Studies on Pyrrolidinones. Synthesis of *N*-Benzhydrylpyroglutamic Acids and Esters

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Catalyzed *N*-alkylation of *N,O*-bistrimethylsilyl pyroglutamic acid with trimethylsilyl benzhydryl ethers yields trimethylsilyl *N*-benzhydrylpyroglutamates. Hydrolysis of these compounds or saponification of the methyl esters gives the corresponding acids.

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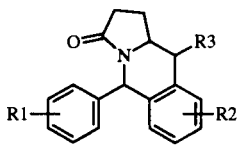
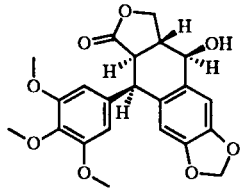
Enroute to the synthesis of azaanalogs **1** [1] of known and efficient anticancer agents podophyllotoxin **2**, epipodophyllotoxins **3** and azatoxin **4** we need a general and versatile access to acids **5**.

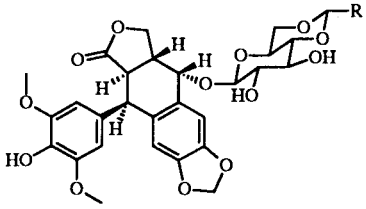
Scheme 1



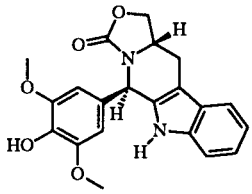
1



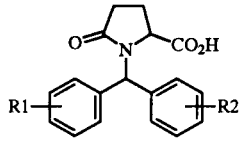
2 podophyllotoxin



3 R = Me etoposide
R = thenyl teniposide



4 azatoxin

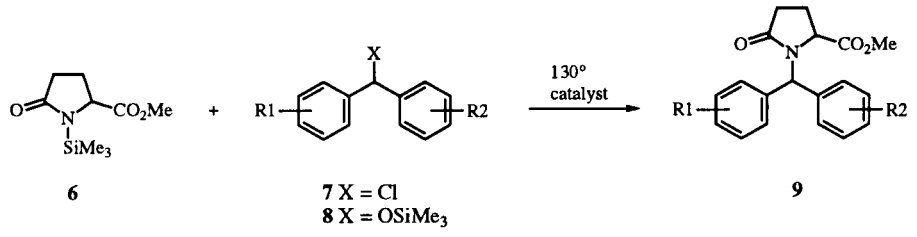


5

In a preliminary note [2], we previously reported that the known reaction of methyl *N*-trimethylsilylpyroglutamate **6** [3,4] with benzyl [4] or benzhydryl chlorides [5] can be catalyzed by a variety of catalysts (triflic acid, trimethylsilyl triflate, tin chloride, iodine...). We have also shown that the same results were obtained when benzhydryl chlorides **7** are changed by trimethylsilyl benzhydryl ethers **8** (Scheme 2).

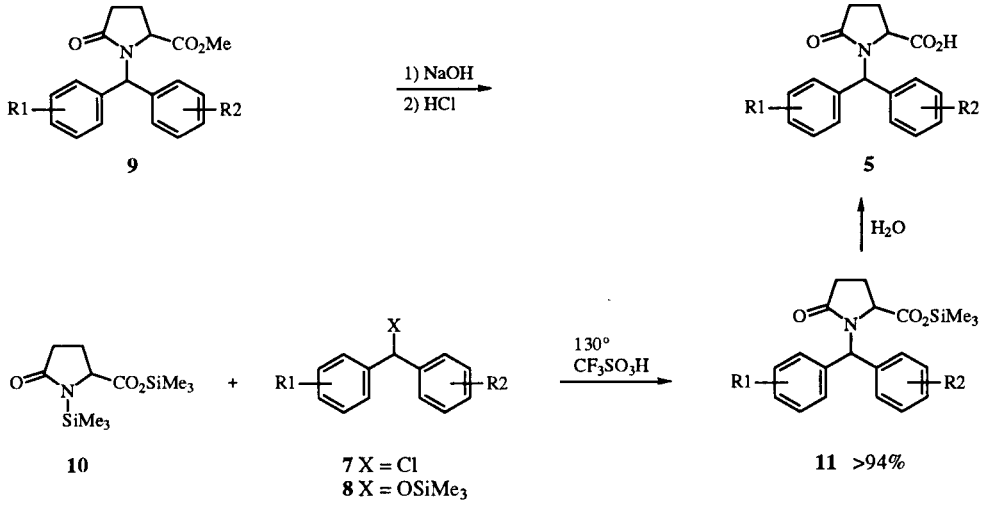
This reaction pathway, followed by the saponification of methyl ester **9** provides a rapid, easy and convenient route to obtain acids **5**, but needs a two-step procedure. The yields of the saponifications are not quantitative. Our recent results showing exclusive *N*-acylation [6] and *N*-alkylation [4,7] of *N,O*-bistrimethylsilyl pyroglutamic acid (**10**) [8], led us to use this compound with chlorides **7**

Scheme 2



6 **7** X = Cl, **8** X = $OSiMe_3$ **9**

Scheme 3

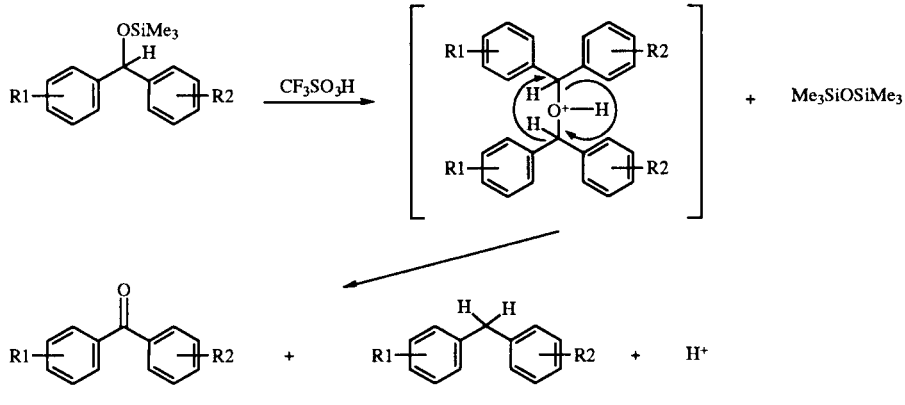


9 **5** **10** **7** X = Cl, **8** X = $OSiMe_3$ **11** >94%

and silyl ethers **8** to provide near quantitative yields of silyl esters **11** and acids **5** (Scheme 3).

It is interesting to note that, in the same way as for the *N*-silyl compound **6** [2], no acid catalysed disproportion-

Scheme 4



Scheme 5

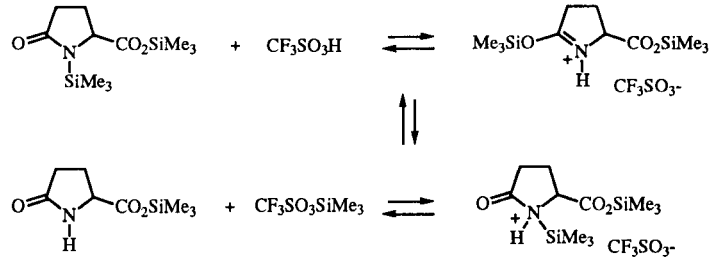


Table 1

Yields and Physical Properties of Esters **9**

No.	R_1	R_2	Yield % [c]	MP°C (ethyl acetate)	$[\alpha]^D_{20}$ (%, solvent)	IR (KBr) ν cm^{-1}	^1H NMR δ ppm ($CDCl_3$)
9a [a]	H	H	99 [d] 96 [e] 62 [i]	132 132 [i]	-201 [i] (1.39, dichloromethane)	1735, 1695 (C=O), 1605, 1510 (C=C)	1.97-2.13 (m, 1H), 2.36-2.58 (m, 2H), 2.65-2.83 (m, 1H), 3.23 (s, 3H), 4.26 (d, J = 7.7 Hz, 1H), 6.58 (s, 1H), 7.08-7.15 (m, 2H), 7.19-7.39 (m, 8H)
9b [a]	4-Cl	H	91 [d,f]	146 [f]	-149 (0.19, dichloromethane)	1735, 1690 (C=O), 1605, 1510 (C=C)	[f]: 1.85-2.62 (m, 4H), 3.19 (s, 1.5H), 3.25 (s, 1.5H), 4.05-4.21 (m, 1H), 6.34 (s, 0.5H), 6.39 (s, 0.5H), 6.82-7.28 (m, 9H)
9c [a]	4-Cl	4'-Cl	95 [e]	137	-181 (0.25, dichloromethane)	1730, 1640 (C=O), 1600, 1585 (C=C)	1.95-2.6 (m, 4H), 3.26 (m, 3H), 3.95- 4.21 (m, 1H), 6.39 (s, 1H), 6.9-7.35 (m, 8H)
9d [a]	4-F	4'-F	97 [d]	127	-143 (0.23, dichloromethane)	1740, 1695 (C=O), 1605, 1510 (C=C)	2-2.7 (m, 4H), 3.26 (s, 3H), 3.97-4.23 (m, 1H), 6.43 (s, 1H), 6.7-7.3 (m, 8H)
9e [b]	4-OMe	4'-OMe	99 [d] 91 [e] 41 [i]	116		1750, 1690 (C=O), 1605, 1585, 1510, 1450 (C=C)	2-2.07 (m, 1H), 2.36-2.52 (m, 2H), 2.65- 2.76 (m, 1H), 3.30 (s, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 4.23 d, J = 8.2 Hz, 1H), 6.47 (s, 1H), 6.83 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H), 7.15 (d, J= 8.7 Hz, 2H)
9f [b]	4-OMe	3',4'-(OCH_2O)	94 [e,f]	143 [g]		1750, 1695 (C=O), 1610, 1580, 1510, 1490, 1460 (C=C) [f]	[g]: 1.98-2.08 (m, 1H), 2.31-2.50 (m, 2H), 2.62-2.77 (m, 1H), 3.37 (s, 3H), 3.79 (s, 3H), 4.20 (d, J = 8.3 Hz, 1H), 5.92 (s, 2H), 6.38 (s, 1H), 6.68-6.77 (m, 3H), 6.86 (d, J = 8.7 Hz, 1H), 7.03 (d, J = 8.7 Hz, 2H) [h]: 1.98-2.08 (m, 1H), 2.31-2.50 (m, 2H), 2.62-2.77 (m, 1H), 3.28 (s, 3H), 3.78 (s, 3H), 4.20 (d, J = 8.4 Hz, 1H), 5.93 (s, 2H), 6.38 (s, 1H), 6.68-6.77 (m, 3H), 6.81 (d, J = 8.7 Hz, 2H), 7.12 (d, J = 8.7 Hz, 2H)
9g [b]	4-OMe	3',4',5'-($OMe)_3$	96 [e,f]	130 [g] 138 [h]		[g]: 1745, 1690 (C=O), 1590, 1510, 1410 (C=C) [h]: 1735, 1685 (C=O), 1590, 1510, 1405 (C=C)	[g]: 2.04-2.11 (m, 1H), 2.35-2.53 (m, 2H), 2.69-2.75 (m, 1H), 3.31 (s, 3H), 3.79 (s, 9H), 3.83 (s, 3H), 4.25 (d, J = 8.4 Hz, 1H), 6.36 (s, 2H), 6.42 (s, 1H), 6.83 (d, J = 8.5 Hz, 2H), 7.15 (d, J = 8.5 Hz, 2H) [h]: 2-2.07 (m, 1H), 2.35-2.52 (m, 2H), 2.70-2.75 (m, 1H), 3.31 (s, 3H), 3.79 (s, 6H), 3.82 (s, 3H), 3.83 (s, 3H), 4.21 (d, J = 8.5 Hz, 1H), 6.45 (s, 3H), 6.88 (d, J = 8.6 Hz, 2H), 7.05 (d, J = 8.6 Hz, 2H)
9h [b]	3,4-($OMe)_2$	H	91 [e,f]	137 [g]		1740, 1690 (C=O), 1590, 1510, 1440, 1430 (C=C)	[g]: 2-2.08 (m, 1H), 2.36-2.53 (m, 2H), 2.65-2.78 (m, 1H), 3.27 (s, 3H), 3.82 (s, 3H), 3.86 (s, 3H), 4.25 (d, J = 7.5 Hz, 1H), 6.52 (s, 1H), 6.71-6.79 (m, 3H), 7.12 (d, J = 7.6 Hz, 1H), 7.22-7.36 (m, 4H) [h]: 2-2.08 (m, 1H), 2.36-2.53 (m, 2H), 2.65-2.78 (m, 1H), 3.25 (s, 3H), 3.76 (s, 3H), 3.88 (s, 3H), 4.23 (d, J = 7.4 Hz, 1H), 6.50 (s, 1H), 6.63-6.86 (m, 3H), 7.12 (d, J = 6.8 Hz, 1H) 7.22-7.36 (m, 4H)
9i [b]	3,4-(OCH_2O)	3',4'-(OCH_2O)	97 [e]	147		1750, 1690 (C=O), 1620, 1605, 1505, 1490, 1440 (C=C)	1.99-2.08 (m, 1H), 2.35-2.50 (m, 2H), 2.62-2.75 (m, 1H), 1.38 (s, 3H), 4.20 (d, J = 8 Hz, 1H), 5.93 (s, 1H), 5.94 (s, 1H), 6.31 (s, 1H), 6.56-6.77 (m, 6H)
9j [b]	3,4,5-($OMe)_3$	H	95 [e,f]	118 [g]		1760, 1750, 1710, 1690 (C=O), 1590, 1505, 1460 (C=C) [f]	[g]: 2.01-2.11 (m, 1H), 2.37-2.53 (m, 2H), 2.67-2.74 (m, 1H), 3.26 (s, 3H), 3.78 (s, 6H), 3.84 (s, 3H), 4.26 (d, J = 8 Hz, 1H), 6.37 (s, 2H), 6.48 (s, 1H), 7.12 (d, J = 7.5 Hz, 1H), 7.22-7.38 (m, 4H)

Table 1 (continued)
Yields and Physical Properties of Esters **9**

No.	R_1	R_2	Yield % [c]	MP°C (ethyl acetate)	$[\alpha]^{D}_{20}$ (%, solvent)	IR (KBr) ν cm^{-1}	^1H NMR δ ppm ($CDCl_3$)
							[h]: 2.01-2.11 (m, 1H), 2.37-2.53 (m, 2H), 2.67-2.74 (m, 1H), 3.31 (s, 3H), 3.78 (s, 6H), 3.83 (s, 3H), 4.26 (d, J = 8 Hz, 1H), 6.45 (s, 2H), 6.52 (s, 1H), 7.13 (d, J = 7.5 Hz), 7.23-7.35 (m, 4H)
9k [b]	3,4,5-$(OMe)_3$	3',4'-(OCH_2O)	96 [e, f]	187 [g]		1740, 1680 (C=O), 1590, 1505, 1490, 1460 (C=C)	[g]: 2.04-2.12 (m, 1H), 2.32-2.52 (m, 2H), 2.68-2.77 (m, 1H), 3.40 (s, 3H), 3.80 (s, 6H), 3.84 (s, 3H), 4.23 (d, J = 8.7 Hz, 1H), 5.95 (s, 2H), 6.35 (s, 2H), 6.36 (s, 1H) 6.70-6.76 (m, 3H) [h]: 2-2.07 (m, 1H), 2.32-2.51 (m, 2H), 2.7-2.77 (m, 1H), 3.32 (s, 3H), 3.80 (s, 6H), 3.84 (s, 3H), 4.23 (d, J = 8.7 Hz, 1H), 5.96 (s, 2H), 6.37 (s, 1H), 6.45 (s, 2H), 6.7-6.76 (m, 3H)
9l [b]	3,4,5-$(OMe)_3$	3',4',5'-$(OMe)_3$	82 [e]	95		1735, 1690 (C=O), 1585, 1500, 1450 (C=C)	2-2.88 (m, 4H), 3.33 (s, 3H), 3.80 (s, 12H), 3.85 (s, 6H), 4.22 (d, J = 8 Hz, 1H), 6.36 (s, 2H), 6.44 (s, 1H), 6.47 (s, 2H)

[a] From L ester **6**. [b] From DL ester **6**. [c] Crude yield. [d] From chloride **7**. [e] From silyl ester **8**. [f] Diastereomeric mixture. [g] Isomer 1. [h] Isomer 2. [i] [lit 5a].

ation (Scheme 4) [10] of the trimethylsilyl ether **8** to diphenylmethanes and benzhydryl ketones was observed when triflic acid was added to the mixture of compounds **8** and **10**, thus indicating that the catalyst was not this acid but trimethylsilyl triflate obtained by an equilibrium such as the one reported in Scheme 5.

As might be expected from previous results of reactions of *N*-trimethylsilylpyroglutamic derivatives [5], there is no racemization of the acidic function; asymmetrical silylbenzhydryl ethers give the desired coupling products as a diastereomeric mixture of esters, which generally can not be separated by crystallization [11].

Table 2
Yields and Physical Properties of Acids **5**

No.	R_1	R_2	Yield % [a]	MP°C (Solvent)	IR (KBr) ν cm^{-1}	^1H NMR δ ppm
5a	H	H	93 [b]	203 (MeOH)	1720, 1620 (C=O), 1605, 1580, 1510 (C=C)	($CDCl_3$): 1.80-2.90 (m, 4 H), 4.05-4.34 (m, 1H), 6.25 (s, 1H), 7.20 (m, 10H)
5e	4-OMe	4'-OMe	87 [b]	207 (MeOH)	1720, 1620 (C=O), 1605, 1580, 1510, 1450 (C=C), 1180 (C-O)	($CDCl_3$/DMSO-d_6): 2.05-2.12 (m, 1H), 2.35-2.46 (m, 2H), 2.57-2.70 (m, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 4.14 (d, J = 8 Hz, 1H), 6.37 (s, 1H), 6.80 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 7.04 (d, J = 8.6 Hz, 2H), 7.16 (d, J = 8.6 Hz, 2H)
5f	4-OMe	3',4'-(OCH_2O)	74 [b] [d]	206 (MeOH) [d]	[d]: 1720, 1620 (C=O), 1600, 1580, 1510, 1485, 1445 (C=C), 1170 (C-O)	[e] ($CDCl_3$/DMSO-d_6): 2.06-2.13 (m, 1H), 2.34-2.46 (m, 2H), 2.58-2.68 (m, 1H), 3.77 (s, 3H), 4.12 (d, J = 7.9 Hz, 1H), 5.94 (s, 2H), 6.30 (s, 1H), 6.59-6.79 (m, 3H), 6.80 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 8.3 Hz, 2H) [f] ($CDCl_3$/DMSO-d_6): 2.06-2.13 (m, 1H), 2.34-2.46 (m, 2H), 2.58-2.68 (m, 1H), 3.79 (s, 3H), 4.12 (d, J = 7.9 Hz, 1H), 5.92 (s, 2H), 6.30 (s, 1H), 6.59-6.79 (m, 3H), 6.85 (d, J = 8.3 Hz, 2H), 7.05 (d, J = 8.3 Hz, 2H)

Table 2 (continued)
Yields and Physical Properties of Acids **5**

No.	R_1	R_2	Yield % [a]	MP°C (Solvent)	IR (KBr) ν cm^{-1}	^1H NMR δ ppm
5g	4-OMe	3',4',5'-$(OMe)_3$	92 [b] [d]	[g]	[d]: 3000 (O-H), 1730, 1690-1650 (C=O), 1610, 1590, 1460 (C=C), 1125 (C-O)	[e] ($CDCl_3$) : 2.11-2.19 (m, 1H), 2.33-2.49 (m, 2H), 2.63-2.73 (m, 1H), 3.71 (s, 6H), 3.78 (s, 3H), 3.80 (s, 3H), 4.14 (d, J = 8.3 Hz, 1H), 6.39 (s, 1H), 6.44 (s, 2H), 6.87 (d, J = 8.7 Hz, 2H), 7.90 (s, 0.1H) [h] [f] ($CDCl_3$): 2.11-2.19 (m, 1H), 2.33-2.49 (m, 2H), 2.63-2.73 (m, 1H), 3.71 (s, 3H), 3.78 (s, 6H), 3.83 (s, 3H), 4.18 (d, J = 8.5 Hz, 1H), 6.33 (s, 2H), 6.37 (s, 1H), 6.71 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 7.90 (s, 0, 1H) [h]
5h	3,4-$(OMe)_2$	H	83 [b] [d]	[g]	[d]: 3550, 3100 (O-H), 1740, 1690-1640 (C=O), 1605, 1595, 1525, 1495, 1465, 1450 (C=C), 1130 (C-O)	[d] ($CDCl_3$): 2.06-2.13 (m, 1H), 2.32-2.48 (m, 2H), 2.58-2.70 (m, 1H), 3.73 (s, 3H), 3.75 (s, 1.5H), 3.85 (s, 1.5H), 4.15 (d, J = 7.9 Hz, 0.5H), 4.20 (d, J = 8 Hz, 0.5H), 6.38 (s, 0.5H), 6.45 (s, 0.5H), 6.61-6.86 (m, 3H), 7.10 (d, J = 7.3 Hz, 1H), 7.16-7.35 (m, 4H), 8.68 (s, 0, 1H) [h]
5i	3,4-(OCH_2O)	3',4'-(OCH_2O)	81 [b]	229 (MeOH)	2910 (O-H), 1735, 1640 (C=O), 1505, 1490, 1450 (C=C), 1150 (C-O)	($CDCl_3$): 2.02-2.20 (m, 1H), 2.35-2.55 (m, 2H), 2.59-2.77 (m, 1H), 4.16 (d, J = 7.7 Hz, 1H), 5.88 (s, 2H), 5.95 (s, 2H), 6.29 (s, 1H), 6.58 (s, 2H), 6.65-6.79 (m, 4H)
5j	3,4,5-$(OMe)_3$	H	79 [c] [e]	[g]	[d]: 3640, 3000 (O-H), 1740, 1700, 1650 (C=O), 1590, 1510, 1460 (C=C), 1125 (C-O)	[e] ($CDCl_3$): 2.04-2.16 (m, 1H), 2.30-2.49 (m, 2H), 2.63-2.71 (m, 1H), 3.71 (s, 6H), 3.77 (s, 3H), 4.15 (d, J = 8.3 Hz, 1H), 6.35 (s, 1H), 6.43 (s, 2H), 7.12 (d, J = 7.4 Hz, 1H), 7.19-7.37 (m, 4H), 8.54 (s, 0, 1H) [h] [f] ($CDCl_3$): 2.04-2.16 (m, 1H), 2.30-2.49 (m, 2H), 2.63-2.71 (m, 1H), 3.78 (s, 6H), 3.83 (s, 3H), 4.19 (d, J = 8.3 Hz, 1H), 6.36 (s, 2H), 6.43 (s, 1H), 7.12 (d, J = 7.4 Hz, 1H), 7.19-7.37 (s, 4H), 8.54 (s, 0, 1H) [h]
5k	3,4,5-$(OMe)_3$	3',4'-(OCH_2O)	81 [b] [d] 94 [c] [d]	222 [d] (MeOH)	[d]: 3650, 3050 (O-H), 1740, 1650 (C=O), 1600, 1590, 1520, 1450 (C=C), 1130 (C-O)	[d] ($CDCl_3$/DMSO-d_6): 2.05-2.15 (m, 1H), 2.31-2.48 (m, 2H), 2.63-2.72 (m, 1H), 3.65 (s, 3H), 3.70 (s, 4.5H), 3.93 (s, 1.5H), 4.18 (d, J = 7.5 Hz, 0.5H), 4.25 (d, J = 7.5 Hz, 0.5H), 5.99 (s, 1H), 6.00 (s 1H), 6.42 (s, 3H), 6.62-6.87 (m, 3H)
5l	3,4,5-$(OMe)_3$	3',4',5'-$(OMe)_3$	80 [b]	171 (MeOH)	3450 (OH), 1735, 1630 (C=O), 1590, 1500, 1450 (C=C), 1120 (C-O)	(acetone-d_6): 2.02-2.70 (m, 4H), 3.70 (s, 3H), 3.74 (s, 9H), 3.77 (s, 6H), 4.30 (d, J = 7.7 Hz, 1H), 6.25 (s, 1H), 6.25 (s, 1H), 6.51 (s, 2H), 6.61 (s, 2H)

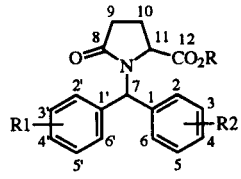
[a] Crude yield. [b] From DL ester **9**. [c] From DL ester **11**. [d] Diastereomeric mixture. [e] Isomer 1. [f] Isomer 2. [g] Oil. [h] Deuterium oxide exchangeable.

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, 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.

Table 3

NMR Spectra of DL Compounds **5** and **9**



5, 9

Scheme 6

Numbering used in Table 3

No.	R_1	R_2	^{13}C NMR δ ppm ($CDCl_3$)
5f	4-OMe	3',4'-(OCH_2O)	[a] ($CDCl_3$/DMSO-d_6): 24.7 (C_{10}), 29.9 (C_9), 55.3 (4-OMe), 58.6 (C_{11}), 59.0 (C_7), 101.1 (3',4'-OCH_2O), 108.0 ($C_{2'}$), 110.7 ($C_{5'}$), 113.9 (C_2 and C_6), 124.0 ($C_{6'}$), 128.4 (C_3 and C_5), 131.4 (C_1), 132.6 ($C_{1'}$), 147.2 ($C_{4'}$), 147.4 ($C_{3'}$), 158.8 (C_4), 174.2 (C_8), 175.7 (C_{12})
5i	3,4-(OCH_2O)	3',4'-(OCH_2O)	24.5 (C_{10}), 29.7 (C_9), 58.4 (C_{11}), 59.3 (C_7), 101.1 (3,4-OCH_2O and 3',4'-(OCH_2O), 108.1 (C_2 and $C_{2'}$), 110.8 (C_5 and $C_{5'}$), 120.1 (C_6 and $C_{6'}$), 124.3 (C_1 and $C_{1'}$), 147.1 (C_3 and $C_{3'}$), 148.2 (C_4 and $C_{4'}$), 175.8 (C_8), 176.4 (C_{12})
5l	3,4,5-$(OMe)_3$	3',4',5'-$(OMe)_3$	25.6 (C_{10}), 28.7 (C_9), 56.5 (3-OMe, 3'-OMe, 5-OMe and 5'-OMe), 59.5 (C_{11}), 60.6 (C_7), 61.2 (4-OMe and 4'-OMe), 106.0 (C_2 and $C_{2'}$), 108.7 (C_6 and $C_{6'}$), 135.0, 136.6 (C_1, $C_{1'}$,C_4 and $C_{4'}$), 154.1 (C_3 and $C_{3'}$), 154.4 (C_5 and $C_{5'}$), 174.4 (C_8), 176.1 (C_{12})
9g	4-OMe	3',4',5'-$(OMe)_3$	[a]: 24.6 (C_{10}), 29.7 (C_9), 51.9 (CO_2*Me*), 55.4 (4'-OMe), 56.1 (3-OMe and 5-OMe), 58.3 (C_{11}), 59.0 (C_7), 60.8 (4-OMe), 107.3 (C_2 and C_6) 114.1 ($C_{3'}$ and $C_{5'}$), 128.6 (C_2 and $C_{6'}$), 130.5 (C_1), 133.9 ($C_{1'}$), 139.8 (C_4), 153.1 (C_3 and C_5), 159.1 ($C_{4'}$), 172.8 (C_8), 175.7 (C_{12})
9i	3,4-(OCH_2O)	3',4'-(OCH_2O)	24.5 (C_{10}), 29.8 (C_9), 52.0 (CO_2*Me*), 58.6 (C_{11}), 59.1 (C_7), 101.3 (3,4-OCH_2O and 3',4'-OCH_2O), 108.1 (C_2 and $C_{2'}$), 110.7 (C_5 and $C_{5'}$), 120.2 (C_6 and $C_{6'}$), 124.2 (C_1 and $C_{1'}$), 147.5 (C_3 and $C_{3'}$), 148.1 (C_4 and $C_{4'}$), 172.7 (C_8), 175.6 (C_{12})
9k	3,4,5-$(OMe)_3$	3',4'-(OCH_2O)	[a]: 24.6 (C_{10}), 29.8 (C_9), 52.0 (CO_2*Me*), 56.2 (3-OMe and 5-OMe), 58.6 (C_{11}), 59.4 (C_7), 60.9 (4-OMe), 101.3 (3',4'-OCH_2O), 104.7 (C_2 and C_6), 108.1 ($C_{2'}$), 110.6 ($C_{5'}$), 124.0 ($C_{6'}$), 131.8 ($C_{1'}$), 134.7 (C_1), 147.5, 147.8 ($C_{3'}$, $C_{4'}$ and C_4), 153.5 (C_3 and C_5), 172.6 (C_8), 175.6 (C_{12})
9l	3,4,5-$(OMe)_3$	3',4',5'-$(OMe)_3$	24.8 (C_{10}), 29.7 (C_9), 52.0 (CO_2*Me*), 56.3 (3-OMe, 5-OMe, 3'-OMe and 5'-OMe), 58.3 (C_{11}), 59.6 (C_7), 60.8 (4-OMe and 4'-OMe), 104.9 (C_2, $C_{2'}$, C_6 and $C_{6'}$), 133.7 (C_4 and $C_{4'}$), 137.6 (C_1 and $C_{1'}$), 153.3 (C_3, C_5, $C_{3'}$ and $C_{5'}$), 172.7 (C_8), 175.7 (C_{12})

[a] Isomere (see Tables 1 and 2).

Table 4

Elemental Analysis of New Compounds, % Calcd./Found

No.	Formula	C	H	N	O
5a (L)	$C_{18}H_{17}NO_3$	73.20	5.80	4.74	16.25
		73.07	5.85	4.73	15.99
5c (DL)	$C_{20}H_{21}N0_5$	67.59	5.96	3.94	22.38
		67.39	5.95	3.93	22.57
5f (DL)	$C_{20}H_{19}NO_6$	65.03	5.18	3.79	25.99
		65.08	5.16	3.79	26.19
5g (DL)	$C_{22}H_{25}NO_7$	63.61	6.07	3.37	26.96
		63.74	6.30	3.17	26.74
5h (DL)	$C_{20}H_{21}NO_5$	67.59	5.96	3.94	22.51
		67.31	6.23	3.85	22.56
5i (DL)	$C_{20}H_{17}NO_7$	62.66	4.47	3.65	29.21
		62.39	4.77	3.46	29.31
5j (DL)	$C_{21}H_{23}NO_6$	65.44	6.02	3.63	24.91
		65.51	6.29	3.46	24.94
5k (DL)	$C_{22}H_{23}NO_8$	61.53	5.40	3.26	29.81
		61.36	5.43	3.30	29.93
5l (DL)	$C_{24}H_{29}NO_9$	60.62	6.15	2.95	30.28
		60.63	6.26	2.87	29.97
9b (L)	$C_{19}H_{18}ClNO_3$	66.38	5.28	4.07	13.96
		66.21	5.27	4.07	13.94
9c (L)	$C_{19}H_{17}Cl_2NO_3$	60.33	4.53	3.70	12.69
		60.71	4.79	3.84	12.89
9d (L)	$C_{19}H_{17}F_2NO_3$	66.08	4.96	4.06	
		65.84	4.79	3.89	
9f (DL)	$C_{21}H_{21}NO_6$	65.79	5.52	3.65	25.04
		65.55	5.51	3.64	25.19
9g (DL)	$C_{23}H_{27}NO_7$	64.32	6.34	3.26	26.08
		64.00	6.36	3.27	26.21
9h (DL)	$C_{21}H_{23}NO_5$	68.28	6.28	3.79	21.65
		68.31	6.37	3.78	21.69
9i (DL)	$C_{21}H_{19}NO_7$	63.47	4.82	3.52	28.18
		63.03	4.85	3.47	28.52
9j (DL)	$C_{22}H_{25}NO_6$	66.15	6.31	3.51	24.03
		66.46	6.40	3.56	24.32
9k (DL)	$C_{23}H_{25}NO_8$	62.30	5.68	3.16	28.86
		62.16	5.57	3.10	29.20
9l (DL)	$C_{25}H_{31}NO_9$	61.34	6.38	2.86	29.42
		61.42	6.45	2.98	29.05

Experimental Procedure for the Synthesis of Methyl Esters **9** from **6** and **7**.

Methyl *N*-(4,4'-Difluorobenzhydryl)pyroglutamate (**9d**).

Triflic acid (0.05 ml, 0.56 mmole) was added *via* syringe to a stirred mixture of 4,4'-difluorobenzhydryl chloride (5 g, 21 mmoles) and *N*-silyl ester **6** (5 g, 23.2 mmoles). The solution was heated under nitrogen for 2 hours at 130° in a vessel equipped with a short distillation head. During the course of the reaction, chlorotrimethylsilane evolved. The nmr yields were 100%. After cooling, the mixture was diluted with dichloromethane and washed with water. The solvents were removed under vacuum affording 7 g of **9d** as a white solid, yield 97%.

Experimental Procedure for the Synthesis of Methyl Esters **9** from **6** and **8**.

Methyl *N*-(3,4,5,3',4',5'-Hexamethoxybenzhydryl)pyroglutamate (**9l**).

Triflic acid (0.05 ml, 0.56 mmole) was added *via* syringe to a stirred mixture of 3,4,5,3',4',5'-hexamethoxybenzhydryl trimethylsilyl ether (6.5 g, 18 mmoles) and *N*-silyl ester **6** (4.6 g, 21 mmoles). The solution was heated under nitrogen for 1 hour at 130° in a vessel equipped with a short distillation head. During the course of the reaction, hexamethyldisiloxane evolved. The nmr yields were 100%. After cooling, the mixture was diluted with dichloromethane and washed with water. The solvents were removed under vacuum affording 7.2 g of **9l** as a white solid, yield 82%.

Experimental Procedure for the Synthesis of Silyl Esters **11** from **8** and **10**.

Trimethylsilyl *N*-(3,4-Methylenedioxy-3',4',5'-trimethoxybenzhydryl)pyroglutamate (**11k**).

Triflic acid (0.05 ml, 0.56 mmole) was added *via* syringe to a stirred mixture of 3,4-methylenedioxy-3',4',5'-trimethoxybenzhydryl trimethylsilyl ether (3.7 g, 9.4 mmoles) and silyl compound **10** (2.6 g, 9.5 mmoles). The solution was heated under nitrogen for 30 minutes at 130° in a vessel equipped with a short distillation head. During the course of the reaction, hexamethyldisiloxane evolved. The nmr yields were 100%; ^{1}H nmr (deuteriochloroform): δ ppm 0.08 (s, 9H), 2.02-2.75 (m 4H), 3.78 (s, 6H), 3.82 (s, 3H), 4.15 (d, J = 7.7 Hz, 0.5H), 4.23 (d, J = 7.7 Hz, 0.5H), 5.87 (s, 1H), 5.94 (s, 1H), 6.34 (s, 3H), 6.49-6.73 (m, 3H).

Experimental Procedure for the Synthesis of Acids **5** from **9**.

N-(3,4,5,3',4',5'-Hexamethoxybenzhydryl)pyroglutamic Acid (**5l**).

A suspension of methyl ester **9l** (6.8 g, 14 mmoles) in 2 *N* sodium hydroxide (15 ml), was refluxed for 4 hours. After cooling, the aqueous phase was washed with dichloromethane then acidified, giving a white solid, yield 80%.

Experimental Procedure for the Synthesis of Acids **5** from **11**.

N-(3,4-Methylenedioxy-3',4',5'-trimethoxybenzhydryl)pyroglutamic Acid (**5k**).

Silyl ester **11k** (4.7 g, 9.4 mmoles) in dichloromethane (5 ml) was hydrolysed by water (10 ml), then the aqueous phase was extracted with dichloromethane. A 2 *N* sodium hydroxide solution (15 ml) was added to the organic phases and the aqueous phase was acidified with hydrochloric acid. The precipitate was filtered then washed with water, giving a white solid, yield 94%.

REFERENCES AND NOTES

[1] The synthesis of compounds **1** will be described in a next publication.

[2] B. Rigo, P. Gautret, A. Legrand, J. P. Hénichart and D. Couturier, *Synlett*, 998 (1997).

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[5a] F. Effenberger, W. Müller and H. Isak, *Chem. Ber.*, **120**, 45 (1987); [b] F. Effenberger, W. Müller, R. Keller, W. Wild and T. Ziegler, *J. Org. Chem.*, **55**, 3064 (1990).

[6a] B. Rigo, C. Lespagnol and M. Pauly, *J. Heterocyclic Chem.*, **25**, 59 (1988); [b] B. Rigo, B. Erb, S. El Ghammarti, P. Gautret and D. Couturier, *J. Heterocyclic Chem.*, **32**, 1599 (1995).

[7] B. Rigo, P. Gautret, A. Legrand, S. El Ghammarti and D. Couturier, *Synth. Commun.*, **24**, 2069 (1994).

[8] A synthesis of compound **10** by using trimethylsilyl chloride and triethylamine was previously reported [6a]. A more convenient synthesis of **10** from the saccharin catalyzed reaction of pyroglutamic acid with hexamethyldisilazane is described in reference 9.

[9] S. El Ghammarti, B. Rigo, H. Meijdi, J.-P. Hénichart and D. Couturier, *J. Heterocyclic Chem.*, to be published.

[10] P. Gautret, S. El Ghammarti, A. Legrand, D. Couturier and B. Rigo, *Synth. Commun.*, **26**, 707 (1996).

[11] A general specific synthesis of each diastereoisomer will be reported in a later publication.