Studies on Pyrrolidinone. Synthesis of Aza Analogs of Podophyllotoxin and Related Compounds

Anne Legrand, Benoît Rigo* and Philippe Gautret

Laboratoire de Chimie Organique et Environnement, Ecole des Hautes Etudes Industrielles, 13, rue de Toul, 59046 Lille, France

Jean-Pierre Henichart

Institut de Chimie Pharmaceutique de Lille, Université de Lille 2, 3 rue du Professeur Laguesse, 59006 Lille, France

Daniel Couturier

Laboratoire de Chimie Organique et Environnement, Université des Sciences et Technologies de Lille, 59655 Villeneuve d'Ascq, France

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The Friedel-Crafts cyclisation of *N*-benzhydrylpyroglutamic acids whose aromatic rings are substituted by methoxy or methylenedioxy groups gives podophyllotoxin analogs whose lactone ring was changed to a lactam.

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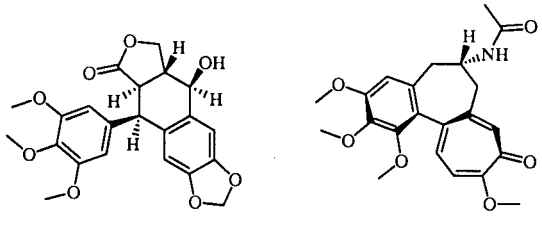
Podophyllotoxin (**1**) is an effective inhibitor of cell division which was shown to act as a spindle poison [1,3], interacting with tubulin at the colchicine (**2**) site [1,4]. This compound is too toxic to be useful for cancer therapy [5,7]. In order to obtain less toxic products many derivatives of podophyllotoxin have been synthesized [3,7-9]. While some aza analogs **3** [10] of podophyllotoxin (**1**) lack strong anticancer activity, some other compounds, such as cyclic carbamates **4** have been reported to display good antitumor activity and only a low toxicity [11,12]. In this paper, we report the synthesis of aza analogs **5** whose lactone ring was changed to a pyrrolidinone ring [13] (Scheme 1).

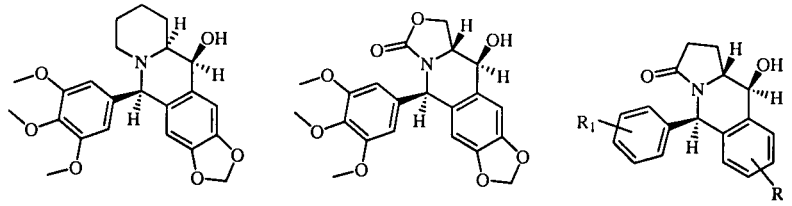
Friedel-Crafts cyclization of acid **6** [14a,b] was accomplished by using its acid chloride and aluminium trichloride (Scheme 2). In that latter case, other Lewis acids such as tin chloride or boron trifluoride did not catalyze the reaction. With oxygenated groups as aromatic substitutents, good cyclization yields were obtained by using trifluoroacetic anhydride and boron trifluoride etherate [15]. For acids **6**, **8**, **10** [14], only one ketones **7**, **9**, **11** were obtained. Interestingly, as for other trimethoxybenzylpyroglutamic acids [16], the cyclization of acid **10** leads to a dimethoxyphenol (**11**) (Scheme 2).

Acids **12** and **15** possess an asymetric benzhydryl group and were obtained as a mixture of isomers [14]. This mixture was submitted to the same cyclization conditions as for **8** and **10**. A mixture of ketones was thus obtained, which was easily separated. In a similar case, we showed

Scheme 1

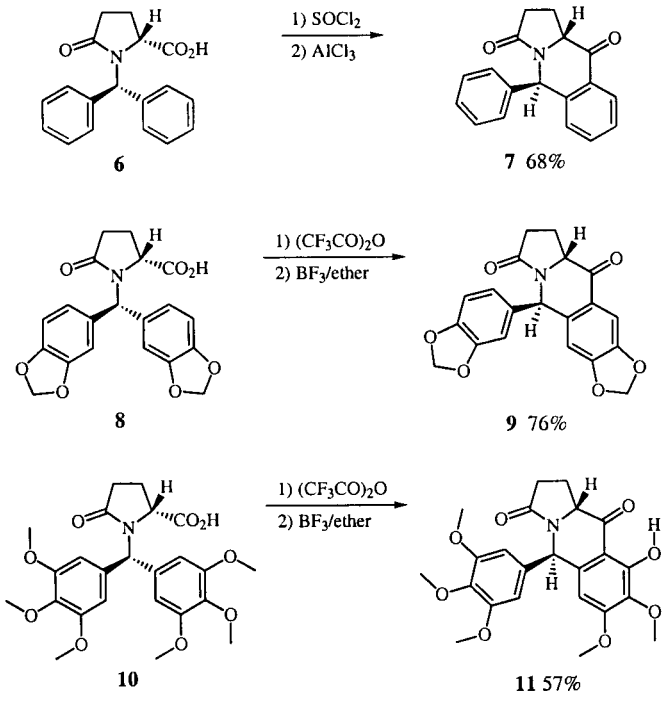


1 **2**



3 **4** **5**

Scheme 2



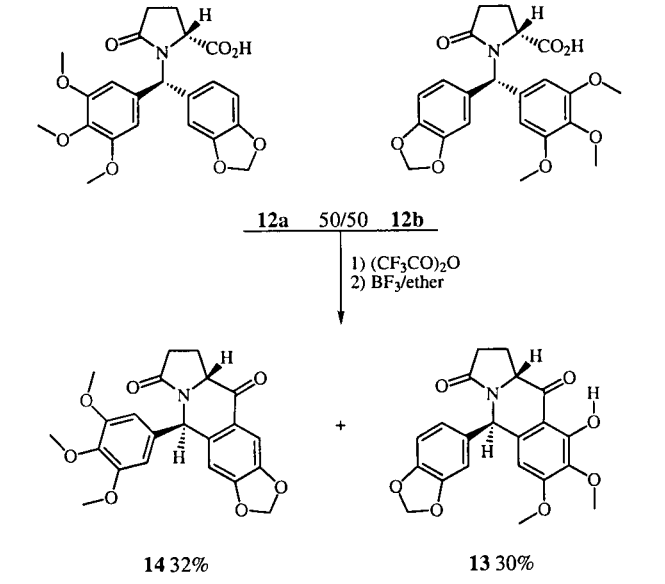
6 **7** 68%

8 **9** 76%

10 **11** 57%

that each isomer of such acids gave only one ketone [16]. In the same way as for ketone **11**, the cyclization of acid **12b** yields a dimethoxyphenol (**13**). This phenol is soluble in dilute sodium hydroxide, thus providing an easy purification of ketones **13** and **14** (Scheme 3).

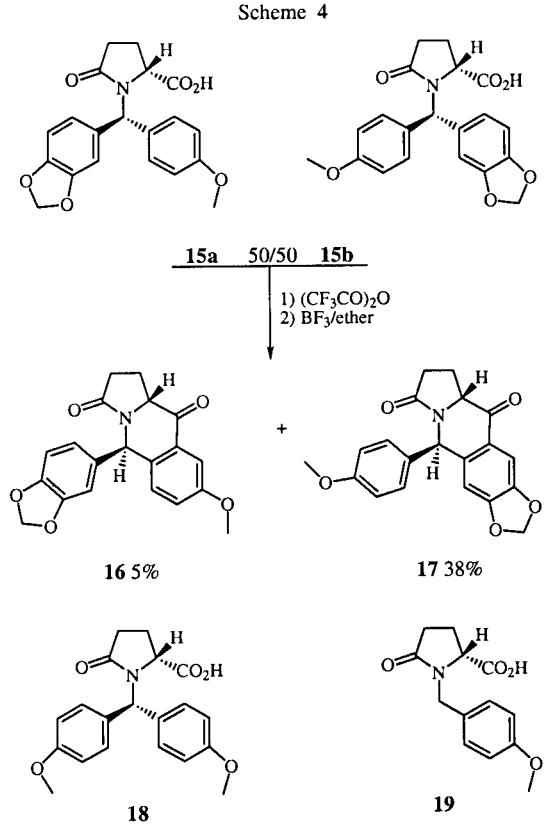
Scheme 3



14 32% **13** 30%

In these reactions, it was found to be very difficult to perform a cyclization on a *p*-methoxyphenyl group: a low yield in ketone **16** was obtained, and we were unsuccessful in cyclizing to acid **18**. Furthermore, in other work many difficulties were observed during the cyclization of acid **19** [17] (Scheme 4).

Scheme 4



16 5% **17** 38%

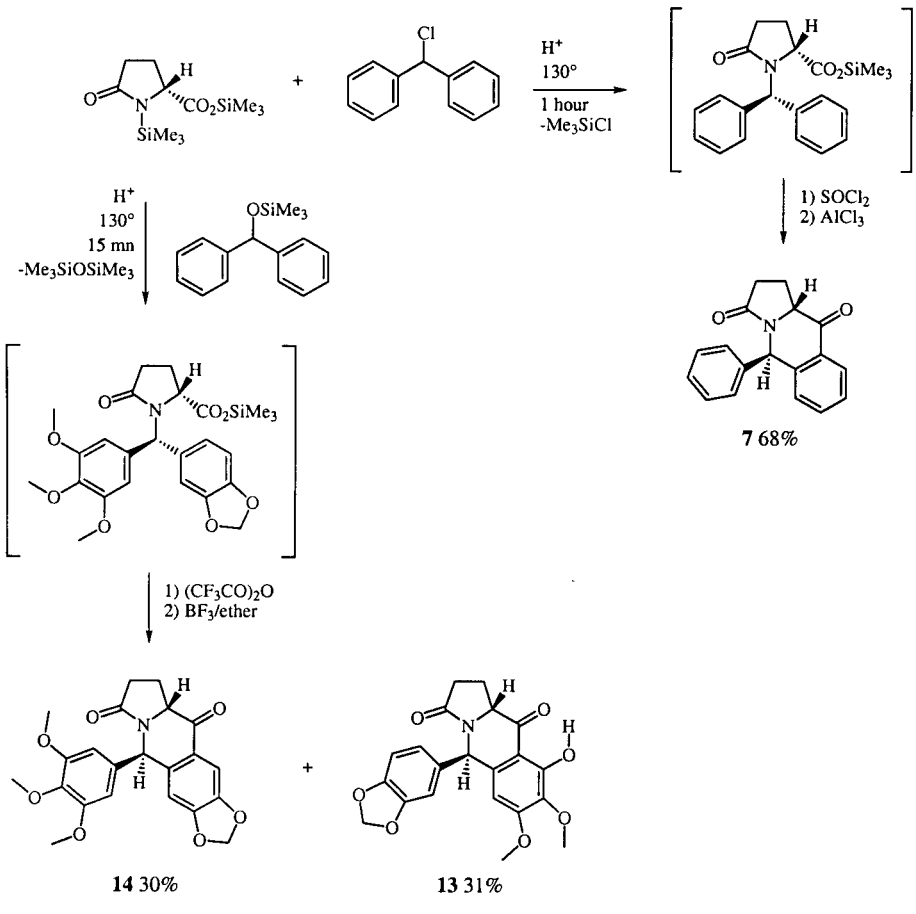
18 **19**

It is interesting to note that, as for other pyroglutamic derivatives [14c], the Friedel-Crafts cyclization can be performed without isolating the intermediate acid: indeed, starting from *N,O*-disilylpyroglutamic acid [23], the condensation with a benzhydryl chloride or a benzyhydryl trimethylsilyl ether [24] gives a trimethylsilyl ester [14a,b]. The one-pot reaction of this ester with an activating agent (thionyl chloride or trifluoroacetic anhydride) yields an acid chloride (or a mixed anhydride), whose cyclization gives the ketone (Scheme 5).

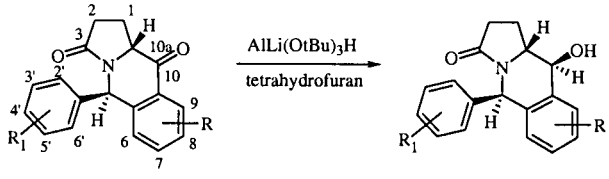
In the picropodophyllotoxin or azapodophyllotoxin series, lithium tri-*tert*-butoxyalumino hydride was used to obtain a compound with an hydroxy and a trimethoxyphenyl group in the *syn* position [14a,18]. By using this reagent, ketones **9, 13, 14, 16** and **17** were reduced to alcohols **5a-e** in excellent yields (Scheme 6). The similarity for the values of $J_{10\text{-}10a}$ between **5c** (9.3 Hz) and azapodophyllotoxin **20** (9.1 Hz) [11c] (Scheme 7) provided us the information that products **5** have the configuration of the biologically active compounds in the podophyllotoxin series.

In order to obtain a dimethoxyphenol similar to that found in etoposide **21a**, teniposide **21b** or azatoxin **22**, ketone **14** and alcohol **5c** were treated with hydrobromic

Scheme 5

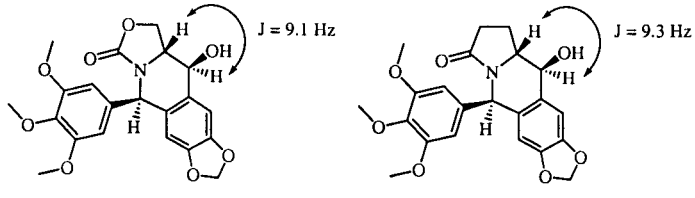


Scheme 6



9	R = 7,8-(OCH_2O)	R_1 = 3',4'-(OCH_2Ol)	**5a** 91%
13	R = 7,8-($OMe)_2$, 9-OH	R_1 = 3',4'-(OCH_2O)	**5b** 93%
14	R = 7,8-(OCH_2O)	R_1 = 3',4',5'-($OMe)_3$	**5c** 92%
16	R = 8-OMe	R_1 = 3',4'-(OCH_2O)	**5d** 89%
17	R = 7,8-(OCH_2O)	R_1 = 4'-OMe	**5e** 90%

Scheme 7

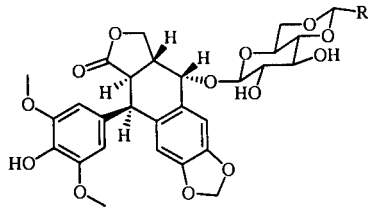


20 **5c**

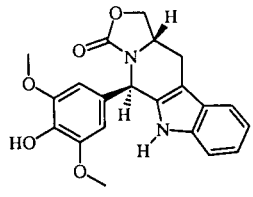
acid. Phenol **23** was thus obtained in 23% yield. A small amount of diphenol **24** was also seen in the nmr spectrum of the crude product **23**, and other ether cleaving reagents such as the mixture of sodium iodide and trimethylchlorosilane in acetonitrile yields either an inseparable mixture or the formation of a triphenol. The elemental analysis performed on the crude compound **25** confirmed that the hydroxy group had not been replaced by bromine (compound **26**). We were unsuccessful in purifying compounds **24** or **25** (Scheme 8). In fact, many methods [19] were attempted in order to obtain an activated product such as **26**, starting from alcohol **5c** or silyloxy ether **27** (Scheme 8), however we have never obtained these products. As for other unsucessful replacement of a hydroxy group by bromine, an intramolecular participation by the nitrogen atom can lead to a rapid decomposition of the halide as it is formed [20].

All products described in this paper as well as their acid or esters precursors [14a,b] were tested for inhibition of tubulin polymerization, following the protocol described in the literature [21]. The best inhibitor was the strict analog **5c** of the podophyllotoxin (IC_{50} = 5 μm). These ketones and alcohols were also screened for antitumor activity in the standard NCI tests [22], but none had interesting properties.

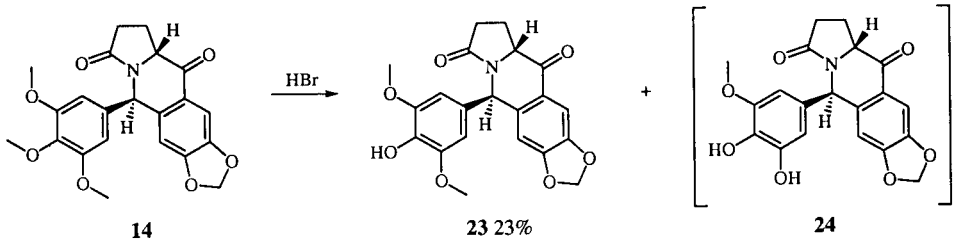
Scheme 8



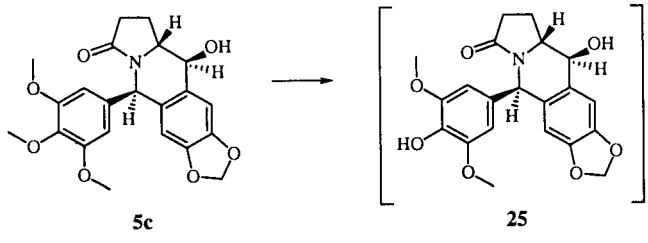
21a R = Me etoposide
21b R = thienyl teniposide



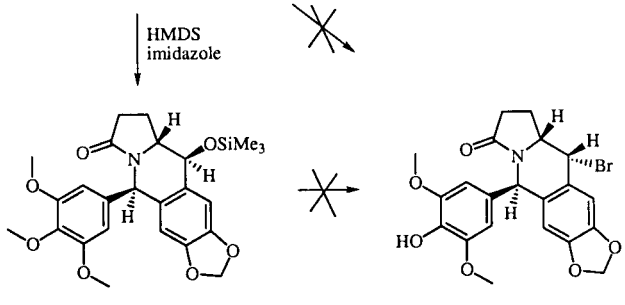
22 azatoxin



14 **23** 23% **24**



5c **25**



27 100% **26**

Table 1

Elemental Analysis of New Compounds, % Calcd./Found

No.	Formula	C	H	N	O
5a	$C_{20}H_{17}NO_6$	65.39	4.66	3.81	26.13
		65.30	4.51	3.98	26.04
5b	$C_{21}H_{21}NO_7$	63.15	5.30	3.51	28.04
		63.29	5.25	3.68	28.29
5c	$C_{22}H_{23}NO_7$	63.92	5.61	3.39	27.09
		63.72	5.69	3.41	27.24
5d	$C_{20}H_{19}NO_5$	67.98	5.42	3.96	22.64
		68.01	5.44	3.87	22.39
5e	$C_{20}H_{19}NO_5$	67.98	5.42	3.96	22.64
		67.96	5.72	3.80	22.84
7	$C_{18}H_{15}NO_2$	77.96	5.45	5.05	11.54
		77.65	5.48	4.71	11.90

Table 1 (continued)

No.	Formula	C	H	N	O
9	$C_{20}H_{15}NO_6$	65.75	4.14	3.83	26.28
		65.83	4.48	3.59	26.60
11	$C_{23}H_{25}NO_8$	62.30	5.68	3.16	28.86
		61.90	5.87	2.89	29.01
13	$C_{21}H_{19}NO_7$	63.47	4.82	3.52	28.18
		63.19	4.88	3.43	28.38
14	$C_{22}H_{21}NO_7$	64.23	5.15	3.40	27.22
		64.31	5.23	3.26	26.85
16	$C_{20}H_{17}NO_5$	68.37	4.88	3.99	22.77
		68.52	4.87	4.03	22.58
17	$C_{20}H_{17}NO_5$	68.37	4.88	3.99	22.77
		68.15	5.02	3.72	23.11
23	$C_{21}H_{19}NO_7$	63.47	4.82	3.52	28.18
		63.61	4.81	3.43	28.26

Table 2

^{13}C NMR Spectrum of Some of the Compounds

5c	(Deuteriochloroform): 21.6 (C_1), 29.5 (C_2), 55.2 (C_5), 56.2 ($C_{3'}$-O*Me*, $C_{5'}$-O*Me*), 56.6 (C_{10a}), 60.8 ($C_{4'}$-O*Me*), 71 (C_{10}), 101.2 (OCH_2O), 105.7 (C_9), 106 ($C_{2',6'}$), 107.6 (C_6), 127.3 (C_{9a}), 131.8 (C_7), 137.4 ($C_{1'}$), 147.2 (C_8), 147.5 (C_7), 153.3 ($C_{3'}$,$C_{5'}$), 172 (C_3)
9	(Deuteriochloroform): 20.9 (C_1), 30.3 (C_2), 54.1 (C_5), 58.2 (C_{10a}), 101.5 (C_7-OCH_2O-C_8), 102.4 ($C_{3'}$-OCH_2O-$C_{4'}$), 106.3 (C_9), 107.6 (C_{12}), 108.4 ($C_{2'}$), 108.9 ($C_{5'}$), 122 ($C_{6'}$), 132.6 (C_{5a}), 135.6 (C_{9a}), 138.8 ($C_{1'}$), 147.8 ($C_{3'}$), 148.5 (C_8,$C_{4'}$), 153.3 (C_7), 173.5 (C_3), 193.2 (C_{10}).
11	(Deuteriochloroform): 20.8 (C_1), 30.2 (C_2), 54.3 (C_{10a}), 56.4 (C_7-O*Me*), 56.5 ($C_{3'}$-O*Me*, C5'-O*Me*), 57.7 (C_8-O*Me*), 60.9 ($C_{4'}$-O*Me*), 70.0 (C_5), 103.9 (C_9), 105.5 ($C_{2'}$,$C_{6'}$), 110.8 (C_{9a}), 134.3, 135.8, 138.3 (C_{5a}, C_8, $C_{1'}$,$C_{4'}$), 153.7 ($C_{3'}$,$C_{5'}$) 157.2 (C_7 or C_9), 159.6 (C_7 or C_9), 173.3 (C_3, C_1), 199.8 (C_{10})
13	(Deuteriochloroform): (20.9 C_1), 30.2 (C_2), 53.8 (C_5), 56.4 (C_7-O*Me*), 57.4 (C_{10a}), 60.9 (C_8-O*Me*), 101.5 (-OCH_2O-), 103.3 (C_6), 108.7 ($C_{5'}$), 110.8 (C_{9a}), 159.5 (C_9) 173.2 (C_3), 199.8 (C_{10})
14	(Deuteriochloroform): 21.5 (C_1), 30.2 (C_2), 54.6 (C_5), 56.3 ($C_{3'}$-O*Me*, $C_{5'}$-O*Me*), 58.3 (C_{10a}), 60.9 ($C_{4'}$-O*Me*), 102.4 (-OCH_2O-), 105.8 ($C_{2'}$, $C_{6'}$), 106.2 (C_9), 107.7 (C_6), 125.6 (C_{9a}), 134.3 (C_{5a}), 138.3 ($C_{4'}$), 138.6 ($C_{1'}$), 148.5 (C_8), 153.3 (C_7), 153.7 ($C_{3'}$,$C_{5'}$), 173.5 (C_3), 193.2 (C_{10})
23	(Deuteriochloroform): 20.9 (C_1), 30.3 (C_2), 56.4 (C_5), 56.5 ($C_{3'}$-O*Me*, $C_{5'}$-O*Me*), 58.3 (C_{10a}), 102.4 (-OCH_2O-), 105.4 ($C_{2'}$, $C_{6'}$), 106.2 (C_9), 107.7 (C_6), 125.6 (C_{9a}), 129.8 ($C_{4'}$), 135.1 (C_{5a}), 138.8 ($C_{1'}$), 147.4 ($C_{3'}$,$C_{5'}$), 148.4 ($C_{8'}$), 153.3 (C_7), 173.5 (C_3), 193.3 (C_{10})

Table 3

Yield and Physical Properties of New Compounds

No.	Yield %	MP (solvent)	$[\alpha]_{20}^{D}$ (%, solvent)	IR (Potassium bromide) ν cm^{-1}	^{1}H NMR (solvent) δ ppm
5a	91	246 (ethyl acetate)		3220 (broad, OH), 1650, 1645 (C=O), 1620, 1505, 1485, 1145, (C=C), 1240 (C=O)	(Deuteriochloroform and dimethyl-d_6 sulfoxide): 1.98-2.43 (m, 4 H, $H_{1,2}$), 3.45-3.61 (m, 1 H, H_{10a}), 4.22 (dd, J = 9.2, 7.6 Hz, 1 H, H_{10}), 5.91 (s, 4 H, OCH_2O), 6.05 (s, 1 H_5), 6.45 (s, 1 H, H_6), 6.63-6.90 (m, 3 H, $H_{2',3',6'}$), 7.09 (s, 1 H, H_9)
5b	92	224 (ethyl acetate)		3340 (OH), 1650 (C=O), 1610, 1595, 1500, 1490, 1450 (C=C), 1235 (C-O)	(Deuteriochloroform and dimethyl-d_6 sulfoxide): 1.95-2.35 (m, 4 H, $H_{1,2}$), 3.56 (m, 1 H, H_{10a}), 3.65 (s, 3 H, OMe), 3.71 (s, 3 H, OMe), 4.68 (d, J = 9.2 Hz, 1 H, H_{10}), 5.94 (s, 1 H, H_5), 5.99 (s, 2 H, OCH_2O), 6.16 (s, 1 H, H_6), 6.63-6.82 (m, 3 H, $H_{2',3',6'}$)
5c	92	216-218 (ethyl acetate)		3400 (OH), 1680 (C=O), 1595, 1505, 1485, 1460 (C=C), 1240, 1130 (C-O)	(Deuteriochloroform and dimethyl-d_6 sulfoxide): 2.02-2.45 (m, 4 H, $H_{3,4}$), 3.21 (d, J = 7.7 Hz, 1 H, OH), 3.62-3.69 (m, 1 H, H_{10a}), 3.75 (s, 6 H, $C_{3'}$-OMe, $C_{5'}$-OMe), 3.80 (s, 3 H, $C_{4'}$-OMe), 4.40 (dd, J = 9.3, 7.7 Hz, 1 H, H_{10}), 5.91 (d, J = 1.3 Hz, 1 H, OCH_2O), 5.94 (d, J = 1.3 Hz, 1 H, OCH_2O), 6.04 (s, 1 H, H_5), 6.41 (s, 1 H, H_6), 6.48 (s, 2 H, $H_{2',5'}$), 7.12 (s, 1 H, H_9).
5e	90	231-232 (ethyl acetate)	24 (0.01, dichloromethane/ dimethyl sulfoxide 2/1)	3220 (OH), 1650 (C=O), 1610, 1590, 1505, 1485, 1445 (C=C), 1240 (C-O)	(Deuteriochloroform and dimethyl-d_6 sulfoxide): 2.14-2.41 (m, 4 H, $H_{1,2}$), 3.61-3.65 (m, 1 H, H_{10a}), 3.76 (s, 3 H, OMe), 4.30 (dd, J = 8.6, 7.2 Hz, 1 H, H_{10}), 5.87 (d, J = 7.2 Hz, OH) 5.92 (d, J = 1.2 Hz, 1 H, OCH_2O), 5.93 (d, J = 1.2 Hz, 1 H, OCH_2O), 5.99 (s, 1 H, H_5), 6.32 (s, 1 H, H_6), 6.80 (d, J = 8.6 Hz, 2 $H_{2',6'}$), 7.16 (s, 1 H, H_9), 7.18 (d, J = 8.6 Hz, 2 H, $H_{3',5'}$)
7	68	(oil)		1695, 1670 (C=O), 1600, 1500, 1450 (C=C)	(Deuteriochloroform): 2.25-2.63 (m, 4 H, $H_{1,2}$), 3.98-4.40 (m, 1 H, H_{10a}), 6.57 (s, 1 H, H_5), 6.94-7.78 (m, 8 H, ArH), 7.99-8.22 (m, 1 H, H_9)
9	76	182-184 (toluene)	35 (0.01, dichloromethane)	1680 (C=O), 1615, 1500, 1480, 1450 (C=C), 1250 (C-O)	(Deuteriochloroform): 2.24-2.44 (m, 4 H, $H_{1,2}$), 4.13-4.18 (m, 1 H, H_{10a}), 5.92 (s, 2 H, $C_{3'}$-OCH_2O -$C_{4'}$), 6.05 (s, 2 H, C_7-OCH_2O-C_8), 6.36 (s, 1 H, H_5), 6.56-6.70 (m, 4 H, ArH), 7.51 (s, 1 H, H_9)
11	57	57-59 (ethyl acetate)		3450 (broad OH), 1730, 1685 (C=O), 1585, 1500, 1450 (C=C), 1130 (C-O)	(Deuteriochloroform): 2.29-2.57 (m, 4 H, $H_{1,2}$), 3.77 (s, 6 H, C_3, OMe, $C_{5'}$, OMe), 3.81 (s, 3 H, $C_{4'}$, OMe), 3.90 (s, 3 H, C_8, OMe), 3.93 (s, 3 H, C_7, OMe), 4.25 (t, J = 7.2 Hz, H_{10a}), 6.37 (s, 3 H, $H_{6,2',6'}$), 6.42 (s, 1 H, H_5), 12.20 (s, 1 H, OH)
13	30	166 (ethyl acetate)		1700, 1635 (C=O), 1615, 1570, 1500, 1490, 1460 (C=C), 1235 (C-O)	(Deuteriochloroform): 2.24-2.45 (m, 4 H, $H_{1,2}$), 3.85 (s, 3 H, C_7 OMe), 3.86 (s, 3 H, C_8, OMe), 4.13-4.18 (m, 1 H, H_{10a}), 5.90 (s, 2 H, OCH_2O),

Table 3 (continued)

No.	Yield %	MP (solvent)	$[\alpha]_{20}^{D}$ (%, solvent)	IR (Potassium bromide) ν cm^{-1}	^{1}H NMR (solvent) δ ppm
				(C=C), 1235 (C-O)	4.13-4.18 (m, 1 H, H_{10a}), 5.90 (s, 2 H, OCH_2O), 6.31 (s, 1 H, H_5 or H_6), 6.34 (s, 1 H, H_5 or H_6), 6.53 (dd, J = 8, 1.7 Hz, 1 H, $H_{2'}$), 6.64 (d, J = 1.7 Hz, 1 H, $H_{6'}$), 6.67 (d, J = 8 Hz, 1 H, $H_{3'}$), 8.20 (s, 1 H, OH)
14	32	192-196 (toluene)		1695, 1675 (C=O), 1625, 1590, 1500, 1465 (C=C), 1240 (C-O)	(Deuteriochloroform): 2.25-2.46 (m, 4 H, $H_{1,2}$), 3.73 (s, 6 H, $C_{3'}$- OMe, $C_{5'}$-OMe), 3.80 (s, 3 H, $C_{4'}$-OMe), 4.18-4.23 (m, 1 H, H_{10a}), 6.05 (d, J = 1.1 Hz, 1 H, OCH_2O), 6.07 (d, J = 1.1 Hz, 1 H, OCH_2O), 6.37 (s, 2 H, $H_{2',6'}$), 6.38 (s, 1 H, H_5), 6.65 (s, 1 H, H_6), 7.53 (s, 1 H, H_9)
16	5	177 (toluene)		1690 (C=O), 1610, 1500, 1490 (C=C), 1250 (C-O)	(Deuteriochloform): 2.25-2.45 (m, 4 H, $H_{1,2}$), 3.85 (s, 3 H, OMe), 4.17-4.21 (m, 1 H, H_{10a}) 5.89 (s, 2 H, OCH_2O), 6.42 (s, 1 H, H_{10a}, 6.51-6.53 (m, 1 H, $H_{6'}$), 6.64-6.67 (m, 2 H, $H_{2',5'}$), 7.14 (s, 2 H, $H_{6,7}$) 7.55 (s, 1 H, H_9)
17	38	175 (toluene)		1700, 1685 (C=O), 1605, 1500, 1490 (C=C), 1250 (C-O)	(Deuteriochloroform): 2.24-2.46 (m, 4 H, $H_{1,2}$), 3.85 (s, 3 H, OMe), 4.18-4.20 (m, 1 H, H_{10a}), 6.05 (d, J = 1.2 Hz, 1 H, OCH_2O), 6.07 (d, J = 1.2 Hz, 1 H, OCH_2O), 6.37 (s, 1 H, H_5), 6.65 (s, 1 H, H_8), 6.80 (d, J = 8.6 Hz, 2 H, $H_{2',6'}$), 7.18 (d, J = 8.6 Hz, 2 H, $H_{3',5'}$), 7.53 (s, 1 H, H_9)
23	25	150-152 (methanol)		3200 (broad, OH), 1670 (C=O), 1605, 1500, 1460 (C=C), 1120 (C-0)	(Deuteriochloroform): 2.25-2.54 (m, 4 H, $H_{1,2}$), 3.79 (s, 6 H, OMe), 4.22 (m, 1 H, H_{10a}), 5.59 (s, 1 H, OH), 6.09 (s, 2 H, OCH_2O), 6.41 (s, 3 H, $H_{5,2',6'}$), 6.67 (s, 1 H, H_6), 7.53 (s, 1 H, H_9)
27	100	156-160			(Deuteriochloroform): 0.30 (s, 9 H, $OSiMe_3$), 1.95-2.50 (m, 4 H, $H_{1,2}$), 3.7-3.9 (m, 1 H, H_{10a}), 3.79 (s, 6 H, C3,-OMe), 3.83 (s, 3 H, C4, -OMe), 4.45 (d, J = 9.5 Hz, 1 H, H_{10}), 5.93 (d, J = 1.2 Hz, 1 H, OCH_2O), 5.96 (d, J = 1,2 Hz, 1 H, OCH_2O), 6.05 (s, 1 H, H_5), 6.40 (s, 1 H, H_6), 6.50 (s, 2 H, $H_{2',5'}$), 6.95 (s, 1 H, H_9)

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. The numbering used for the nmr descriptions are shown in Scheme 7. 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 from UCIB (Ivry-la-Bataille, France), which can provide this chemical in bulk quantities.

7,8-Methylenedioxy-5-(3',4',5'-trimethoxyphenyl)-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-3,10-dione (**14**) and 7,8-Dimethoxy-9-hydroxy-5-(3',4'-methylenedioxyphenyl)-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-3,10-dione (**13**).

Starting from the Mixture of Acids **12a,b.**

Trifluoroacetic anhydride (27.6 ml, 198 mmoles) was added to a stirred suspension of a 50/50 mixture of acids **12a,b** (77.5 g, 180 mmoles) in dichloroethane (1200 ml), under a nitrogen atmosphere. When the mixture became clear, boron trifluoride etherate (180 ml, 1440 mmoles) was added. The mixture was then refluxed for 7 hours. The solvents were evaporated and methylene dichloride and water were added. Washing the organic phases with 2*N* sodium hydroxide, followed by acidification yields phenol **13** as a crude oil which was crystallized from ethyl acetate. The organic layer obtained after the basic washes gives ketone **14** as a crude oil which was crystallized from toluene. Alternatively, these compounds can be purified by silica gel chromatography (ethyl acetate-heptane, 40/60).

One-pot Synthesis of Ketones **13** and **14** Starting From *N,O*-Bistrimethylsilylpyroglutamic Acid.

Under a nitrogen atmosphere, triflic acid (0.05 ml) was added *via* a syringe to a stirred mixture of *N,O*-bistrimethylsilylpyroglutamic acid [23] (2.6 g, 9.5 mmoles) and 3,4,5,4'-tetramethoxybenzhydrol [24] (9.4 mmoles). The mixture was heated to 130° and the hexamethyldisiloxane formed was distilled during about 15 minutes. Dichloroethane (100 ml), trifluoroacetic acid (1.5 ml, 12 mmoles), then boron trifluoride etherate (9.3 ml, 76 mmoles) were added. The mixture was refluxed for 7 hours. Products **13** (31%) and **14** (30%) were obtained as in the previous example.

One-pot Synthesis of 5-Phenyl-1,2,3,5,10,10a-hexahydrobenz-[f]indolizine-3,10-dione (**7**).

Under nitrogen atmosphere, triflic acid (0.05 ml) was added *via* a syringe to a stirred mixture of *N,O*-bistrimethylsilylpyroglutamic acid [23] (13.5 g, 49.4 mmoles) and benzhydryl chloride (10 g, 49.3 mmoles). The mixture was heated to 130° and the

chlorotrimethylsilane formed was distilled (about one hour). Dichloromethane (50 ml) and thionyl chloride (7 g, 5.1 ml, 59.1 mmoles) were added and the mixture was refluxed for seven hours. Volatile products were removed by distillation, methylene dichloride (50 ml) was added, then aluminum trichloride (20 g, 150 mmoles) in small portions at room temperature. The mixture was stirred for one night, then poured into ice cold water. The compound was extracted with dichloromethane and the organic phases were washed with water. The dried solution was refluxed with activated carbon for four hours. Evaporation gave a 75% yield of the crude compound. The oil obtained after silica gel chromatography (diethyl ether) was dissolved in diisopropyl ether (250 ml) and the solution was cooled to -40°. The white crystals obtained by filtration at low temperature and washed with heptane gave the oily pure compound (67%) at room temperature.

7,8-Methylenedioxy-5-(4'-methoxyphenyl)-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-3,10-dione (**17**).

Trifluoroacetic anhydride (26 ml, 184 mmoles) was added to a stirred suspension of a 50/50 mixture of acids **15a,b** (11.1 g, 30 mmoles) in dichloroethane (300 ml) under a nitrogen atmosphere. When the mixture became clear, boron trifluoride etherate (23 ml, 187 mmoles) was added. The mixture was then refluxed for 4 hours. The solvents were evaporated and methylene dichloride and water were added. The organic layer was washed with water, then dried, and the solvent was evaporated. Silica gel chromatography of the residue (ethyl acetate-heptane, 50/50) yields the ketones **16** and **17** which were crystallized from toluene.

7,8-Methylenedioxy-5-(3',4'-methylenedioxyphenyl)-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-3,10-dione (**9**).

Trifluoroacetic anhydride (40 ml, 283 mmoles) was added to a suspension of acid **8** (15 g, 39 mmoles) in dichloroethane (500 ml) under a nitrogen atmosphere. When the mixture became clear, boron trifluoride etherate (34 ml, 276 mmoles) was added. The mixture was then refluxed for 4 hours. The solvents were evaporated then methylene dichloride and water were added. The organic layer was washed with water, then dried and the solvent was evaporated, giving a crude oil which was crystallized from toluene, giving a white solid in 76% yield.

9-Hydroxy-7,8-dimethoxy-5-(3',4',5'-trimethoxyphenyl)-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-3,10-dione (**11**).

Trifluoracetic anhydride (0.6 ml, 4.4 mmoles) was added to a suspension of acid **10** (1.9 g, 4 mmoles) in dichloroethane (20 ml), under a nitrogen atmosphere. When the mixture became clear, boron trifluoride etherate (5 ml, 40 mmoles) was added. The mixture was then refluxed for 6 hours. The precipitate that had appeared in the course of the reaction was filtered, washed with cold water and dissolved in methylene dichloride. The organic layer was dried and the solvent was evaporated. The residue was purified by recrystallization in ethyl acetate, giving a white solid, yield 57%.

10-Hydroxy-8-methoxy-5-(3',4'-methylenedioxyphenyl)-1,2,3,5,10,10a-hexahydrobenz [*f*]indolizin-3-one (**5e**).

A solution of ketone **16** (1.1 g, 3.2 mmoles) in tetrahydrofuran (125 ml) was added dropwise to a suspension of lithium tri-*tert*-butoxyaluminohydride (3.1 g) in tetrahydrofuran (37 ml). The mixture was stirred at room temperature for 2 hours. Ammonium chloride (65 ml of a saturated aqueous solution), then citric acid (65 ml of a saturated aqueous solution) were added slowly. Methylene dichloride was added, the organic layer was dried and the solvents were evaporated, giving a crude oil which was crystallized from ethyl acetate, affording 89% yield in compound **5e**.

The other alcohols **5** were obtained following the same procedure.

7,8-Methylenedioxy-5-(4'-hydroxy-3',5'-dimethoxyphenyl)-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-3,10-dione (**23**).

Acetyl bromide (9.4 ml, 126.4 mmoles) was added slowly *via* a syringe to a solution of methyl alcohol (5.2 ml, 126.4 mmoles) cooled at -10°. A solution of ketone **14** (2.6 g, 6.32 mmoles) in methylene dichloride (30 ml) was slowly added. The mixture was stirred for two days at room temperature and washed with a saturated solution of sodium hydrogenocarbonate. The organic phases were dried and the solvent was evaporated, giving a crude oil which was crystallized in methyl alcohol, yield 25%.

10-Trimethylsilyloxy-7,8-methylenedioxy-5-(3',4',5'-trimethoxyphenyl)-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizin-3-one (**27**).

Chlorotrimethysilane (0.05 ml) was added *via* a syringe to a stirred suspension of alcohol **23** (2 g, 5 mmoles) and imidazole (0.050 g) in hexamethyldisilazane (5 ml). The mixture was refluxed for 2 hours under a nitrogen atmosphere. The precipitate obtained after cooling, was filtered, yielding 100% of the expected compound as a white solid, mp 156-160°.

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* Email: rigo@hei.fr

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