Studies on Pyrrolidinones: Some Attempts to Improve the Synthesis of Methyl *N*-(3,4,4',5-Tetramethoxybenzhydryl)pyroglutamate (HEI 81) by Using *N*-Acyl Iminium Salts Methodologies.

Anne Bourry, Franck Pitard and Benoît Rigo*

Groupe de Recherche sur l'Inhibition de la Prolifération Cellulaire (EA 2692),
Ecole des Hautes Etudes Industrielles, 13, rue de Toul, 59046 Lille, France

Gérard Sanz

Janssen Research Foundation, Campus de Maigremont, 27106 Val de Reuil, France

Fabrice Camus, Bernadette Norberg and François Durant

Laboratoire de Chimie Moléculaire Structurale, Facultés Universitaire Notre-Dame de la Paix,
61 rue de Bruxelles, 5000 Namur, Belgique

Daniel Couturier

Laboratoire d'Ingéniérie Moléculaire, Université des Sciences et Technologies, 59655 Villeneuve d'Ascq,
France

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Some ways to use the *N*-acyl iminium salt methodologies to synthesize a new inhibitor of tubulin polymerization, methyl *N*-(3,4,4',5-tetramethoxybenzhydryl)pyroglutamate (HEI 81) were studied. The most interesting reactions utilize a new pyroglutamic lactone (3-(3,4,5-trimethoxyphenyl)dihydropyrrolo[1,2-*c*]oxazole-1,5-dione).

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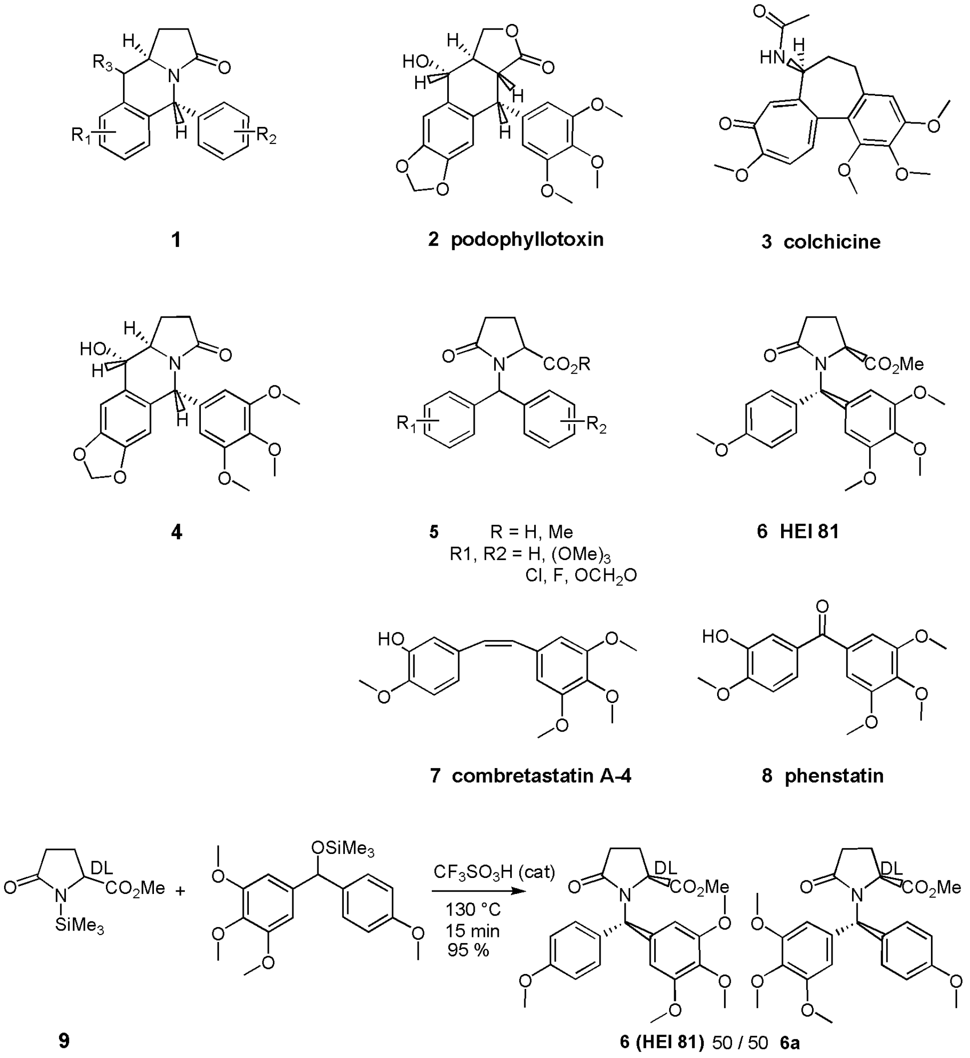
We recently described [1] the synthesis of azaanalogs **1** of the efficient anticancer agent podophyllotoxin (**2**) that interacts with tubulin at the colchicine (**3**) site [2]. From all the cyclic compounds synthesized, only the strict analog **4** of podophyllotoxin (**2**), yields inhibition of tubulin polymerization (IC_{50} = 5 μ*M*), but none had interesting antitumor activity in the standard NCI test [3]. Esters and acids **5** which are the starting materials for compounds **1** were also submitted to the same screening. Methyl *N*-(3,4,4',5-tetramethoxybenzhydryl) pyroglutamate (HEI 81) (**6**) emerged from these tests. The middle anticancer properties of HEI 81 (IC_{50} = 4.1 10^{-7} *M* (MCF-7 cells)) are interesting because of its atypical structure. This compound is related to combretastatin A-4 (**7**) [4] and phenstatin (**8**) [5] (Scheme 1), but to date it was assumed important that the junction of the aromatic rings in these series was realized by a sp2 carbon atom [5]. Important also is the 50-60° dihedral angle between the aromatic rings of active compounds [6]. In HEI 81, a π-π interaction orients the methyl ester group just above the trimethoxyphenyl ring, imposing a dihedral angle of 49° [7]. In this paper, we report some attempts to obtain compound **6** stereoselectively by using an *N*-acyl iminium salt methodology.

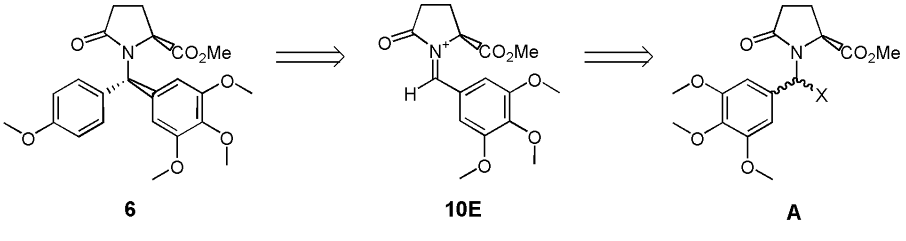
The previous synthesis of ester **6**, starting from DL-methyl *N*-trimethylsilylpyroglutamate (**9**) yielded a 50/50 mixture of two racemics (Scheme 2) [1a]. The biologically active compound HEI 81 is the *RR* enantiomer [8]. In order to obtain the right configuration of the aromatic rings, we tried to utilize the methyloxycarbonyl group of methyl pyroglutamate to induce an asymmetric addition of anisole on an acyliminium salt **10*E*** (Scheme 2). This approach is based on analog amidoalkylations of pyroglutamic acid derivatives. According to Roth [9], there are two reasons for a presumed stereoselectivity in such a reaction. 1: Steric hindrance of the methoxycarbonyl group on the lactam ring must direct the approach of the new aromatic ring as a nucleophile to the *N*-acyliminium ion from its opposite side. 2: The planarity requirements of the *N*-acyliminium cation, with less steric repulsion, is better fulfilled by the *E* rotamer **10** than by the corresponding *Z* rotamer. In the beginning of this work, the exact configuration of HEI 81 was not known thus all the reactions described in this paper were realized starting from DL pyroglutamic acid [8a].

The first reaction based on Scheme 2 was realized by using silyl ether **11**. The best yield of ester **6**, among many other compounds, was 5 % (boron trifluoride etherate, 1 equivalent/dichloromethane/24 hours/20 °C) (Scheme 3). In order to test the reactivity of an aromatic other than anisole, the same reaction was performed with benzodioxole, with no more success. Interestingly when the catalyst was triflic acid (0.3 equivalent, CH_2Cl_2, 20 °C, 4 hours), diester **12** was isolated in 45 % yield. The same yield of product **12** was obtained when compound **11** was treated with trimethylchlorosilane (4 equivalents, 70 °C, 10 hours). Due to the lack of symmetry in the structure of **12**, the

Scheme 1

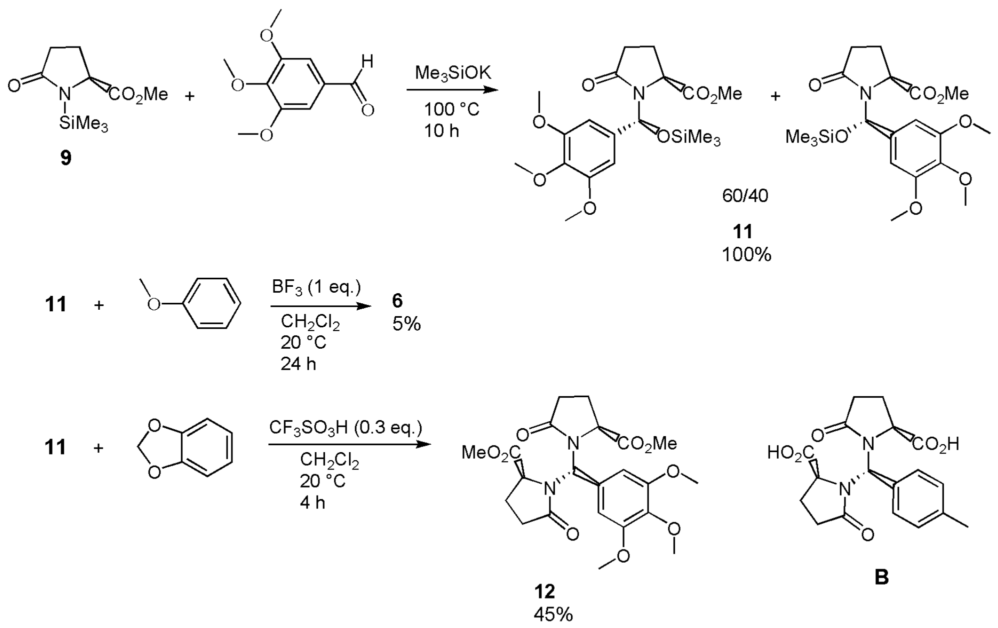


Scheme 2



methyl ester groups yield two peaks (3.34 and 3.43 ppm) in ^{1}H nmr spectrum (Scheme 3). Confirmation of the spatial structure of diester **12** was obtained from the similarities of it's ^{1}H NMR spectrum with that of a rather similar compound B, for which X-ray analysis has been performed during another work (Figure 1) (Scheme 3) [19]. A possible route for the formation of compound **12** starts from hydrolysis of silyl ether **11**: acid catalyzed elimination of trimethylsilanol yields acyliminium salt **10** then water and methyl pyroglutamate **13** whose reaction with **10** yields **12** (Scheme 4). As for compound **11**, it was formed [8b] by reaction of methyl *N*-trimethylsilylpyroglutamate (**9**) [10] with 3,4,5-trimethoxybenzaldehyde. Without catalyst, the yield of **11** was only 1 % (100 °C, 1 hour), but it was obtained quantitatively when potassium trimethylsilanolate was added (5 %, 100 °C, 10 hours) (Scheme 3).

Scheme 3



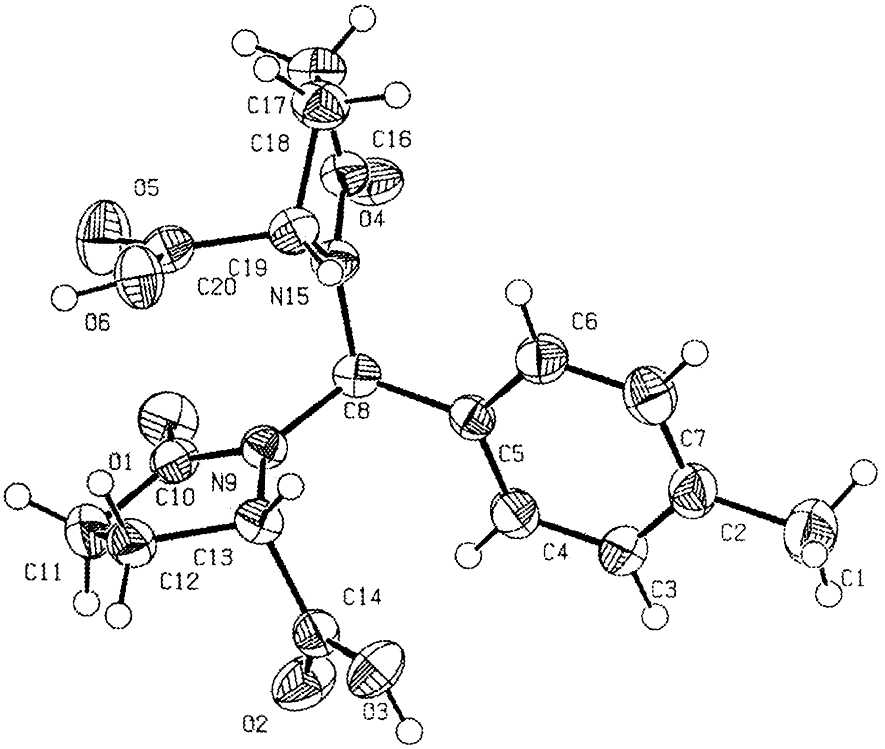
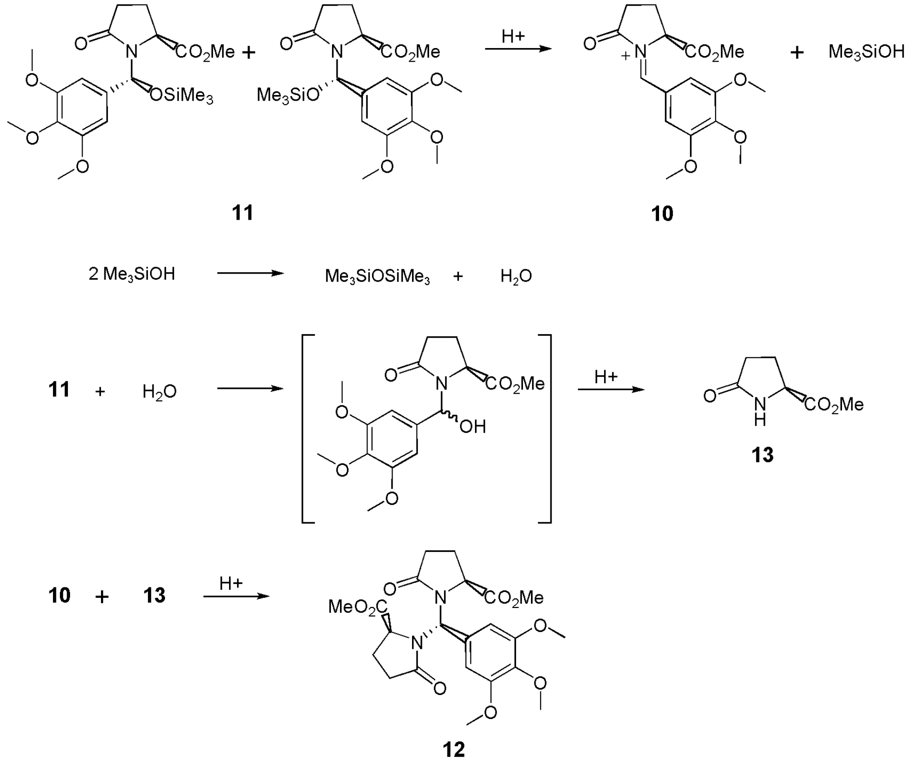


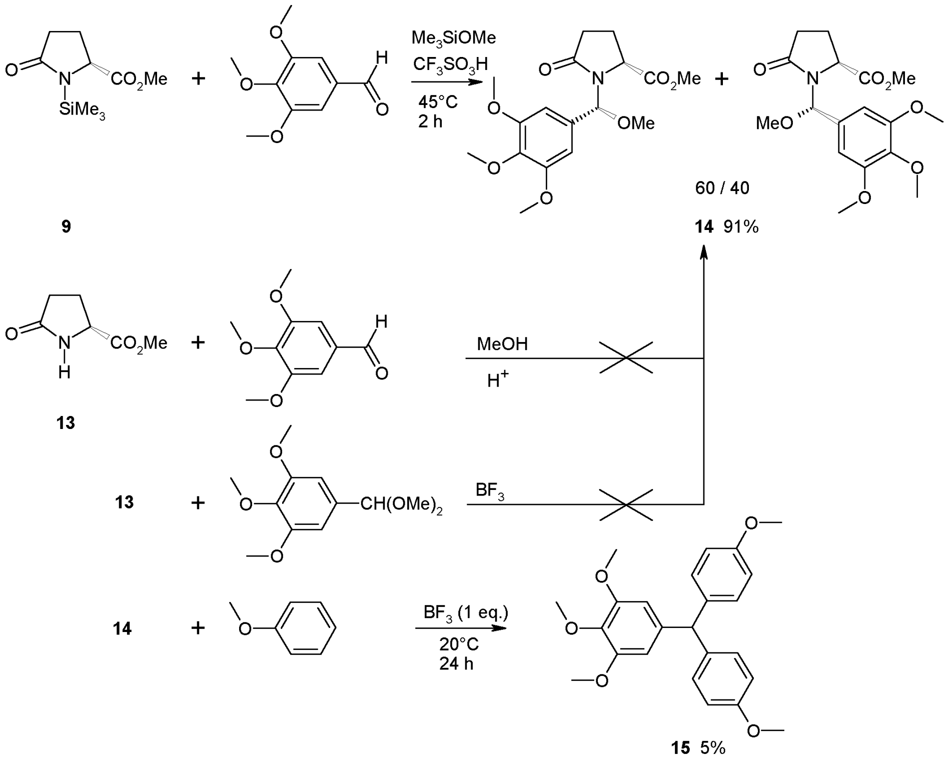
Figure 1. ORTEP representation of compound B with ellipsiods at the 50% propability level.

In order to avoid hydrolysis of the precursor to the *N*-acyliminium salt **10**, reaction of methyl ether **14** with anisole was attempted (Scheme 5). No reaction was obtained without catalyst (100 °C, 10 hours), and decomposition to trimethoxybenzaldehyde and ester **13** was observed with triflic acid (0.1 equivalent, 80 °C, 8 hours) or aluminum chloride (1 equivalent, 70 °C, 7 hours). Interestingly, when the catalyst was boron trifluoride

Scheme 4



Scheme 5

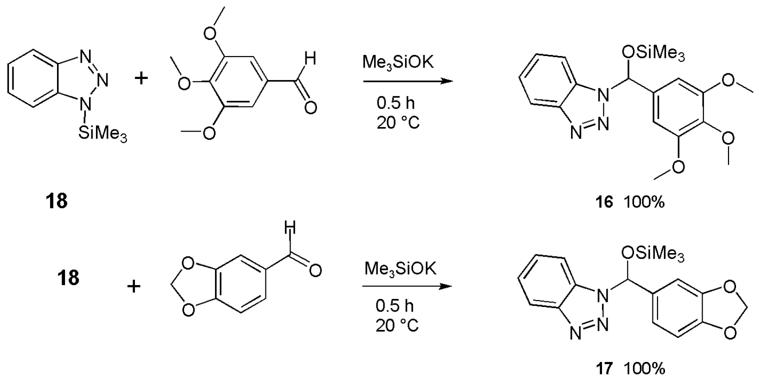


etherate (neat, 1 equivalent, 20 °C, 24 hours), the triphenylmethane **15** was obtained in 5 % yield as the only one isolated product. Ether **14** [8b] was obtained in 91 % yield by performing an acid catalyzed condensation of methyl

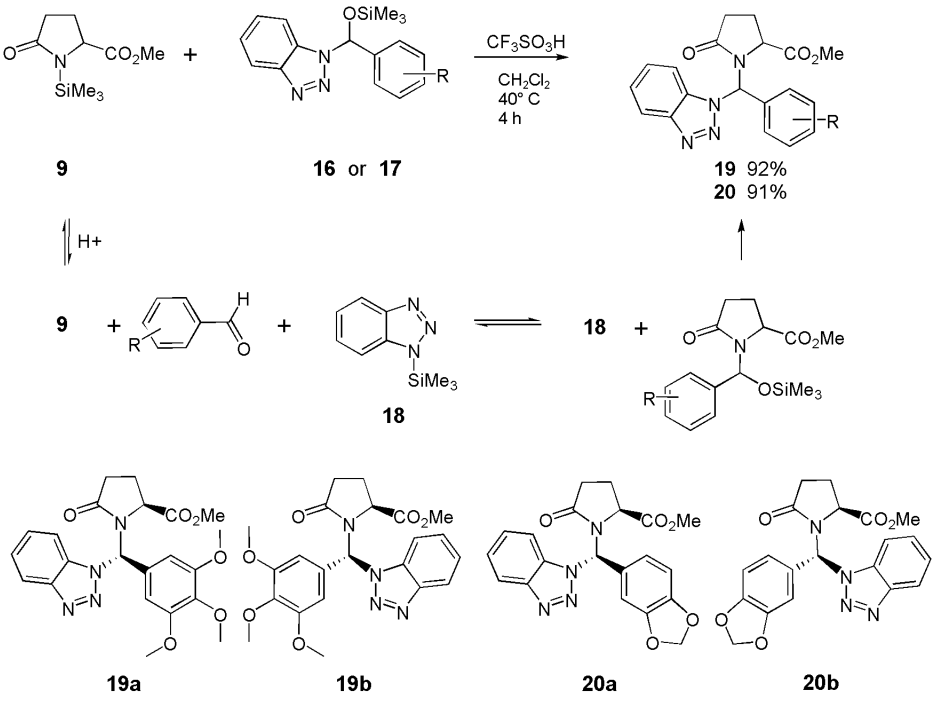
N-trimethylsilylpyroglutamate (**9**) and trimethylsilyloxymethane with 3,4,5-trimethoxybenzaldehyde. No reaction was observed starting from methyl pyroglutamate (**13**) and trimethoxybenzaldehyde in methanol (triflic acid, 0.1 equivalent, 3 days, 70 °C) or trimethoxybenzaldehyde dimethyl acetal (boron trifluoride etherate, 1 equivalent, 10 hours, 20 °C) (Scheme 5).

Another possible way to obtain the acyliminium salt **10** was to start from a benzotriazole derivative [13]. Katritsky described such compounds, obtained from carbamates or lactams [14], whose reaction with another aromatic was described [15]. Starting compounds **16** and **17** of our projected synthesis (Scheme 7 and 8) were formed by the reaction of *N*-trimethylsilylbenzotriazole (**18**) [16] with the corresponding aldehyde (Scheme 6). Without catalyst, heating 14 hours at 100 °C was necessary to obtain 96 % of **17**; by using a low amount of potassium trimethylsilanolate as catalyst, silyl ethers **16** and **17** were formed quantitatively at room temperature in 30 minutes (exothermic reaction). In a similar way as described for *O*-trimethylsilylbenzydrols [1a,1b,17], reaction of silyl ethers **16** or **17** with methyl *N*-trimethylsilylpyroglutamate (**9**) gave a near quantitative yield of esters **19 a,b** or **20 a,b** as a 50/50 mixture of two racemics which could be separated by recrystallization from ethyl acetate (Scheme 7). Interestingly, a ^{1}H nmr spectrum performed during the reaction show the formation of *N*-trimethylsilylbenzotriazole (**18**) and the aromatic aldehyde. A possible route for this reaction is described in Scheme 7. During the reaction of **19** or **20** with anisole, whatever the catalyst used (aluminum chloride, zinc chloride, boron

Scheme 6

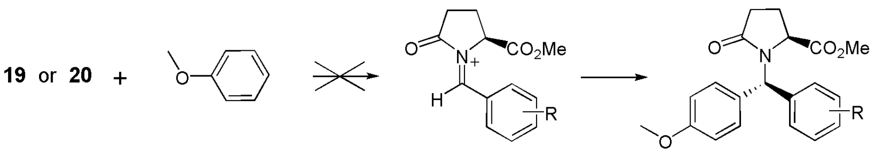


Scheme 7



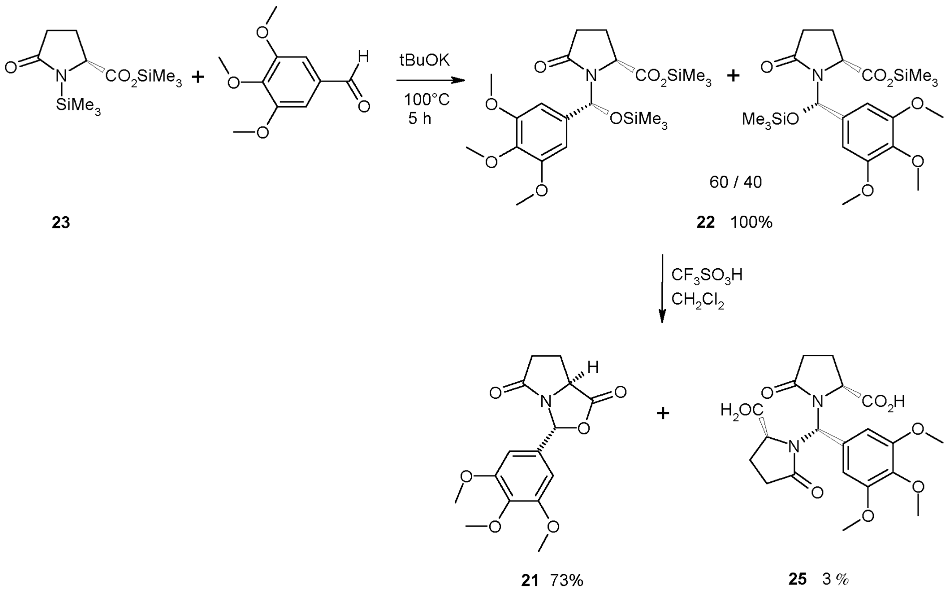
fluoride or triflic acid), the solvent (methylene dichloride, carbon tetrachloride, nitromethane or anisole excess), and the temperature (room temperature or reflux), only decomposition of the reaction mixture was observed (Scheme 8).

Scheme 8



The last attempt to obtain stereoselectively HEI 81 through the addition of anisole on the acyliminium salt **10** was more successful. Failure of the former reactions described in this paper can be explained by reversion of **10** to the precursor A (Scheme 2, X = OMe, $OSiMe_3$, benzotriazole) or by its decomposition caused by hydrolysis or methanolysis. We postulate that lactone **21** could be a possible *N*-acyliminium precursor possessing less possibility for side reactions (Scheme 9) [18]. Thus compound **21** was synthesized from silyl ester **22** obtained by reaction of *N*,*O*-bistrimethylsilylpyroglutamic acid (**23**) [12] with 3,4,5-trimethoxybenzaldehyde (Scheme 9). The reaction giving the lactone **21** is based on a general approach on the cyclization of disilylated compounds [20]. Interestingly, silyl ether **22** was obtained as a 70/30 % [8b] mixture of two racemics whose cyclization yield lactone **21** as a single stereoisomer (formation of an *N*-acyliminium salt can explain this result). A very small amount of dimer **25** could also be extracted from the reaction mixture (Scheme 9) (The X-ray spectrum of diacid B [19] (Scheme 3) is reported in Figure 1).

Scheme 9



The reaction of lactone **21** with anisole was studied by using a variety of solvents (dichloromethane, chloroform, dichloroethane, heptane, tetrahydrofuran, nitromethane), catalysts (aluminum chloride, zinc chloride, magnesium bromide, boron fluoride, bromotrimethylsilane, bismuth triflate, yttrium triflate, trimethylsilyl triflate, trifluoroacetic anhydride/trifluoroacetic acid mixture, silica) and temperatures (0 °C, 20 °C, reflux) (Scheme 10). A selection of the results is given in Table 1.

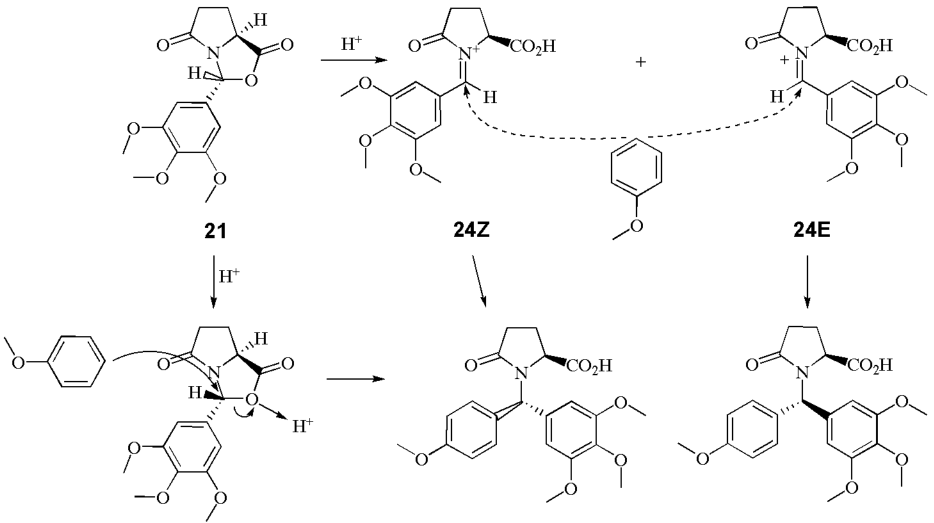
Table 1

Reaction of Lactone **21** with Anisole at 20 °C

Catalyst	Mole eq.	Solvent	t (h)	Yield (%)	Ratio **26a**/**26b**
$CF_3SO_3SiMe_3$	0.1	dichloroethane	72	No reaction	
CF_3SO_3H	0.7	_____	96	48	66/34
$MgBr_2$	1.7	dichloroethane	15	17	66/34
BF_3/ether	1	tetrahydrofuran	72	10	60/40
$AlCl_3$	0.5	nitromethane	48	47	66/34
$AlCl_3$	4	heptane	72	40	71/29
$AlCl_3$	4	nitromethane	12	34	85/15

As it can be observed from Table I, a mixture of acids **26a** and **26b** [1b] was always obtained. Attack of anisole on the endo face of the bicyclic lactone **21** can explain the formation of **26b** or alternatively opening of the lactone ring can give an intermediate *N*-acyliminium salt as two rotamers **24*E*** and **24*Z*** (Scheme 10) [24]. Interestingly when silica was used as catalyst in nitromethane or methylene dichloride, nitrostyrene **27** or acid **25** were formed. Hydrolysis of lactone **21** can again explain these results (Scheme 11).

Scheme 10



The diverse *N*-acyliminium salts syntheses described here are interesting and can be utilized for other projects, but because the pharmacomodulation realized on the structure of HEI 81 (**6**) didn't give an improvement of the biological properties [21], no more studies were performed in order to obtain a better synthesis of this compound.

EXPERIMENTAL

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 ^{1}H and 50 MHz for ^{13}C, using tetramethylsilane as an internal reference. 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.

Methyl 1-[Trimethylsilanyloxy-(3,4,5-trimethoxyphenyl)-methyl]pyroglutamate (**11**).

Methyl *N*-trimethylsilylpyroglutamate (**9**) (16.45 g, 0.076 mol) was added (syringe) to a mixture of 3,4,5-trimethoxybenzaldehyde (15 g, 0.076 mol) and potassium trimethylsilanolate (0.375 g, 0.003 mol). After heating at 100 °C for 10 hours a 100 % nmr yield of ester **11** was obtained.

Scheme 11

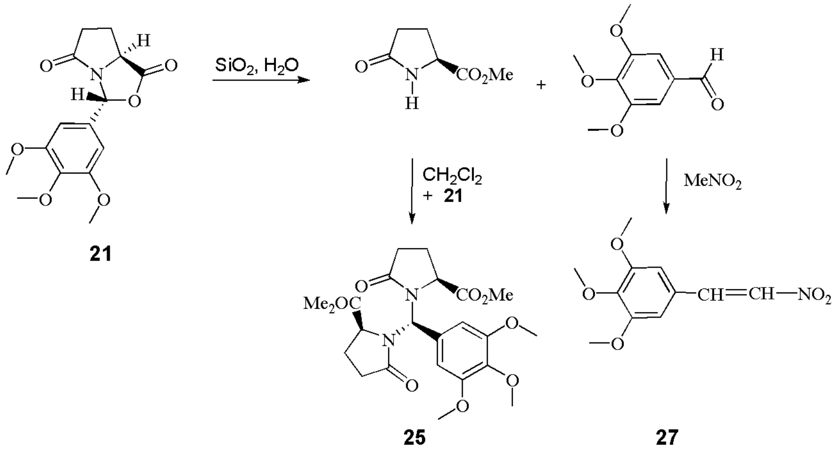


Table 2

Crystal Data and Bond Distances [Å] of **B**

Orthorhombic	$P2_12_12_1$
a = 9.077 (1) Å	Z = 4
b = 11.065 (1) Å	D_x = 1.393 Mg m^{-3}
c = 17.106 (1) Å	R_{int} = 0.017
V = 1718.1 (3) $Å^3$	T = 293 (2) K
C19-N15-C8-N9 45.5 (2)°	C13-N9-C8-C5 28.8 (2)°

Table 3

Elemental Analysis of New Compounds (Calcd./Found)

N°	Formula	C	H	N	O
12	$C_{22}H_{28}N_2O_9$	56.89	6.08	6.03	31.00
		56.75	6.01	5.81	31.38
14	$C_{17}H_{23}NO_7$	57.78	6.56	3.96	31.69
		57.95	6.38	4.33	31.38
19	$C_{22}H_{24}N_4O_6$	55.99	5.49	12.72	21.79
		55.87	5.67	12.99	21.44
20	$C_{20}H_{18}N_4O_5$	60.91	4.60	14.21	20.28
		61.26	4.79	13.91	20.01
21	$C_{15}H_{17}NO_6$	58.63	5.58	4.56	31.24
		58.75	5.68	4.70	30.92
25	$C_{20}H_{24}N_2O_9$	55.04	5.54	6.42	32.99
		54.92	5.68	6.50	33.25

Table 4

Yields and Physical Properties of New compounds

N°	Yield (%)	MP °C (solvent)	IR (KBr) ν cm^{-1}
11	100	ND	ND
12	45	145-6 (AcOEt)	1745, 1735, 1705, 1680, 1590, 1505, 1460, 1120
14	91	88-90 (ether)	1735, 1690, 1585, 1500, 1455, 1450, 1115
16	100	ND	ND
17	100	ND	ND
19	92	148-9 (AcOEt)	2360, 1760, 1720, 1600, 1510, 1470, 1130
20	91	**20a** : 137-9 (AcOEt) **20b** : 148-9 (AcOEt)	2360, 1750, 1740, 1700, 1610, 1500, 1490, 1440, 1240
21	71	220	1755, 1720, 1590, 1510, 1465, 1120
22	100	ND	ND
25	< 3	145-7 (H_2O)	1725, 1705, 1685, 1645, 1585, 1500, 1455, 1450, 1125
26	table 1	oil	1740, 1700-1640, 1610, 1590, 1510, 1460, 1130

Methyl 1-[[2-(Methoxycarbonyl)-5-oxopyrrolidin-1-yl](phenyl)-methyl]pyroglutamate (**12**).

A stirred mixture of compound **11** (16 g, 0.041 mol) and trimethylchlorosilane (20 ml, 0.160 mol) was refluxed for 10 hours. Methylene dichloride was added and the mixture was washed four times with water. The organic phase was dried (sodium sulfate) then evaporated. Ethyl acetate was added and the solution was cooled (-40 °C) for 10 hours, giving ester **12**.

Methyl 1-[Methoxy-(3,4,5-trimethoxyphenyl)methyl]pyroglutamate (**14**).

3, 4, 5-Trimethoxybenzaldehyde (12 g, 0.056 mol) and methyl trimethylsilyl ether (16 g, 0.152 mol) were refluxed under nitrogen. Methyl *N*-trimethylsilylpyroglutamate (**9**) (12.1 g, 0.056 mol) then triflic acid (0.2 ml, 0.34 g, 2.3 mmol) was added (syringe). After refluxing for 2 hours, the solution was evaporated and methylene dichloride was added. The solution was washed with water, dried (sodium sulfate) then evaporated. The oil obtained crystallized in ether (-40 °C) and compound **14** was recristallized from ether.

1-[Trimethylsilyloxy-(3,4,5-trimethoxyphenyl)methyl]benzotriazole (**16**).

N-Trimethylsilylbenzotriazole (**18**) (20 g, 0.105 mol) was added to a stirred mixture of 3,4,5-trimethoxybenzaldehyde (20.5 g, 0.105 mol) and potassium *tert*-butoxide (0.020 g, 0.18 mmol) (exothermic). The water sensitive product **16** was obtained after 30 minutes of stirring.

1-(Benzo[1,3]dioxol-5-yl-trimethylsilyloxymethyl)benzotriazole (**17**).

This product was obtained by using the same procedure as for **16**, starting from piperonal (15.7 g, 0.105 mol).

Methyl 1-[Benzotriazol-1-yl-(3,4,5-trimethoxyphenyl)-methyl]pyroglutamate (**19**).

Triflic acid (0.17 g, 0.1 ml, 1.1 mmol) was added (syringe) to a stirred mixture of compound **16** (20 g, 0.052 mol) and methyl *N*-trimethylsilylpyroglutamate (**9**) (11.1 g, 0.052 mol) in dichloromethane (20 ml). The solution was refluxed for 4 hours, washed with water and dried (sodium sulfate), giving product **19** as an oil. Crystallization from ethyl acetate gave **19a** and **19b**.

Methyl 1-(Benzo[1,3]dioxol-5-yl-benzotriazol-1-yl-methyl)-pyroglutamate (**20**).

This compound was obtained by using the same procedure as for **19**, starting from compound **17** (0.052 mol).

3-(3,4,5-Trimethoxyphenyl)dihydropyrrolo[1,2-*c*]oxazole-1,5-dione (**21**) and

Trimethylsilyl 1-[Trimethylsilyloxy-(3,4,5-trimethoxyphenyl)-methyl]pyroglutamate (**22**).

N,*O*-Bis-trimethylsilylpyroglutamic acid (**23**) (90 g, 0.330 mol) was added (syringe) to a stirred mixture of 3,4,5-trimethoxybenzaldehyde (60 g, 0.306 mol) and potassium *tert*-butoxide (0.41 g, 0.36 mmol). After heating at 100 °C for 4.5 hours, bis trimethylsilyl compound **22** was quantitatively obtained. This product was dissolved in methylene dichloride

Table 5

NMR Spectra of New Compounds

N°	NMR ($CDCl_3$) δ ppm
11	^{1}H: 0.16 (s, 4H), 0.19 (s, 5H), 1.85-2.07 (m, 1H), 2.07-2.47 (m, 2H), 2.57-2.86 (m, 1H), 3.20 (s, 1.8H), 3.76 (s, 1.2H), 3.82 (s, 2.1H), 3.86 (s, 6.9H), 3.8-3.9 (0.6H), 4.35 (dd, J = 9, 1.5 Hz, 0.4H), 6.58-6.68 (m, 3H)
12	^{1}H: 1.80-2.77 (m, 8H), 3.34 (s, 3H), 3.43 (s, 3H), 3.83 (s, 3H), 3.84 (s, 6H), 4.61 (d, J = 6.8 Hz, 1H), 4.72 (d, J = 7 Hz, 1H), 6.10 (s, 1H), 6.66 (s, 2H)
	^{13}C: 23.2, 24.4, 29.7, 30.7, 51.7, 52.1, 56.2, 59.9, 60.8, 63.1, 68.1, 106.6, 129.8, 138.1, 152.8, 172.0, 173.3, 175.9, 176.2
14	^{1}H: 1.95-2.19 (m, 1H), 2.20-2.60 (m, 2H), 2.60-3 (m, 1H), 3.22 (s, 1.1H), 3.41 (s, 1.1H), 3.45 (s, 1.9H), 3.78 (s, 1.9H), 3.82, 3.83, 3.84, 3.85, 3.86 (5 s, 9H), 3.8-3.9 (0.6H), 4.27 (dd, J = 8.6, 1.5 Hz, 0.4H), 6.21, (s, 0.6H), 6.22 (s, 0.4H), 6.59 (s, 1.2H), 6.61 (s, 0.8H)
15	^{1}H: 3.73 (s, 6H), 3.79 (s, 6H), 3.83 (s, 3H), 5.38 (s, 1H), 6.31 (s, 2H), 6.83 (dt, J = 8.9, 2.6 Hz, 4H), 7.03 (dt, J = 8.9, 2.6 Hz, 4H)
16	^{1}H: 0.10 (s, 9H), 3.80 (s, 6H), 3.83 (s, 3H), 6.74 (s, 2H), 7.27-7.38 (m, 3H), 7.52 (s, 1H), 7.99-8.08 (m, 1H)
17	^{1}H: 0.07 (s, 9H), 5.94 (d, J = 1.3 Hz, 1H), 5.96 (d, J = 1.3 Hz, 1H), 6.77 (d, J = 8.7 Hz, 1H), 6.93-7.0 (m, 1H), 6.95 (s, 1H), 7.29-7.35 (m, 3H), 7.48 (t, J = 1.8 Hz, 1H)
19a	^{1}H: 2.01-2.21 (m, 1H), 2.21-2.55 (m, 2H), 2.55-2.75 (m, 1H), 3.36 (s, 3H), 3.80 (s, 6H), 3.87 (s, 3H), 4.58 (d, J = 7.9 Hz, 1H), 6.57 (s, 2H), 7.44 (td, J = 7.5, 1.1 Hz, 1H), 7.58 (td, J = 7.6, 1.1 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 8.09 (d, J = 8.5 Hz, 1H), 8.11 (s, 1H)
	^{13}C: 24.9, 29.1, 52.7, 56.3, 57.1, 60.9, 64.6, 104.9, 110.3, 119.8, 124.6, 128.3, 128.9, 133.8, 138.8, 145.5, 153.7, 171.4, 175.8
19b	^{1}H: 1.96-2.20 (m, 1H), 2.30-2.60 (m, 2H), 2.60-2.80 (m, 1H), 3.39 (s, 3H), 3.79 (s, 6H), 3.81 (s, 3H), 5.08 (d, J = 7.9 Hz, 1H), 6.56 (s, 2H), 7.34-7.54 (m, 3H), 7.84 (s, 1H), 8.09 (d, J = 7.9 Hz, 1H)
	^{13}C: 24.1, 29.2, 51.9, 56.4, 58.4, 60.8, 66.2, 104.7, 109.9, 118.5, 124.5, 128.0, 128.5, 132.6, 138.7, 144.2, 153.5, 172.4, 175.9
20	^{1}H: 2-2.18 (m, 1H), 2.3-2.6 (m, 2H), 2.6-2.8 (m, 1H), 3.32 (s, 1.5 H), 3.42 (s, 1.5H), 4.59 (d, J = 7.9 Hz, 0.5H), 5.03 (d, J = 7.9 Hz, 0.5H), 5.95 (dd, J = 2.2, 1.3 Hz, 1H), 6 (s, 1H), 6.7-6.8 (m, 3H), 7.3-7.9 (m, 4H), , 8.09 (d, J = 8Hz, 1H)
21	^{1}H: 2.04-2.40 (m, 2H), 2.40-2.79 (m, 2H), 3.87 (s, 3H), 3.89 (s, 6H), 4.16 (dd, J = 8.7, 3.9 Hz, 1H), 6.63 (s, 2H), 7.73 (s, 1H)
	^{13}C: 21.6, 29.6, 56.4, 56.7, 60.9, 76.6, 103.5, 128.4, 138.8, 153.8, 169.3, 174.4
22	^{1}H: 0.18 (s, 9.7H), 0.33 (s, 8.3H), 1.80-2.22 (m, 1H), 2.22-2.51 (m, 2H), 2.51-2.79 (m, 1H), 3.76 (dd, J = 8.8, 1.3 Hz, 0.7H), 3.84 (s, 1H), 3.85 (s, 8H), 4.36 (dd, J = 8.8, 1.3 Hz, 0.3H), 6.62 (s, 2H), 6.65 (s, 0.3H), 6.67 (s, 0.7H)
25	^{1}H: (CD_3OD): 1.85-2.05 (m, 1H), 2.1-2.3 (m, 1H), 2.3-2.5 (m, 4H), 2.5-2.75 (m, 2H), 3.78 (s, 3H), 3.83 (s, 6H), 4.51 (dd, J = 7, 1 Hz, 1H), 4.62 (dd, J = 7, 2 Hz, 1H), 6.41 (s, 1H), 6.69 (s, 2H)
	^{13}C (CD_3OD): 24.8, 25.4, 30.4, 31.2, 56.6, 60.9, 61.1, 63.0, 67.6, 107.8, 131.3, 139.3, 154.3, 174.9, 175.5, 178.4, 178.6
26a	^{1}H: 2-2.25 (m, 1H), 2.26-2.60 (m, 2H), 2.60-2.87 (m, 1H), 3.75 (s, 3H), 3.79 (s, 6H), 3.83 (s, 3H), 4.16 (t, J = 7.2 Hz, 1H), 6.43 (s, 3H), 6.87 (d, J = 9 Hz, 2H), 7.04 (d, J = 9 Hz, 2H)
26b	^{1}H: 2.04-2.29 (m, 1H), 2.29-2.60 (m, 2H), 2.60-2.88 (m, 1H), 3.73 (s, 3H), 3.79 (s, 6H), 3.85 (s, 3H), 4.16 (t, J = 7.2 Hz, 1H), 6.32 (s, 2H), 6.39 (s, 1H), 6.75 (d, J = 9 Hz, 2H), 7.15 (d, J = 9 Hz, 2H)
26	^{13}C: 24.5, 24.6, 29.8, 55.2, 55.4, 56.1, 56.2, 58.4, 58.6, 59.1, 59.2, 60.7, 60.9, 104.6, 107.7, 113.7, 114.1, 128.5, 129.9, 130.4, 131.9, 133.7, 134.9, 153.1, 153.3, 159.2, 159.5, 176.1, 176.2, 176.3, 176.6

(165 ml), then triflic acid (2 ml, 3.4 g, 22.8 mmol) was added (syringe). After 4 hours, diethyl ether was added and the white solid obtained was filtered. Washing this solid with a sodium hydrogenocarbonate solution remove pyroglutamic acid and a very small amount of diacid **25**. After drying, the solid was refluxed in ether to give lactone **21** as a white powder.

N-(3,4,4',5-Tetramethoxybenzhydryl)pyroglutamic Acid (**26**).

Triflic acid (0.4 ml, 0.68 g, 4.6 mmol) was slowly added (syringe) to a stirred mixture of lactone **21** (2 g, 6.5 mmol) and anisole (2.1 g, 19.5 mmol). After 96 hours methylene dichloride and a solution of potassium carbonate in water were added. The aqueous phase was acidified giving acids **26** as a 66/34 mixture of diastereoisomers.

X-Ray Cristal Structure Determination of **B** [19].

Crystals of compound **B** suitable for X-ray investigations were obtained by slow evaporation of a methanol solution at room temperature. The structure was solved using the SIR97 program [22]; the refinement was performed using SHELXL97 [23].

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