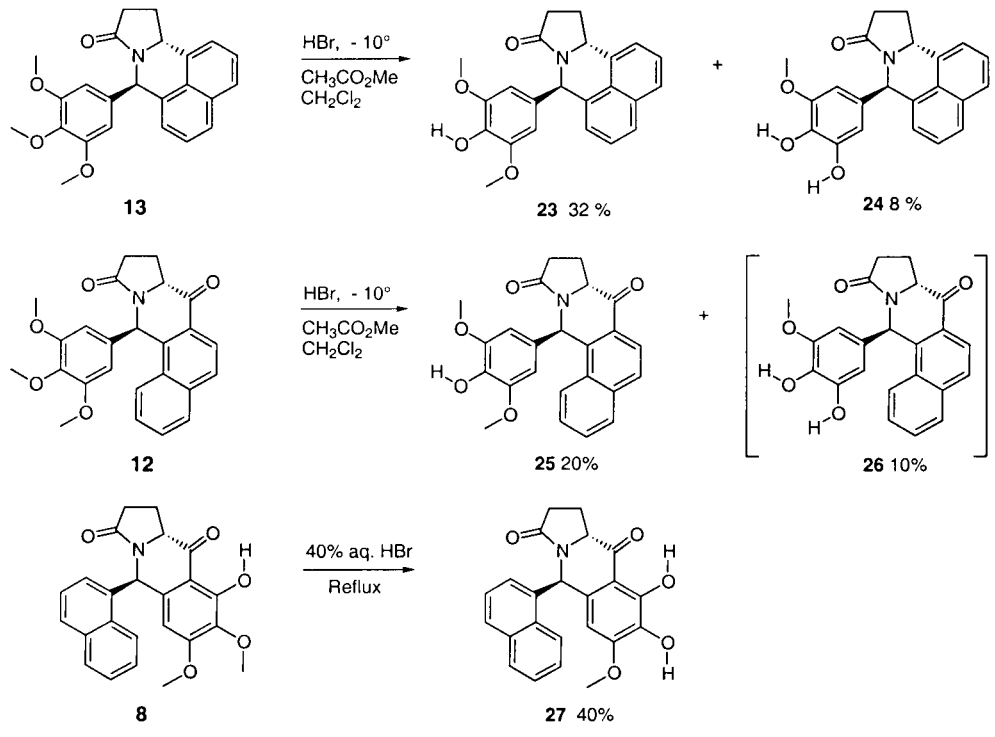


Demethylation of **8**, **12** and **13**:

As with other topoisomerase II inhibitors [13], azatoxin (**6a**) is a 1,3-dimethoxyphenol. To improve the similarities of our compounds with azatoxin, the selective demethylation of ethers **13** and **12** was realized with a solution of hydrobromic acid in methyl acetate and methylene dichloride, formed *in-situ* by the reaction of acetyl bromide with methanol. Under these conditions, 1,3-dimethoxyphenols **23** and **25** were obtained in medium yields; diphenols **24** and **26** were also produced in low yields, but **26** was not isolated and was only observed in the ^{1}H nmr spectrum of the reaction mixture. As for diphenol **27**, it was obtained by refluxing ketone **8** with a 40% aqueous solution of hydrobromic acid (Scheme 9).

In the ^{1}H nmr spectra of the cyclized compounds, the chemical shifts of protons H_3, H_4 and H_5 (Figure 4) are known from the studies of similar products [1,8,9,14], and the comparison of the spectra of all the described compounds allowed us to attribute the chemical shift of H_6, In a first approach, the trans stereochemistry of H_5 and H_6 was deduced from the lack of a NOESY correlation between these protons, and that was verified by an X-ray study (Figures 2 and 3) [3].

Scheme 9



NMR studies on some compounds:

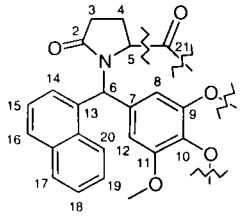


Figure 4. Numbering used for the nmr description of all compounds.

Diphenol **27**:

For the diphenol **27**, the C_{11}-OMe position was obtained from the NOESY correlation of the methoxy group (3.79 ppm) with the H_{12} singlet (6.77 ppm), and only the chemical shifts attribution given in Figure 5 and in Table 1 satisfies the observed COSY and NOESY correlations.

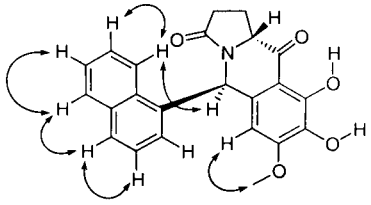


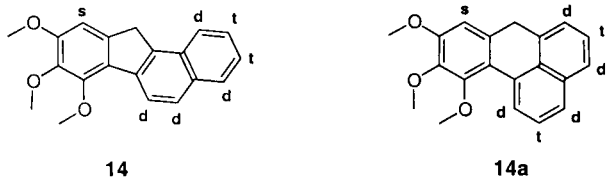
Figure 5. NOESY and COSY correlations observed for diphenol **27**.

their ^{1}H nmr spectra the systems of doublets and triplets indicated in Figure 6.

The chemical shifts of the aromatic protons of product **14** are reported in Table 2. When an irradiation was realized at 7.50 ppm (the middle point of the two triplet systems at 7.45 ppm and 7.54 ppm), the two doublets at 7.95 ppm and 8.01 ppm changed to singlets without modification of the 7.90 ppm and 8.20 ppm doublets. Irradiation of the 8.20 ppm doublet changed only the 7.90 ppm doublet. These data allowed us to know that the structure **14** was that of the by-product obtained during the cyclization of **11**.

All the new compounds were tested *in-vitro* for anti-tumor [15] and for tuberculostatic [16] activity, but none had interesting properties.

Benzofluorene **14**:



14 **14a**

Figure 6. ^{1}H nmr description of compounds **14** and **14a**.

Table 1

COSY (C) and NOESY (N) correlations for diphenol **27**

δ ppm	OMe 3.79 (s, 3 H)	H_{14} 6.86 (d, 1 H)	H_{16} 7.85 (d, 1 H)	H_{17} 7.93 (d, 1 H)	H_{20} 8.60 (d, 1 H)
H_{12} 6.77 (s, 1 H)	N				
H_6 7.12 (s, 1 H)					N
H_{15} 7.40 (t, 1 H)		C	C		
H_{18},H_{19} 7.60 (t, 2 H)				C	C
H_{16} 7.85 (d, 1 H)				N	

Table 2

^{1}H nmr Chemical Shift of Compound **14**

7.01 ppm	1 H s
7.45 ppm	1 H td J_1 = 8.2 Hz J_2 = 1.4 Hz
7.54 ppm	1 H td J_1 = 8.2 Hz J_2 = 1.4 Hz
7.90 ppm	1 H d J = 8.6 Hz
7.95 ppm	1 H d J = 8.6 Hz
8.01 ppm	1 H d J = 8.6 Hz
8.20 ppm	1 H d J = 8.6 Hz

Two structures, **14** and **14a**, were possible for the aromatic by-product isolated during the cyclization of acid **11**. *A-priori* these compounds were thought to show in

EXPERIMENTAL

Single Crystal X-ray Crystallographic Analysis for Compounds **5**, **13** and **12**: A representative crystal was surveyed and data set was collected on a Enraf-Nonius CAD-4 diffractometer. Atomic scattering factors were taken from the International Tables for X-Ray Crystallography [17]. All crystallographic calculations were facilitated by the SHELXL97 system [18]. The CAD-4 EXPRESS software was used for data collection and cell refinement [19]. Data reduction was realized, structures were solved and absorption correction were effected by using the HELENA [20], the SIR92 [21] and the PSI-SCAN [22] programs respectively. The refined structure was plotted using the SHELXL97 [18] and PLATON [23] plotting packages. Crystal details, data collection,

Table 3
Crystal Data and Structure Refinement for Ester **5**

Empirical formula	$C_{28}H_{30}NO_8$
Formula weight	508.55
Temperature	293(2) K
Wavelength	1.54178 Å
Crystal system, space group	Triclinic, P_{-1}
Cell dimensions	a = 9.190(10) Å
	b = 11.333(11) Å
	c = 14.756(10) Å
	α = 89.29(7)°
	β = 73.92(5)°
	γ = 66.72(7)°
	V = 1348.3(2) Å^3
Z, Calculated density, Mg/m^3	2, 1.253
Absorption coefficient, mm^{-1}	0.763
F(000)	538
Crystal size, mm	0.40 x 0.30 x 0.30
θ range for data collection	3.14 to 71.96°
Index ranges	0<=h<=11, -12<=k<=13, -17<=l<=18
Reflections collected/unique	5621 / 5274 [R(int) = 0.0078]
Completeness to 2θ = 71.96	99.7%
Absorption correction	ψ-scan
Max. and min. transmission	0.8035 and 0.7501
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5274 / 0 / 311
Goodness-of-fit on F^2	1.002
Final R indices [I>2σ(I)]	R1 = 0.0652, wR2 = 0.2071
R indices (all data)	R1 = 0.0669, wR2 = 0.2098
Extinction coefficient	0.013(2)
Largest diff. peak and hole	0.354 and -0.600 e. Å^{-3}

Table 4
Atomic Coordinates (x 10^4) and Equivalent Isotropic Dsplacement Parameters (Å^2 x 10^3) for Ester **5**

	x	y	z	U(eq)
C(1)	5886(2)	2741(2)	3165(1)	39(1)
C(2)	6384(2)	1659(2)	3797(1)	38(1)
C(3)	7774(2)	536(2)	3378(1)	45(1)
C(4)	8348(2)	-457(2)	3923(1)	46(1)
C(5)	7514(2)	-333(2)	4886(1)	44(1)
C(6)	6137(2)	799(2)	5299(1)	44(1)
C(7)	5564(2)	1802(2)	4755(1)	41(1)
C(8)	5602(2)	2309(2)	2282(1)	43(1)
C(9)	4870(3)	1458(2)	2329(1)	54(1)
C(10)	4543(3)	1082(3)	1524(2)	74(1)
C(11)	4990(4)	1553(3)	684(2)	85(1)
C(12)	5748(3)	2419(2)	601(1)	71(1)
C(13)	6047(2)	2828(2)	1411(1)	54(1)
C(14)	6742(3)	3758(2)	1321(2)	68(1)
C(15)	7151(4)	4208(3)	464(2)	96(1)
C(16)	6898(5)	3785(4)	-332(2)	107(1)
C(17)	6215(4)	2921(4)	-269(2)	102(1)
N(18)	4480(2)	3913(1)	3673(1)	38(1)
C(19)	4669(2)	4995(2)	3894(1)	44(1)
C(20)	2972(2)	6032(2)	4382(2)	52(1)
C(21)	1859(2)	5316(2)	4630(1)	51(1)
C(22)	2755(2)	4103(2)	3892(1)	40(1)
O(23)	9706(2)	-1587(1)	3584(1)	66(1)
C(24)	10636(4)	-1725(2)	2616(2)	84(1)
O(25)	8049(2)	-1343(1)	5414(1)	53(1)
C(26)	9158(3)	-1240(2)	5877(2)	65(1)
O(27)	5427(2)	839(1)	6247(1)	60(1)
C(28)	3996(3)	1962(2)	6711(2)	72(1)
O(29)	6000(2)	5082(1)	3722(1)	59(1)
C(30)	2108(2)	4425(2)	3036(1)	43(1)
O(31)	922(2)	4010(2)	3089(1)	66(1)
C(32)	102(4)	4348(5)	2364(2)	106(1)
O(33)	2532(2)	5032(1)	2430(1)	58(1)
O(41)	9701(4)	9573(3)	268(2)	133
O(42)	9245(6)	9144(5)	-945(4)	193
C(43)	9221(8)	8998(7)	-188(6)	168
C(44)	8624(11)	8072(9)	284(6)	219

*U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Table 5
Bond Lengths (Å) and Bonds Angles (°) for Ester **5**

C(1)-N(18)	1.458(2)	C(24)-H(24A)	0.9600
C(1)-C(8)	1.521(2)	C(24)-H(24B)	0.9600
C(1)-C(2)	1.532(2)	C(24)-H(24C)	0.9600
C(1)-H(1)	0.9800	O(25)-C(26)	1.415(2)
C(2)-C(7)	1.381(2)	C(26)-H(26A)	0.9600
C(2)-C(3)	1.390(2)	C(26)-H(26B)	0.9600
C(3)-C(4)	1.392(2)	C(26)-H(26C)	0.9600
C(3)-H(3)	0.9300	O(27)-C(28)	1.421(3)
C(4)-O(23)	1.362(2)	C(28)-H(28A)	0.9600
C(4)-C(5)	1.393(3)	C(28)-H(28B)	0.9600
C(5)-O(25)	1.380(2)	C(28)-H(28C)	0.9600
C(5)-C(6)	1.388(3)	C(30)-O(33)	1.195(2)
C(6)-O(27)	1.363(2)	C(30)-O(31)	1.332(2)
C(6)-C(7)	1.398(2)	O(31)-C(32)	1.437(3)
C(7)-H(7)	0.9300	C(32)-H(32A)	0.9600
C(8)-C(9)	1.368(3)	C(32)-H(32B)	0.9600
C(8)-C(13)	1.431(2)	C(32)-H(32C)	0.9600
C(9)-C(10)	1.412(3)	O(41)-C(43)	1.214(7)
C(9)-H(9)	0.9300	O(41)-O(41)#1	1.424(6)
C(10)-C(11)	1.366(4)	O(42)-C(43)	1.123(8)
C(10)-H(10)	0.9300	C(43)-C(44)	1.453(10)
C(11)-C(12)	1.398(4)	C(44)-H(44A)	0.9600
C(11)-H(11)	0.9300	C(44)-H(44B)	0.9600
C(12)-C(13)	1.419(3)	C(44)-H(44C)	0.9600
C(12)-C(17)	1.423(4)	N(18)-C(1)-C(8)	110.88(13)
C(13)-C(14)	1.420(3)	N(18)-C(1)-C(2)	113.47(13)
C(14)-C(15)	1.369(3)	C(8)-C(1)-C(2)	113.11(13)
C(14)-H(14)	0.9300	C(5)-C(6)-C(7)	120.6(2)
C(15)-C(16)	1.384(6)	C(2)-C(7)-C(6)	119.3(2)
C(15)-H(15)	0.9300	C(2)-C(7)-H(7)	120.3
C(16)-C(17)	1.346(6)	N(18)-C(1)-H(1)	106.3
C(16)-H(16)	0.9300	C(8)-C(1)-H(1)	106.3
C(17)-H(17)	0.9300	C(2)-C(1)-H(1)	106.3
N(18)-C(19)	1.360(2)	C(7)-C(2)-C(3)	120.6(2)
N(18)-C(22)	1.454(2)	C(7)-C(2)-C(1)	122.37(14)
C(19)-O(29)	1.221(2)	C(3)-C(2)-C(1)	116.94(14)
C(19)-C(20)	1.510(2)	C(2)-C(3)-C(4)	119.9(2)
C(20)-C(21)	1.510(3)	C(2)-C(3)-H(3)	120.0
C(20)-H(20A)	0.9700	C(4)-C(3)-H(3)	120.0
C(20)-H(20B)	0.9700	O(23)-C(4)-C(3)	124.5(2)
C(21)-C(22)	1.550(2)	O(23)-C(4)-C(5)	115.5(2)
C(21)-H(21A)	0.9700	C(3)-C(4)-C(5)	120.0(2)
C(21)-H(21B)	0.9700	O(25)-C(5)-C(6)	120.7(2)
C(22)-C(30)	1.521(2)	O(25)-C(5)-C(4)	119.7(2)
C(22)-H(22)	0.9800	C(6)-C(5)-C(4)	119.6(2)
O(23)-C(24)	1.420(3)	O(27)-C(6)-C(5)	115.2(2)

Table 5 (continued)

O(27)-C(6)-C(7)		H(21A)-C(21)-H(21B)	109.0
124.2(2)C(6)-C(7)-H(7)	120.3	N(18)-C(22)-C(30)	112.12(13)
C(9)-C(8)-C(13)	120.1(2)	N(18)-C(22)-C(21)	102.21(13)
C(9)-C(8)-C(1)	120.0(2)	C(30)-C(22)-C(21)	108.16(14)
C(13)-C(8)-C(1)	119.9(2)	N(18)-C(22)-H(22)	111.3
C(8)-C(9)-C(10)	120.7(2)	C(30)-C(22)-H(22)	111.3
C(8)-C(9)-H(9)	119.6	C(21)-C(22)-H(22)	111.3
C(10)-C(9)-H(9)	119.6	C(4)-O(23)-C(24)	117.2(2)
C(11)-C(10)-C(9)	119.7(3)	O(23)-C(24)-H(24A)	109.5
C(11)-C(10)-H(10)	120.1	O(23)-C(24)-H(24B)	109.5
C(9)-C(10)-H(10)	120.1	H(24A)-C(24)-H(24B)	109.5
C(10)-C(11)-C(12)	121.5(2)	O(23)-C(24)-H(24C)	109.5
C(10)-C(11)-H(11)	119.2	H(24A)-C(24)-H(24C)	109.5
C(12)-C(11)-H(11)	119.2	H(24B)-C(24)-H(24C)	109.5
C(11)-C(12)-C(13)	119.3(2)	C(5)-O(25)-C(26)	113.12(14)
C(11)-C(12)-C(17)	122.1(3)	O(25)-C(26)-H(26A)	109.5
C(13)-C(12)-C(17)	118.6(3)	O(25)-C(26)-H(26B)	109.5
C(12)-C(13)-C(14)	118.2(2)	H(26A)-C(26)-H(26B)	109.5
C(12)-C(13)-C(8)	118.6(2)	O(25)-C(26)-H(26C)	109.5
C(14)-C(13)-C(8)	123.1(2)	H(26A)-C(26)-H(26C)	109.5
C(15)-C(14)-C(13)	120.1(3)	H(26B)-C(26)-H(26C)	109.5
C(15)-C(14)-H(14)	119.9	C(6)-O(27)-C(28)	118.1(2)
C(13)-C(14)-H(14)	119.9	O(27)-C(28)-H(28A)	109.5
C(14)-C(15)-C(16)	121.7(3)	O(27)-C(28)-H(28B)	109.5
C(14)-C(15)-H(15)	119.2	H(28A)-C(28)-H(28B)	109.5
C(16)-C(15)-H(15)	119.2	O(27)-C(28)-H(28C)	109.5
C(17)-C(16)-C(15)	119.8(3)	H(28A)-C(28)-H(28C)	109.5
C(17)-C(16)-H(16)	120.1	H(28B)-C(28)-H(28C)	109.5
C(15)-C(16)-H(16)	120.1	O(33)-C(30)-O(31)	124.6(2)
C(16)-C(17)-C(12)	121.5(3)	O(33)-C(30)-C(22)	124.9(2)
C(16)-C(17)-H(17)	119.2	O(31)-C(30)-C(22)	110.37(14)
C(12)-C(17)-H(17)	119.2	C(30)-O(31)-C(32)	116.2(2)
C(19)-N(18)-C(22)	113.30(13)	O(31)-C(32)-H(32A)	109.5
C(19)-N(18)-C(1)	121.95(13)	O(31)-C(32)-H(32B)	109.5
C(22)-N(18)-C(1)	124.37(12)	H(32A)-C(32)-H(32B)	109.5
O(29)-C(19)-N(18)	124.6(2)	O(31)-C(32)-H(32C)	109.5
O(29)-C(19)-C(20)	127.3(2)	H(32A)-C(32)-H(32C)	109.5
N(18)-C(19)-C(20)	108.12(14)	H(32B)-C(32)-H(32C)	109.5
C(21)-C(20)-C(19)	104.39(14)	C(43)-O(41)-O(41)#1	112.4(6)
C(21)-C(20)-H(20A)	110.9	O(42)-C(43)-O(41)	122.9(8)
C(19)-C(20)-H(20A)	110.9	O(42)-C(43)-C(44)	120.1(8)
C(21)-C(20)-H(20B)	110.9	O(41)-C(43)-C(44)	117.0(8)
C(19)-C(20)-H(20B)	110.9	C(43)-C(44)-H(44A)	109.5
H(20A)-C(20)-H(20B)	108.9	C(43)-C(44)-H(44B)	109.5
C(20)-C(21)-C(22)	103.95(14)	H(44A)-C(44)-H(44B)	109.5
C(20)-C(21)-H(21A)	111.0	C(43)-C(44)-H(44C)	109.5
C(22)-C(21)-H(21A)	111.0	H(44A)-C(44)-H(44C)	109.5
C(20)-C(21)-H(21B)	111.0	H(44B)-C(44)-H(44C)	109.5
C(22)-C(21)-H(21B)	111.0		

refinement parameters, coordinates, anisotropic temperature factors, distances and angles are summarized in Tables 3-11.

Melting points are uncorrected. The ir spectra were recorded on a Perkin-Elmer 700 spectrometer and the nmr spectra on a Varian Gemini 2000 at 200 MHz for ^1H and 50 MHz for ^{13}C, using tetramethylsilane as an internal reference. The numbering used in the nmr description of products is shown in Figure 4. Elemental analyses were performed by the Service Central de Microanalyses (CNRS, Vernaison, France). Melting points, ir spectra and elemental analyses were not determined for moisture sensitive compounds. Pyroglutamic acid was a gift of UCIB, Ivry-la-Bataille, France, which can provide this chemical in bulk quantities. All compounds were synthesized starting from *dl* pyroglutamic acid.

Table 6

Crystal Data and Structure Refinement for Ketone **12**.

Empirical formula	$C_{25}H_{23}NO_5$
Formula weight	417.44
Temperature	293(2) K
Wavelength	1.54178 Å
Crystal system, space group	Monoclinic, $P^2_{1/c}$
Unit cell dimensions	a = 10.868(10) Å b = 12.937(10) Å c = 15.049(10) Å α = 90° β =96.01(4)° γ = 90° V = 2104.3(3) Å^3
Absorption coefficient	0.752 mm^{-1}
Z, Calculated density, Mg/m^3	4, 1.318
F(000)	880
Crystal size, mm	0.30 x 0.30 x 0.15
θ range for data collection	4.09 to 71.90°
Index ranges	-11<=h<=13, 0<=k<=15, -18<=l<=18
Reflections collected/unique	7065/4129 [R(int) = 0.0193]
Completeness to 2θ = 71.90	95.5%
Absorption correction	Analytical
Max. and min. transmission	0.8956 and 0.8059
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4129/0/281
Goodness-of-fit on F^2	1.053
Final R indices [I>2σ(I)]	R1 = 0.0399, wR2 = 0.1121
R indices (all data)	R1 = 0.0491, wR2 = 0.1188
Extinction coefficient	0.0047(4)
Largest diff. peak and hole	0.158 and -0.146 e. Å^{-3}

1-Naphthyl-(3,4,5-trimethoxylphenyl)carbinol.

A few drops of dibromoethane were added to a suspension of magnesium (25.8 g, 1.068 mol) in tetrahydrofuran (200 ml). Once the reaction began, a solution of 1-bromonaphthalene (200 g, 0.966 mol) in tetrahydrofuran (250 ml) was added slowly while keeping the temperature at 55°. After stirring for 4 hours at the same temperature, a solution of 3,4,5-trimethoxybenzaldehyde (189.5 g, 0.966 mol) in tetrahydrofuran (450 ml) was added slowly, then the mixture was heated at 60° for 2 hours. The solvent was evaporated, and a solution of ammonium chloride (280 g) in water (1200 ml) was added. After extraction with methylene dichloride, drying and evaporation, the alcohol was obtained as an oil which crystallized in toluene as a colorless solid, yield 89%, mp 50° (toluene; the compound crystallized with 1/2 molecule of toluene); ir (potassium bromide):ν cm^{-1} 3100-3400 (b, O-H), 1600, 1500, 1450 (C=C), 1170 (C–O); ^1H nmr (deuteriochloroform): δ ppm 2.57 (bs, deuterium oxide-exchangeable, 1 H, OH), 3.77 (s, 4.5 H, OCH_3), 3.82 (s, 4.5 H, OCH_3), 3.82 (s, 4.5 H, OCH_3), 6.42 (s, 1 H, H_6), 6.62 (s, 2 H, H_8 and H_{12}), 7.10-7.60 (m, 4 H), 7.70-7.90 (m, 2 H), 8-8.20 (m, 1 H); ^{13}C nmr (deuteriochloroform): δ ppm 56.1 (C_9-O*C*H$_3$, C_{11}-O*C*H$_3$), 60.9 (C_{10}-O*C*H$_3$), 73.7 (C_6), 104.2 (C_8, C_{12}), 124.0, 124.8, 125.8, 126.4, 128.8, 128.9, 129.2 (C_{14}-C_{20}), 130.9, 134.1, 138.0, 138.8, 139.9 (C_7, C_{10}, C_{13}, C_{22}, C_{23}), 153.4 (C_9, C_{11}).

Anal. Calcd. for $C_{20}H_{20}O_4$, 1/2C_7H_8: 76.19; H 6.53; O, 17.28. Found: C, 76.01; H, 6.53; O, 17.33.

1-Naphthyl-(3,4,5-trimethoxylphenyl)carbinol Trimethylsilyl Ether (**3**).

Chlorotrimethylsilane (1 ml) was added *via* syringe to a mixture of hexamethyldisilazane (250 ml) and 1-naphthyl-(3,4,5-

Table 7

Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$ x 10^3) for Ketone **12**.

	x	y	z	U(eq)
C(1)	5728(1)	917(1)	1826(1)	48(1)
C(2)	6810(1)	1283(1)	2485(1)	46(1)
C(3)	7712(1)	1946(1)	2237(1)	50(1)
C(4)	8680(1)	2242(1)	2868(1)	51(1)
C(5)	8724(1)	1890(1)	3743(1)	51(1)
C(6)	7783(1)	1258(1)	3993(1)	51(1)
C(7)	6840(1)	939(1)	3361(1)	50(1)
C(8)	5918(1)	1058(1)	852(1)	43(1)
C(9)	5232(1)	1764(1)	318(1)	51(1)
C(10)	5424(2)	1870(1)	-596(1)	62(1)
C(11)	6297(2)	1313(1)	-952(1)	64(1)
C(12)	7031(1)	597(1)	-428(1)	55(1)
C(13)	7983(2)	18(2)	-779(1)	74(1)
C(14)	8676(2)	-671(2)	-265(1)	82(1)
C(15)	8464(2)	-829(1)	617(1)	75(1)
C(16)	7574(1)	-287(1)	983(1)	58(1)
C(17)	6832(1)	450(1)	480(1)	46(1)
N(18)	4594(1)	1428(1)	2018(1)	62(1)
C(19)	3770(2)	1018(2)	2523(1)	83(1)
C(20)	2775(2)	1825(3)	2603(2)	116(1)
C(21)	3012(2)	2675(3)	1966(2)	123(1)
C(22)	4298(2)	2458(2)	1673(1)	74(1)
O(23)	9630(1)	2875(1)	2688(1)	70(1)
C(24)	9529(2)	3396(2)	1865(1)	95(1)
O(25)	9666(1)	2205(1)	4365(1)	65(1)
C(26)	10601(2)	1449(2)	4554(1)	78(1)
O(27)	7870(1)	1004(1)	4875(1)	70(1)
C(28)	6841(2)	500(1)	5191(1)	71(1)
O(29)	3849(1)	160(2)	2860(1)	102(1)
C(30)	4331(1)	2458(1)	680(1)	64(1)
O(31)	3665(1)	3028(1)	201(1)	99(1)

* U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Table 8

Bond Lengths (Å) and angles (°) for Ketone **12**

C(1)-N(18)	1.454(2)	C(12)-C(17)	1.419(2)
C(1)-C(8)	1.512(2)	C(12)-C(13)	1.423(2)
C(1)-C(2)	1.531(2)	C(13)-C(14)	1.357(3)
C(1)-H(1)	0.9800	C(13)-H(13)	0.9300
C(2)-C(3)	1.383(2)	C(14)-C(15)	1.386(3)
C(2)-C(7)	1.388(2)	C(14)-H(14)	0.9300
C(3)-C(4)	1.395(2)	C(15)-C(16)	1.358(2)
C(3)-H(3)	0.9300	C(15)-H(15)	0.9300
C(4)-O(23)	1.366(2)	C(16)-C(17)	1.416(2)
C(4)-C(5)	1.390(2)	C(16)-H(16)	0.9300
C(5)-O(25)	1.375(2)	N(18)-C(19)	1.343(2)
C(5)-C(6)	1.391(2)	N(18)-C(22)	1.454(2)
C(6)-O(27)	1.361(2)	C(19)-O(29)	1.220(3)
C(6)-C(7)	1.387(2)	C(19)-C(20)	1.516(3)
C(7)-H(7)	0.9300	C(20)-C(21)	1.497(4)
C(8)-C(9)	1.382(2)	C(20)-H(20A)	0.9700
C(8)-C(17)	1.426(2)	C(20)-H(20B)	0.9700
C(9)-C(10)	1.420(2)	C(21)-C(22)	1.535(3)
C(9)-C(30)	1.474(2)	C(21)-H(21A)	0.9700
C(10)-C(11)	1.346(2)	C(21)-H(21B)	0.9700
C(10)-H(10)	0.9300	C(22)-C(30)	1.498(2)
C(11)-C(12)	1.408(2)	C(22)-H(22)	0.9800
C(11)-H(11)	0.9300	O(23)-C(24)	1.405(2)

Table 8 Continued

C(24)-H(24A)	0.9600	C(16)-C(15)-C(14)	120.6(2)
C(24)-H(24B)	0.9600	C(16)-C(15)-H(15)	119.7
C(24)-H(24C)	0.9600	C(14)-C(15)-H(15)	119.7
O(25)-C(26)	1.418(2)	C(15)-C(16)-C(17)	121.4(2)
C(26)-H(26A)	0.9600	C(15)-C(16)-H(16)	119.3
C(26)-H(26B)	0.9600	C(17)-C(16)-H(16)	119.3
C(26)-H(26C)	0.9600	C(16)-C(17)-C(12)	117.99(13)
O(27)-C(28)	1.419(2)	C(16)-C(17)-C(8)	122.88(12)
C(28)-H(28A)	0.9600	C(12)-C(17)-C(8)	119.12(12)
C(28)-H(28B)	0.9600	C(19)-N(18)-C(1)	124.3(2)
C(28)-H(28C)	0.9600	C(19)-N(18)-C(22)	115.4(2)
C(30)-O(31)	1.217(2)	C(1)-N(18)-C(22)	120.37(13)
N(18)-C(1)-C(8)	110.02(11)	O(29)-C(19)-N(18)	124.9(2)
N(18)-C(1)-C(2)	109.87(11)	O(29)-C(19)-C(20)	127.9(2)
C(8)-C(1)-C(2)	114.65(11)	N(18)-C(19)-C(20)	107.2(2)
N(18)-C(1)-H(1)	107.3	C(21)-C(20)-C(19)	106.5(2)
C(8)-C(1)-H(1)	107.3	C(21)-C(20)-H(20A)	110.4
C(2)-C(1)-H(1)	107.3	C(19)-C(20)-H(20A)	110.4
C(3)-C(2)-C(7)	120.52(11)	C(21)-C(20)-H(20B)	110.4
C(3)-C(2)-C(1)	122.33(11)	C(19)-C(20)-H(20B)	110.4
C(7)-C(2)-C(1)	117.13(11)	H(20A)-C(20)-H(20B)	108.6
C(2)-C(3)-C(4)	119.52(12)	C(20)-C(21)-C(22)	105.8(2)
C(2)-C(3)-H(3)	120.2	C(20)-C(21)-H(21A)	110.6
C(4)-C(3)-H(3)	120.2	C(22)-C(21)-H(21A)	110.6
O(23)-C(4)-C(5)	115.58(11)	C(20)-C(21)-H(21B)	110.6
O(23)-C(4)-C(3)	124.21(12)	C(22)-C(21)-H(21B)	110.6
C(5)-C(4)-C(3)	120.21(12)	H(21A)-C(21)-H(21B)	108.7
O(25)-C(5)-C(4)	119.82(12)	N(18)-C(22)-C(30)	109.18(13)
O(25)-C(5)-C(6)	120.42(12)	N(18)-C(22)-C(21)	103.8(2)
C(4)-C(5)-C(6)	119.70(11)	C(30)-C(22)-C(21)	113.8(2)
O(27)-C(6)-C(7)	124.62(13)	N(18)-C(22)-H(22)	109.9
O(27)-C(6)-C(5)	115.30(11)	C(30)-C(22)-H(22)	109.9
C(7)-C(6)-C(5)	120.07(12)	C(21)-C(22)-H(22)	109.9
C(6)-C(7)-C(2)	119.89(12)	C(4)-O(23)-C(24)	118.10(12)
C(6)-C(7)-H(7)	120.1	O(23)-C(24)-H(24A)	109.5
C(2)-C(7)-H(7)	120.1	O(23)-C(24)-H(24B)	109.5
C(9)-C(8)-C(17)	119.42(12)	H(24A)-C(24)-H(24B)	109.5
C(9)-C(8)-C(1)	121.58(12)	O(23)-C(24)-H(24C)	109.5
C(17)-C(8)-C(1)	119.00(11)	H(24A)-C(24)-H(24C)	109.5
C(8)-C(9)-C(10)	120.16(13)	H(24B)-C(24)-H(24C)	109.5
C(8)-C(9)-C(30)	121.71(13)	C(5)-O(25)-C(26)	113.51(13)
C(10)-C(9)-C(30)	118.06(13)	O(25)-C(26)-H(26A)	109.5
C(11)-C(10)-C(9)	121.00(13)	O(25)-C(26)-H(26B)	109.5
C(11)-C(10)-H(10)	119.5	H(26A)-C(26)-H(26B)	109.5
C(9)-C(10)-H(10)	119.5	O(25)-C(26)-H(26C)	109.5
C(10)-C(11)-C(12)	120.70(14)	H(26A)-C(26)-H(26C)	109.5
C(10)-C(11)-H(11)	119.6	H(26B)-C(26)-H(26C)	109.5
C(12)-C(11)-H(11)	119.6	C(6)-O(27)-C(28)	117.48(11)
C(11)-C(12)-C(17)	119.54(14)	O(27)-C(28)-H(28A)	109.5
C(11)-C(12)-C(13)	122.0(2)	O(27)-C(28)-H(28B)	109.5
C(17)-C(12)-C(13)	118.45(14)	H(28A)-C(28)-H(28B)	109.5
C(14)-C(13)-C(12)	121.2(2)	O(27)-C(28)-H(28C)	109.5
C(14)-C(13)-H(13)	119.4	H(28A)-C(28)-H(28C)	109.5
C(12)-C(13)-H(13)	119.4	H(28B)-C(28)-H(28C)	109.5
C(13)-C(14)-C(15)	120.3(2)	O(31)-C(30)-C(9)	121.8(2)
C(13)-C(14)-H(14)	119.8	O(31)-C(30)-C(22)	121.1(2)
C(15)-C(14)-H(14)	119.8	C(9)-C(30)-C(22)	117.07(13)

trimethoxyphenyl)-carbinol (310 g; 0.956 mol). The mixture was heated at 130° for 2 hours, the excess hexamethyldisilazane was evaporated (sublimation of ammonium chloride), giving a quantitative yield of the silyl ether **3** as a yellow oil; ^{1}H nmr (deuteriochloroform): δ ppm 0.09 (s, 9 H, $OSi(CH_3)_3$), 3.72 (s, 6 H, 9-OCH_3 and 11-OCH_3), 3.79 (s, 3 H, 10-OCH_3), 6.36 (s, 1 H, H6), 6.80 (s, 2 H, H8 and H12), 7.00-8.20 (m, 7 H, ArH).

Table 9

Crystal Data and Structure Refinement for Lactam **13**

Empirical formula	$C_{24}H_{23}NO_4$
Formula weight	389.43
Temperature	293(2) K
Wavelength	1.54178 Å
Crystal system, space group	Monoclinic, $P2_{1/c}$
Cell dimensions	a = 9.909(10) Å
	b = 8.519(10) Å
	c = 23.793(10) Å
	α = 90°
	β = 98.10(4)°
	γ = 90°
	V = 1988.4(3) ≈^{3}
Z, Calculated density, Mg/m^3	4, 1.301
Absorption coefficient, mm^{-1}	0.716
F(000)	824
Crystal size, mm	0.40 x 0.40 x 0.30
θ range for data collection	3.75 to 71.90°
Index ranges	-12<=h<=12, -10<=k<=6, -29<=l<=0
Reflections collected/unique	4760/3902 [R(int) = 0.0118]
Completeness to 2θ = 71.90	93.2%
Absorption correction	ψ−scan
Max. and min. transmission	0.8138 and 0.7626
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3902/0/263
Goodness-of-fit on F^2	1.085
Final R indices [I>2σ(I)]	R1 = 0.0411, wR2 = 0.1170
R indices (all data)	R1 = 0.0432, wR2 = 0.1184
Extinction coefficient	0.0024(3)
Largest diff. peak and hole	0.215 and -0.160 e. ≈$^{-3}$

Table 10

Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters (Å^2 x 10^3) for Lactam **13.**

	x	y	z	U(eq)
C(1)	3009(1)	6469(2)	3552(1)	46(1)
C(2)	2692(1)	4958(2)	3860(1)	47(1)
C(3)	3676(2)	3831(2)	4017(1)	53(1)
C(4)	3343(2)	2478(2)	4297(1)	52(1)
C(5)	2027(1)	2250(2)	4416(1)	50(1)
C(6)	1049(1)	3405(2)	4269(1)	53(1)
C(7)	1375(2)	4752(2)	3987(1)	54(1)
C(8)	4510(1)	6772(2)	3559(1)	46(1)
C(9)	5278(2)	7413(2)	4027(1)	57(1)
C(10)	6686(2)	7674(2)	4043(1)	64(1)
C(11)	7315(2)	7277(2)	3593(1)	61(1)
C(12)	6575(1)	6602(2)	3102(1)	52(1)
C(17)	5148(1)	6367(1)	3078(1)	44(1)
C(16)	4392(1)	5764(2)	2571(1)	46(1)
C(15)	5063(2)	5358(2)	2126(1)	57(1)
C(14)	6477(2)	5551(2)	2156(1)	65(1)
C(13)	7214(2)	6168(2)	2629(1)	62(1)
N(18)	2329(1)	6480(1)	2967(1)	45(1)
C(19)	1143(1)	7211(2)	2792(1)	51(1)
C(20)	775(2)	6909(2)	2164(1)	67(1)
C(21)	2073(2)	6302(2)	1981(1)	68(1)
C(22)	2872(1)	5593(2)	2524(1)	49(1)
O(23)	4256(1)	1313(1)	4479(1)	69(1)
C(24)	5654(2)	1636(2)	4476(1)	69(1)
O(25)	1727(1)	946(1)	4716(1)	60(1)
C(26)	977(2)	-248(2)	4392(1)	84(1)
O(27)	-191(1)	3108(2)	4432(1)	75(1)
C(28)	-1200(2)	4292(3)	4326(1)	84(1)
O(29)	483(1)	7967(2)	3098(1)	68(1)

*U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Table 11

Bond lengths (Å)° and Angles (°) for Lactam **13**

C(1)-N(18)	1.460(2)	C(2)-C(3)-C(4)	119.86(13)
C(1)-C(8)	1.508(2)	C(2)-C(3)-H(3)	120.1
C(1)-C(2)	1.535(2)	C(4)-C(3)-H(3)	120.1
C(1)-H(1)	0.9800	O(23)-C(4)-C(5)	115.59(12)
C(2)-C(3)	1.382(2)	O(23)-C(4)-C(3)	124.01(13)
C(2)-C(7)	1.391(2)	C(5)-C(4)-C(3)	120.40(13)
C(3)-C(4)	1.395(2)	O(25)-C(5)-C(4)	119.84(13)
C(3)-H(3)	0.9300	O(25)-C(5)-C(6)	120.53(12)
C(4)-O(23)	1.371(2)	C(4)-C(5)-C(6)	119.44(12)
C(4)-C(5)	1.387(2)	O(27)-C(6)-C(7)	124.78(13)
C(5)-O(25)	1.376(2)	O(27)-C(6)-C(5)	114.91(13)
C(5)-C(6)	1.391(2)	C(7)-C(6)-C(5)	120.30(13)
C(6)-O(27)	1.363(2)	C(6)-C(7)-C(2)	119.86(13)
C(6)-C(7)	1.390(2)	C(6)-C(7)-H(7)	120.1
C(7)-H(7)	0.9300	C(2)-C(7)-H(7)	120.1
C(8)-C(9)	1.372(2)	C(9)-C(8)-C(17)	119.41(13)
C(8)-C(17)	1.425(2)	C(9)-C(8)-C(1)	120.65(12)
C(9)-C(10)	1.407(2)	C(17)-C(8)-C(1)	119.93(11)
C(9)-H(9)	0.9300	C(8)-C(9)-C(10)	121.26(14)
C(10)-C(11)	1.356(2)	C(8)-C(9)-H(9)	119.4
C(10)-H(10)	0.9300	C(10)-C(9)-H(9)	119.4
C(11)-C(12)	1.412(2)	C(11)-C(10)-C(9)	120.27(14)
C(11)-H(11)	0.9300	C(11)-C(10)-H(10)	119.9
C(12)-C(13)	1.415(2)	C(9)-C(10)-H(10)	119.9
C(12)-C(17)	1.422(2)	C(10)-C(11)-C(12)	120.83(14)
C(17)-C(16)	1.423(2)	C(10)-C(11)-H(11)	119.6
C(16)-C(15)	1.373(2)	C(12)-C(11)-H(11)	119.6
C(16)-C(22)	1.502(2)	C(11)-C(12)-C(13)	121.77(14)
C(15)-C(14)	1.403(2)	C(11)-C(12)-C(17)	119.19(13)
C(15)-H(15)	0.9300	C(13)-C(12)-C(17)	119.04(14)
C(14)-C(13)	1.358(2)	C(12)-C(17)-C(16)	119.10(12)
C(14)-H(14)	0.9300	C(12)-C(17)-C(8)	119.02(12)
C(13)-H(13)	0.9300	C(16)-C(17)-C(8)	121.87(12)
N(18)-C(19)	1.343(2)	C(15)-C(16)-C(17)	119.41(13)
N(18)-C(22)	1.460(2)	C(15)-C(16)-C(22)	120.49(12)
C(19)-O(29)	1.227(2)	C(17)-C(16)-C(22)	120.09(11)
C(19)-C(20)	1.511(2)	C(16)-C(15)-C(14)	121.32(14)
C(20)-C(21)	1.506(2)	C(16)-C(15)-H(15)	119.3
C(20)-H(20A)	0.9700	C(14)-C(15)-H(15)	119.3
C(20)-H(20B)	0.9700	C(13)-C(14)-C(15)	120.33(14)
C(21)-C(22)	1.539(2)	C(13)-C(14)-H(14)	119.8
C(21)-H(21A)	0.9700	C(15)-C(14)-H(14)	119.8
C(21)-H(21B)	0.9700	C(14)-C(13)-C(12)	120.74(14)
C(22)-H(22)	0.9800	C(14)-C(13)-H(13)	119.6
O(23)-C(24)	1.413(2)	C(12)-C(13)-H(13)	119.6
C(24)-H(24A)	0.9600	C(19)-N(18)-C(22)	114.34(11)
C(24)-H(24B)	0.9600	C(19)-N(18)-C(1)	124.30(11)
C(24)-H(24C)	0 .9600	C(22)-N(18)-C(1)	121.26(10)
O(25)-C(26)	1.421(2)	O(29)-C(19)-N(18)	125.24(13)
C(26)-H(26A)	0.9600	O(29)-C(19)-C(20)	126.96(13)
C(26)-H(26B)	0.9600	N(18)-C(19)-C(20)	107.79(12)
C(26)-H(26C)	0.9600	C(21)-C(20)-C(19)	104.31(12)
O(27)-C(28)	1.417(2)	C(21)-C(20)-H(20A)	110.9
C(28)-H(28A)	0.9600	C(19)-C(20)-H(20A)	110.9
C(28)-H(28B)	0.9600	C(21)-C(20)-H(20B)	110.9
C(28)-H(28C)	0.9600	C(19)-C(20)-H(20B)	110.9
N(18)-C(1)-C(8)	109.27(10)	H(20A)-C(20)-H(20B)	108.9
N(18)-C(1)-C(2)	111.26(11)	C(20)-C(21)-C(22)	104.58(12)
C(8)-C(1)-C(2)	113.99(11)	C(20)-C(21)-H(21A)	110.8
N(18)-C(1)-H(1)	107.3	C(22)-C(21)-H(21A)	110.8
C(8)-C(1)-H(1)	107.3	C(20)-C(21)-H(21B)	110.8
C(2)-C(1)-H(1)	107.3	C(22)-C(21)-H(21B)	110.8
C(3)-C(2)-C(7)	120.11(12)	H(21A)-C(21)-H(21B)	108.9
C(3)-C(2)-C(1)	121.81(12)	N(18)-C(22)-C(16)	111.27(11)
C(7)-C(2)-C(1)	118.07(12)	N(18)-C(22)-C(21)	101.80(11)

Table 11 Continued 1

C(16)-C(22)-C(21)	114.62(12)	O(25)-C(26)-H(26B)	109.5
N(18)-C(22)-H(22)	109.6	H(26A)-C(26)-H(26B)	109.5
C(16)-C(22)-H(22)	109.6	O(25)-C(26)-H(26C)	109.5
C(21)-C(22)-H(22)	109.6	H(26A)-C(26)-H(26C)	109.5
C(4)-O(23)-C(24)	117.44(12)	H(26B)-C(26)-H(26C)	109.5
O(23)-C(24)-H(24A)	109.5	C(6)-O(27)-C(28)	117.31(13)
O(23)-C(24)-H(24B)	109.5	O(27)-C(28)-H(28A)	109.5
H(24A)-C(24)-H(24B)	109.5	O(27)-C(28)-H(28B)	109.5
O(23)-C(24)-H(24C)	109.5	H(28A)-C(28)-H(28B)	109.5
H(24A)-C(24)-H(24C)	109.5	O(27)-C(28)-H(28C)	109.5
H(24B)-C(24)-H(24C)	109.5	H(28A)-C(28)-H(28C)	109.5
C(5)-O(25)-C(26)	115.54(12)	H(28B)-C(28)-H(28C)	109.5
O(25)-C(26)-H(26A)	109.5		

Methyl *N*-[Naphthyl-(3,4,5-trimethoxyphenyl)-methyl]-pyroglutamate (**4, 5**).

Triflic acid (1.5 ml, 16.8 mmol) was added *via* syringe to a stirred mixture of the silyl ether **3** (379 g, 0.956 mol), and silyl compound **1** (224.4 g, 1.04 mol). The solution was heated under nitrogen atmosphere for 1 hour at 130° in a vessel equipped with a short distillation head. During the course of the reaction hexamethyldisiloxane distilled. The nmr yield was 100% as an equimolar diastereomeric mixture of compounds **4** and **5**. After cooling, the mixture was diluted with methylene dichloride and washed with water. The solvent was removed under vacuum to afford a crude oil.The two diastereoisomers **4** and **5** were separated by crystallization: **4** precipitated after addition of ethyl acetate and was filtered as a colorless solid. The organic layer was then evaporated giving compound **5** as an oil which was crystallized as a white solid in cold ethyl acetate solution.

Ester **4**:

Yield 40%, mp 212° (ethyl acetate); ir (potassium bromide): ν cm^{-1} 1730 (C=O), 1685 (C=O), 1585, 1500, 1450 (C=C), 1130 (C–O); ^1H nmr (deuteriochloroform): δ ppm 1.95-2.20 (m, 1H, H_4), 2.20-2.60 (m, 2 H, H_3), 2.60-2.90 (m, 1 H, H_4), 3.39 (s, 3 H, CO_2CH_3), 3.75 (s, 6 H, 9-OCH_3 and 11-OCH_3), 3.82 (s, 3 H, 10-OCH_3), 4.04 (d, J = 8.5 Hz, 1H, H_5), 6.51 (s, 2 H, H_8 and H_{12}), 7.08 (s, 1 H, H_6), 7.19 (d, J = 7.2 Hz, 1 H, H_{14}), 7.40-7.55 (m, 3 H, H_{15}, H_{18} and H_{19}), 7.70-7.90 (m, 3 H, H_{16}, H_{17} and H_{20}); ^{13}C nmr (deuteriochloroform): δ ppm 24.7 (C_4), 29.9 (C_3), 52.0 (CO_2CH_3), 56.2 (C_9-OCH_3, C_{11}-OCH_3), 57.7 (C_5), 59.2 (C_6), 60.8 (C_{10}-OCH_3), 106.9 (C_8 and C_{12}), 123.7, 124.8, 125.0, 126.0, 126.8, 129.0 (C_{14}-C_{20}), 131.4, 133.9, 134.2, 134.7, 137.5 (C_7, C_{10}, C_{13}, C_{22}, C_{23}), 153.2 (C_9, C_{11}), 173.1 (C_2), 175.8 (C_{21}).

Anal. Calcd for $C_{26}H_{27}NO_6$: C, 69.47; H, 6.05; N, 3.12; O, 21.36. Found: C, 69.54; H, 6.17; N, 3.14; O, 21.61.

Ester **5**:

Yield 41%, mp 68° (Methanol) (crystallized with one molecule of methanol); ir (potassium bromide): ν cm^{-1} 1730 (C=O), 1680 (C=O), 1590, 1505, 1450 (C=C), 1130 (C–O); ^1H nmr (deuteriochloroform): δ ppm 1.95-2.24 (m, 1 H, H_4), 2.24-2.91 (m, 3 H, H_3 and H_4), 2.45 (s, 3 H, CO_2CH_3), 3.78 (s, 6 H, 9-OCH_3 and 11-OCH_3), 3.86 (s, 3 H, 10-OCH_3), 4.36 (d, J = 9.4 Hz, 1 H, H_5), 6.35 (s, 2 H, H_8 and H_{12}), 7.21 (s, 1 H, H_6), 7.31-7.42 (m, 2 H, H_{14} and H_{15}), 7.48-7.69 (m, 2H, H_{18} and H_{19}), 7.83 (d, J = 9.4 Hz, 1 H, H_{16} or H_{17}), 7.88 (d, J = 9.4 Hz, 1 H, H_{16} or H_{17}), 8.26 (d, J = 8.4 Hz, 1 H, H_{20}); ^{13}C nmr (deuteriochloroform): δ ppm 24.7 (C_4), 29.8 (C_3), 51.1 (CO_2CH_3), 54.1 (C_5), 56.2 (C_9-OCH_3, C_{11}-OCH_3), 59.0 (C_6), 60.1 (C_{10}-OCH_3), 104.3 (C_8, C_{12}), 124.0, 125.2, 126.4, 127.1, 128.6, 129.3, 129.5 (C_{14}-C_{20}), 132.8, 133.6, 134.8, 135.4, 137.4 (C_7, C_{10}, C_{13}, C_{22}, C_{23}), 153.1 (C_9, C_{11}), 171.5 (C_2), 175.5 (C_{21}).

Anal. Calcd for $C_{26}H_{27}NO_6$,CH_3OH: C, 67.35; H, 6.49; N, 2.91; O, 23.26. Found: C, 67.02; H, 6.19; N, 2.87; O, 23.34.

N-[Naphthyl-(3,4,5-trimethoxyphenyl)-methyl]pyroglutamic Acid (**7**).

This product was obtain in the same way as for acid **11**, starting from ester **5** (100 g, 222.4 mmol); yield 77%, mp 187° (methyl alcohol); ir (potassium bromide): ν cm^{-1} 3400 (broad O–H), 1735 (C=O), 1635 (C=O), 1590, 1450 (C=C), 1130 (C–O); ^1H nmr (dimethyl-d_6-sulfoxide): δ ppm 2.20-2.80 (m, 4 H, H_3 and H_4), 3.61 (s, 3 H, 10-OCH_3), 3.64 (s, 6 H, 9-OCH_3 and 11-OCH_3), 4.10 (d, J = 6.7 Hz, 1 H, H_5), 6.59 (s, 2 H, H_8 and H_{12}), 6.80 (s, 1 H, H_6), 7.36 (d, J = 7.1 Hz, 1 H), 7.43-7.52 (m, 2 H, H_{18} and H_{19}), 7.55 (d, J = 7.1 Hz, 1 H) 7.83-8.00 (m, 3 H, H_{16}, H_{17} and H_{20}); ^{13}C nmr (dimethyl-d_6-sulfoxide): δ ppm 24.2 (C_4), 29.5 (C_3), 55.7 (C_9-OCH_3, C_{11}-OCH_3), 57.3 (C_5), 59.2 (C_6), 59.9 (C_{10}-OCH_3), 107.9 (C_8, C_{12}), 123.5, 123.6, 125.4, 125.7, 126.4, 128.0, 128.7 (C_{14}-C_{20}), 130.4, 133.3, 133.5, 136.1, 137.4 (C_7, C_{10}, C_{13}, C_{22}, C_{23}), 152.5 (C_9, C_{11}), 173.9 (C_2), 174.7 (C_{21}).

Anal. Calcd. for $C_{25}H_{25}NO_6$: C, 68.95; H, 5.79; N, 3.22; O, 22.04. Found: C, 69.21; H, 5.90; N, 3.46; O, 21.75.

N-[Naphthyl-(3,4,5-trimethoxyphenyl)-methyl]pyroglutamic Acid (**11**).

A suspension of compound **4** (100 g, 222.4 mmol) in a solution of 2 N sodium hydroxide (220 ml) was heated at 80° for 4 hours. Then the aqueous layer was washed with methylene dichloride and heated for a few minutes at 40° under vacuum to evaporate the methylene dichloride. The aqueous layer was then slowly acidified with concentrated hydrochloric acid until compound **11** precipitated. The precipitate was filtered, washed with water at 10°, giving compound **11** as a solid, yield 65%, mp 237° (methyl alcohol); ir (potassium bromide): ν cm^{-1} 3400 (broad O–H), 1730 (C=O), 1630 (C=O), 1590, 1500, 1450 (C=C), 1130 (C–O); ^1H nmr (dimethyl-d_6-sulfoxide): δ ppm 2-2.15 (m, 1 H, H_4), 2.30-2.70 (m, 3 H, H_3 and H_4), 3.66 (s, 6 H, 9-OCH_3 and 11-OCH_3), 3.68 (s, 3 H, 10-OCH_3), 4.23 (d, J = 5.6 Hz, 1H, H_5), 6.40 (s, 2 H, H_8 and H_{12}), 7.20 (s, 1 H, H_6), 7.25-7.37 (m, 2 H, H_{14} and H_{15}), 7.40-7.58 (m, 2H, H_{18} and H_{19}), 7.75-7.85 (m, 2 H, H_{16} and H_{17}), 8.20 (d, J = 8.2 Hz, 1 H, H_{20}); ^{13}C nmr (dimethyl-d_6-sulfoxide): δ ppm 24.5 (C_4), 29.4 (C_3), 54.8 (C_5), 55.7 (C_9-OCH_3, C_{11}-OCH_3), 58.2 (C_6), 59.9 (C_{10}-OCH_3), 104.7 (C_8, C_{12}), 123.7, 125.1, 125.7, 126.3, 127.7, 128.5 (C_{14}-C_{20}), 132.0, 133.2, 135.0, 135.8, 136.5 (C_7, C_{10}, C_{13}, C_{22}, C_{23}), 152.9 (C_9, C_{11}), 173.0 (C_2), 174.9 (C_{20}).

Anal. Calcd. for $C_{25}H_{25}NO_6$: C, 68.95; H, 5.79; N, 3.22; O, 22.04. Found: C, 68.58; H, 5.82; N, 3.60; O, 21.74.

9-Hydroxy-7,8-dimethoxy-5-naphthyl-1,2,3,5,10,10a-hexahydro-benz[*f*]indolizine-3,10-dione (**8**).

Trifluoroacetic anhydride (19.5 ml, 138 mmol) was added to a suspension of compound **7** (30 g, 68.9 mmol) in dichloroethane (500 ml) under nitrogen atmosphere. When the mixture became clear, boron trifluoride etherate (69.6 ml, 551 mmol) was added. The mixture was then refluxed for 9 hours. During the course of the reaction, a yellow precipitate appeared. It was filtered, washed with water and dissolved in methylene dichloride. The organic layer was dried and the solvent was evaporated, giving the compound **8** as a

yellow solid, yield 70%, mp 230° (ethyl acetate) (decomposition); ir (potassium bromide): ν cm^{-1} 1730 (C=O), 1685 (C=O), 1610, 1500, 1450 (C=C), 1100 (C–O); ^1H nmr (deuteriochloroform): δ ppm 2.10-2.56 (m, 4 H, H_3 and H_4), 3.85 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 4.07 (d, J = 6.6 Hz, 1 H, H_5); 6.38 (s, 1 H, H_{12}), 6.80 (d, J = 6.6 Hz, 1 H, H_{14}), 7.17 (s, 1 H, H_6), 7.31 (t, J = 6.6 Hz, 1 H, H_{15}), 7.51-7.74 (m, 2 H, H_{18} and H_{19}), 7.78-7.97 (m, 2 H, H_{16} and H_{17}), 8.64 (d, J = 9.5 Hz, 1 H, H_{20}), 12.24 (s, 1 H, OH); ^{13}C nmr (deuteriochloroform): δ ppm 19.9 (C_4), 30.0 (C_3), 51.6 (C_5), 56.4 (C_{11}-OCH_3), 58.4 (C_{10}-OCH_3), 61.0 (C_6), 103.2 (C_{12}), 111.6 (C_8), 124.1, 124.9, 126.6, 126.9, 127.6, 128.9, 129.6 (C_{14}-C_{20}), 131.8, 134.1, 134.3, 135.8, 139.7 (C_7, C_{10}, C_{13}, C_{22}, C_{23}), 157.2 (C_9 or C_{11}), 159.6 (C_9 or C_{11}), 173.1 (C_2), 200.2 (C_{21}).

Anal. Calcd. for $C_{24}H_{21}NO_5$: C, 71.45; H, 5.25; N, 3.47; O, 19.83. Found: C,71.24; H, 5.50; N, 3.45; O, 19.94.

Cyclization of Acid **11** (Synthesis of Products **8**, **12**, **13** and **14**).

Trifluoroacetic anhydride (15.6 ml, 110 mmol) was added to a suspension of acid **11** (24 g, 55 mmol) in dichloroethane (500 ml) under nitrogen atmosphere. When the mixture became clear, boron trifluoride etherate (55.7 ml, 441 mmol) was added. The mixture was then refluxed for 9 hours. The solvents were evaporated and water followed by methylene dichloride were added. The organic layer was washed with water, then with a solution of sodium hydrogen carbonate. The organic phase was dried and the solvent was evaporated, giving a mixture of products **8**, **12**, **13** and **14** as a crude oil. This oil was dissolved in a very small quantity of ethyl acetate. After cooling, lactam **13** was obtained as a green solid in a 15% yield. The solution was then concentrated and after cooling giving a 15% yield of ketone **12**. Following the same way the ketone **8** was obtained in a 30% yield. The washing of the crude mixture with heptane gave 2% of compound **14**.

5-(3,4,5-Trimethoxyphenyl)-1,2,3,5,12,12a-hexahydronaphtho-[1,2-*f*]indolizine-3,12-dione (**12**).

Mp 202° (ethyl acetate); ir (potassium bromide): ν cm^{-1} 1670 (C=O), 1590, 1500, 1460 (C=C), 1120 (C–O); ^1H nmr (deuteriochloroform): δ ppm 2.34-2.61 (m, 4 H, H_3 and H_4), 3.68 (s, 6 H, 9-OCH_3 and 11-OCH_3), 3.81 (s, 3 H, 10-OCH_3), 4.36 (m, 1 H, H_5), 6.42 (s, 2 H, H_8 and H_{12}), 7.16 (s, 1 H, H_6), 7.45-7.69 (m, 2 H, H_{18} and H_{19}), 7.86 (m, 3 H, H_{16}, H_{17} and H_{20}), 8.23 (d, J = 8.8 Hz, 1 H, H_{15}); ^{13}C nmr (deuteriochloroform): δ ppm 20.9 (C_4), 30.3 (C_3), 52.4 (C_5), 56.3 (C_9-OCH_3, C_{11}-OCH_3), 58.4 (C_6), 60.8 (C_{10}-OCH_3), 105.6 (C_8, C_{12}), 121.3, 126.1, 127.8, 128.5, 129.0, 129.4 (C_{15}-C_{20}), 129.4, 129.8, 134.0, 136.2, 138.2, 140.2 (C_7, C_{10}, C_{13}, C_{14}, C_{22}, C_{23}), 153.8 (C_9, C_{11}), 173.4 (C_2), 195.3 (C_{21}).

Anal. Calcd for $C_{25}H_{23}NO_5$: C, 71.93; H, 5.55; N, 3.36; O, 19.16. Found: C, 72.05; H, 5.58; N, 3.40; O, 19.12.

5-(3,4,5-Trimethoxyphenyl)-1,2,3,5-tetrahydro-11a*H*-naphto-[1,8-*f*,*g*]indolizine-3-one (**13**).

Mp 188° (ethyl acetate) (decomposition); ir (potassium bromide): ν cm^{-1} 1670 (C=O), 1585, 1500, 1460 (C=C), 1130 (C-O); ^1H nmr (deuteriochloroform): δ ppm (2.08-2.31 (m, 1 H, H_4), 2.48-2.69 (m, 2 H, H_3), 2.70-2.93 (m, 1 H, H_4), 3.65 (s, 6 H, 9-OCH_3 and 11-OCH_3), 3.79 (s, 3 H, 10-OCH_3), 4.98 (t, J = 7.5 Hz, 1 H, H_5), 6.30 (s, 2 H, H_8 and H_{12}), 6.66 (s, 1 H, H_6), 7.33 (d, J = 7.5 Hz, 1 H, H_{14} or H_{19}), 7.38 (d, J = 7.5 Hz, 1 H, H_{14} or H_{19}), 7.52 (t, J = 7.5 Hz, H_{15} or H_{18}), 7.54 (t, J = 7.5 Hz, 1 H, H_{15} or H_{18}), 7.85 (d, J = 7.5 Hz, 2 H, H_{16} and H_{17}); ^{13}C nmr (deuteriochloroform): δ ppm 20.4 (C_4), 31.5 (C_3), 53.6 (C_5), 54.8 (C_6), 56.2 (C_9-OCH_3, C_{11}-OCH_3), 60.8 (C_{10}-OCH_3), 105.6 (C_8, C_{12}), 121.3 (C_{14} or C_{19}), 125.5 (C14 or C_{19}), 125.9 (C_{15} or C_{18}), 126.0 (C_{15} or C_{18}), 127.4 (C_{16} or C_{17}), 127.7 (C_{16} or C_{17}), 131.7 (C_{13}), 133.4 (C_{22} or C_{20}), 135.8 (C_{22} or C_{20}), 137.0 (C_{23}, C_7), 137.6 (C_{10}), 153.4 (C_9, C_{11}), 173.2 (C_2).

Anal. Calcd. for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60; O, 16.43. Found: C, 74.04; H, 5.92; N, 3.67; O, 16.60.

7,8,9-Trimethoxy-11*H*-benzo[*a*]fluorene (**14**).

Mp 138° (ethyl acetate); ir (potassium bromide): ν cm^{-1}, 1460 (C=C), 1100 (C–O); ^1H nmr (deuteriochloroform): δ ppm 3.96 (s, 6 H, 7-OCH_3 and 9-OCH_3), 4.10 (s, 3 H, 8-OCH_3), 4.14 (bs, 2 H, CH_2), 7.01 (s, 1 H, H_{10}), 7.38-7.57 (m, 2 H), 7.85 (t, J = 8.4 Hz, 1 H, H_2 or H_3), 7.88-7.90 (m, 2 H), 8.19 (d, J = 8.4 Hz, 1 H, H_1 or H_4); ^{13}C nmr (deuteriochloroform): δ ppm 36.2 (C_{11}), 56.4 (C_9-OCH_3), 61.0 (C_7-OCH_3 or C_8-OCH_3), 61.3 (C_7-OCH_3 or C_8-OCH_3), 104.9 (C_9), 121.4, 123.9, 125.0, 126.4, 127.9, 129.0 (C_1-C_6), 128.4, 130.5, 132.1, 138.6, 138.8, 139.6, 141.6, 149.2 (C_{4a}, C_{6a}, C_{6b}, C_7, C_8, C_{10a}, C_{11a}, C_{11b}), 153.2 (C_{10}).

Anal. Calcd. for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92; N, 15.67. Found: C, 78.08; H, 6.15; O, 15.39.

9,10-Dihydroxy-7,8-dimethoxy-5-naphthyl-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-3-one (**21**).

Sodium borohydride (0.52 g, 13.8 mmol) was slowly added to a suspension of compound **8** (3 g, 74 mmol) in ethyl alcohol (150 ml). The mixture was refluxed for 5 hours. After cooling, glacial acetic acid (15 ml) was added and the solvent was removed in vacuum. The residue was then dissolved in methylene dichloride, washed with water, then a saturated solution of sodium bicarbonate. The organic layer was then dried and the solvent was removed under vacuum, giving compound **21** as a yellow solid which was recrystallized in ethyl acetate, yield 100%, mp 206° (ethyl acetate) (degradation); ir (potassium bromide): ν cm^{-1} 3200 (broad O–H), 1635 (C=O), 1500, 1450 (C=C), 1125 (C–O); ^1H nmr (deuteriochloroform): δ ppm 2.01-2.18 (m, 2 H, H_4), 2.39-2.60 (m, 2 H, H_3), 3.62-3.66 (m, 1 H, H_5), 3.68 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 4.90 (d, J=8.5 Hz, 1 H, H_{21}), 6.15 (s, 1 H, H_{12}), 6.80 (bs, 1 H, C_{21}-OH), 6.95 (s, 1 H, H_6), 7.05 (d, J = 8.5 Hz, 1 H, H_{14}), 7.33 (t, J = 8.5 Hz, 1 H, H_{15}), 7.49-7.70 (m, 2 H, H_{18} and H_{19}), 7.76-7.96 (m, 2 H, H_{16} and H_{17}), 12.06 (s, 1 H, C_9-OH); ^{13}C nmr (deuteriochloroform): δ ppm 22.1 (C_4), 29.7 (C_3), 51.2 (C_5), 55.1 (C_{11}-OCH_3), 55.9 (C_{10}-OCH_3), 61.2 (C_6), 68.2 (C_{21}), 103.5 (C_{12}), 118.1 (C_8), 124.4, 125.0, 126.2, 127.1, 128.2, 128.7, 128.9 (C_{14}-C_{20}), 131.8, 132.1, 133.9, 134.8, 136.6 (C_7, C_{10}, C_{13}, C_{22}, C_{23}), 148.2 (C_9 or C_{11}), 152.1 (C_9 or C_{11}), 172.9 (C_2).

Anal. Calcd. for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45; O, 19./73. Found: C, 70.80; H, 5.54; N, 3.14; O, 19.49.

9-Hydroxy-7,8-dimethoxy-5-naphthyl-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-3-one (**22**).

Triethylsilane (0.8 ml, 5 mmol) was added slowly *via* syringe to a solution of compound **21** (1 g, 2.5 mmol) in trifluoroacetic acid (6 ml) at 10° under nitrogen atmosphere. The mixture was stirred at room temperature for 2 days. Water and dichloromethane were added. The organic layer was washed with water, dried, and the solvent was evaporated, giving a yellow solid which was recrystallized in ethyl acetate/heptane, yield 82%, mp 135° (ethyl acetate/heptane) (degradation); ir (potassium bromide): ν cm^{-1} 3380 (O–H), 1670 (C=O), 1575, 1500, 1450 (C=C), 1130 (C–O); ^1H nmr (deuteriochloroform): δ ppm

1.69-2.10 (m, 2 H, H_4), 2.30-2.72 (m, 3 H, H_3 and H_{21}), 3.04 (dd, J_1 = 5.4 Hz, J_2 = 16.8 Hz, 1 H, H_{21}), 3.66 (s, 3 H, OCH_3), 3.73-3.88 (m, 1 H, H_5), 3.93 (s, 3 H, OCH_3), 6.15 (s, 1 H, H_{12}), 6.90 (d, J = 9.3 Hz, 1 H, H_{14}), 7 (s, 1 H, H_6), 7.31 (t, J = 9.3 Hz, 1 H, H_{15}), 7.48-7.72 (m, 2 H, H_{18} and H_{19}), 7.79 (d, J = 9.3 Hz, 1 H, H_{16}), 7.89 (d, J = 9.3 Hz, 1 H, H_{17}), 8.83 (d, J = 9.3 Hz, 1 H, H_{20}), 12.06 (s, 1 H, OH); ^{13}C nmr (deuteriochloroform): ν 24.0 (C_4), 28.3 (C_3 or C_{21}), 29.6 (C_3 or C_{21}), 49.5 (C_5), 51.3 (C_{11}-OCH_3), 55.8 (C_{10}-OCH_3), 61.1 (C_6), 103.5 (C_{12}), 114.8 (C_8), 124.7, 124.9, 126.2, 127.1, 128.1, 128.6, 128.7 (C_{14}-C_{20}), 130.9, 132.1, 133.9, 134.3, 137.9 (C_7, C_{10}, C_{13}, C_{22}, C_{23}), 147.0 (C_9 or C_{11}), 150.9 (C_9 or C_{11}), 172.8 (C_2).

Anal. Calcd. for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60; O, 16.43. Found: C, 73.90; H, 6.20; N, 3.30; O, 16.60.

5-(4-Hydroxy-3,5-dimethoxyphenyl)-1,2,3,5-tetrahydro-11a*H*-naphto[1,8-*f,g*]indolizine-3-one (**23**).

To a cooled solution (-10°) of methyl alcohol (7.5 ml, 185 mmol) and acetyl bromide (13.7 ml, 185 mmol) was slowly added *via* syringe a solution of compound **13** (3.6 g, 9.2 mmol) in methylene dichloride (50 ml). The precipitate obtained after stirring for two days at room temperature was dissolved in methylene dichloride and washed with a saturated sodium hydrogen carbonate solution. The organic layer was dried and the solvent evaporated. The green oil obtained crystallized in ethyl acetate and methyl alcohol, giving compound **23** as a colorless solid, yield 32%, mp 97° (methyl alcohol) (degradation); ir (potassium bromide): ν cm^{-1} 3440 (broad O–H), 1670 (C=O), 1600, 1510, 1460 (C=C), 1120 (C–O); ^1H nmr (deuteriochloroform): δ ppm 2.05-2.15 (m, 1 H, H_4), 2.49-2.69 (m, 2 H, H_3), 2.67-2.92 (m, 1 H, H_4), 3.68 (s, 6 H, OCH_3), 4.95 (t, J = 7.5 Hz, 1 H, H_5), 5.46 (s, 1 H, OH), 6.31 (s, 2 H, H_8 and H_{12}), 6.65 (s, 1 H, H_6), 7.33 (d, J = 8.0 Hz, 1 H, H_{14} or H_{19}), 7.38 (d, J = 8.0 Hz, 1 H, H_{14} or H_{19}), 7.52 (t, J = 8.0 Hz, 1 H, H_{15} or H_{18}), 7.55 (t, J = 8.0 Hz, 1 H, H_{15} or H_{18}), 7.85 (d, J = 8.0 Hz, 2 H, H_{16} and H_{17}); ^{13}C nmr (deuteriochloroform): δ ppm 26.4 (C_4), 31.5 (C_3), 53.5 (C_5), 54.7 (C_6), 56.4 (C_9-OCH_3, C_{11}-OCH_3), 105.3 (C_8, C_{12}), 121.3 (C_{14} or C_{19}), 125.5 (C_{14} or C_{19}), 125.9 (C_{15} or C_{18}), 126.0 (C_{15} or C_{18}), 127.4 (C_{16} or C_{17}), 127.7 (C_{16} or C_{17}), 131.8 (C_{13}), 132.7 (C_{20} or C_{22}), 133.4 (C_{20} or C_{22}), 134.5 (C_7, C_{21}), 135.9 (C_{10}), 147.1 (C_9, C_{11}), 173.2 (C_2).

Anal. Calcd. For $C_{24}H_{25}NO_5$, CH_3OH: C, 70.75; H, 6.18; N, 3.44; O, 19.63. Found: C, 70.41; H, 6.01; N, 3.29; O, 19.79.

5-(4-Hydroxy-3,5-dimethoxyphenyl)-1,2,3,5,12,12a-hexahydronaphtho[1,2-*f*]indolizine-3,12-dione (**25**).

To a solution of methyl alcohol (7.8 ml, 192 mmol) and acetyl bromide (14.2 ml, 192 mmol) was added slowly *via* syringe a solution of ketone **12** (4 g, 9.6 mmol) in methylene dichloride (50 ml). The precipitate, obtained after stirring three days at room temperature, was dissolved in methylene dichloride and washed with a saturated sodium hydrogen carbonate solution. The organic layer was dried and the solvent evaporated. The residue crystallized in ethyl acetate or methyl alcohol, giving compound **25** as a colorless solid, yield 20%, mp 196° (methyl alcohol) (degradation); ir (potassium bromide): ν cm^{-1} 3300 (broad, O–H), 1680 (broad, C=O), 1600, 1510, 1460 (C=C), 1110 (C–O); ^1H nmr (deuteriochloroform): δ ppm 2.35-2.63 (m, 4 H, H_3 and H_4), 3.72 (s, 6 H, OCH_3), 4.34 (m, 1 H, H_5), 5.51 (s, 1 H, OH), 6.43 (s, 2 H, H_8 and H_{12}), 7.16 (s, 1 H, H_6), 7.45-7.67 (m, 2 H, H_{18} and H_{19}), 7.87-7.98 (m, 3 H, H_{16}, H_{17} and H_{20}), 8.22 (d, J = 8.8 Hz, 1 H, H_{15}); ^{13}C nmr (deuteriochloroform): δ ppm 20.9 (C_4), 30.4 (C_3), 52.4 (C_5), 56.5 (C_9-OCH_3, C_{11}-OCH_3), 58.4 (C_6), 105.4 (C_8, C_{12}), 122.4, 126.2, 127.7, 128.5, 129.0, 129.3 (C_{15}-C_{20}), 129.3, 129.7, 129.8, 135.2, 136.3, 140.4 (C_7, C_{10}, C_{13}, C_{14}, C_{22}, C_{23}), 147.8 (C_9, C_{11}), 173.4 (C_2), 195.3 (C_{21}).

Anal. Calcd. for $C_{24}H_{21}NO_5$: C, 71.45; H, 5.25; N, 3.47; O, 19.83. Found: C, 71.03; H, 5.34; N, 3.60; O, 20.03.

8,9-Dihydroxy-7-methoxy-5-naphthyl-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-3,10-dione (**27**).

A stirred mixture of compound **8** (2 g, 4.9 mmol) and hydrobromic acid (48%, 50 ml) was refluxed for 6 hours. After cooling, the solid was washed with water then stirred in a mixture of methylene dichloride and acetone. Diphenol **27** was obtained as a white solid, yield 40%, mp > 270° (decomposition); ir (potassium bromide): ν cm^{-1} 3440 (O–H), 1685, 1630 (C=O), 1450 (C=C), 1090 (C-O); ^1H nmr (dimethyl-d_6-sulfoxide): δ ppm 2.11-2.40 (m, 4 H, H_3 and H_4), 3.79 (s, 6 H, OCH_3), 4.09 (d, J = 8.5 Hz, 1 H, H_5), 6.77 (s, 1 H, H_{12}), 6.86 (d, , J = 8.5 Hz, 1 H, H_{14}), 7.12 (s, 1 H, H_6), 7.40 (t, J = 8.5 Hz, 1 H, H_{15}, 7.60 (t, J = 8.5 Hz, 2 H, H_{18} and H_{19}), 7.85 (d, J = 8.5 Hz, 1 H, H_{16}), 7.93 (d, J = 8.5 Hz, 1 H, H_{17}), 8.60 (d, J = 8.5 Hz, 1 H, H_{20}), 12.06 (s, 1 H, OH) (the second OH is not visible); ^{13}C nmr (dimethyl-d_6-sulfoxide): δ ppm 19.8 (C_4), 30 (C_3), 51.5 (C_5), 56.5 (OCH_3), 58.5 (C_6), 102.8 (C_{12}), 111.2 (C_8), 124.1, 124.9, 126.6, 126.9, 127.5, 128.9, 129.6 (C_{14}-C_{20}), 131.8, 132.7, 134.1, 134.5, 135.4 (C_7, C_{10}, C_{13}, C_{22}, C_{23}), 150.1 (C_{11}), 153.6 (C_9), 173.2 (C_2), 200.3 (C_{21}).

Anal. Calcd. for $C_{23}H_{19}NO_4$: C, 70.94; H, 4.92; N, 3.60; O, 20.54. Found: C, 70.66; H, 4.90; N, 3.90; O, 20.28.

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