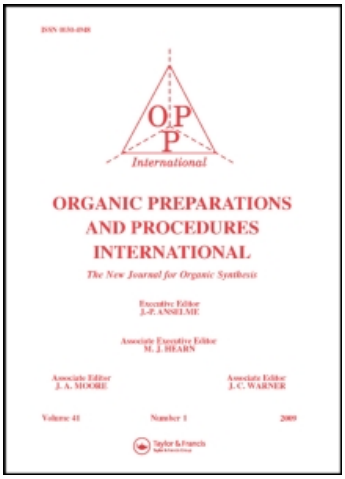
This article was downloaded by:
On: *27 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

PREPARATION OF TRIOLS AND ETHERS RELATED TO PODOPHYLLOTOXIN

M. A. Castro[a]; M. Gordaliza[a]; J. Miguel del Corral[a]; A. San Feliciano[a]
[a] Department of Organic Chemistry, Faculty of Pharmacy, University of Salamanca, Salamanca, Spain

To cite this Article Castro, M. A. , Gordaliza, M. , Corral, J. Miguel del and Feliciano, A. San(1994) 'PREPARATION OF TRIOLS AND ETHERS RELATED TO PODOPHYLLOTOXIN', Organic Preparations and Procedures International, 26: 5, 539 — 547
To link to this Article: DOI: 10.1080/00304949409458052
URL: http://dx.doi.org/10.1080/00304949409458052

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

ORGANIC PREPARATIONS AND PROCEDURES INT., 26 (5), 539-547 (1994)

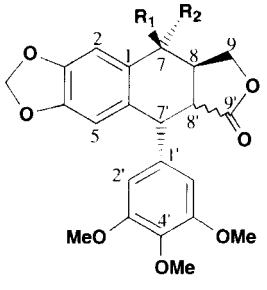
PREPARATION OF TRIOLS AND ETHERS RELATED TO PODOPHYLLOTOXIN

M. A. Castro*, M. Gordaliza, J. M. Miguel del Corral and A. San Feliciano

Department of Organic Chemistry, Faculty of Pharmacy
University of Salamanca, E-37007-Salamanca, SPAIN

Downloaded At: 08:59 27 January 2011

Most of the lignans identified in our phytochemical studies of the chemical composition of different species of the genus *Juniperus* (Fam. Cupressaceae),[1] are related to podophyllotoxin (**1**) which shows potent antiviral, antitumor and antimitotic properties.[2] It is easily obtained from podophyllum resin and can be used as a suitable starting material for the preparation of new bioactive cyclolignans.[3] Certain lignans isolated from the extracts of *Juniperus* and several intermediates used in the semi-synthesis of new structures display oxygenated functions at different positions of the cyclolignan skeleton. Reduction of one of these compounds, podophyllotoxone (**2**), with $NaBH_4$ produced a complex mixture of products: triols resulting from the reduction of ketone and lactone groups are the major products, along with compounds from the opening and reductive cleavage of the lactone ring.[4] The number of chiral carbon atoms in the triols, and hence the number of possible stereoisomers, is high. Where only one stereoisomer is available, precluding comparative analysis, assignment of the stereochemistry at every chiral centre by the simple interpretation of its ^1H NMR spectrum is difficult due to the crowding of the signals and the similarity of the coupling constants. This prompted us to address the synthesis of the complete series of triols resulting from the reduction



R_1	R_2	H-8'	Compound name	
H	OH	β	podophyllotoxin	**1**
=O		β	podophyllotoxone	**2**
OH	H	β	epipodophyllotoxin	**3**
H	OH	α	picropodophyllotoxin	**4**
OH	H	α	epipicropodophyllotoxin	**5**

i) PDC; ii) 1. PCl_3; 2. H_2O; iii) KOH, MeOH

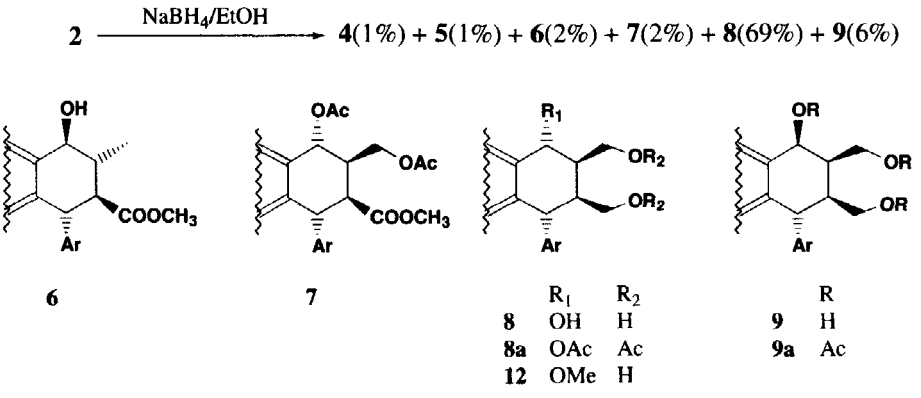
of podophyllotoxin (**1**) and its epimers at positions 7 and 8': epipodophyllotoxin (**3**), picropodophyllotoxin (**4**) and epipicropodophyllotoxin (**5**). The reduction of the four diastereomers was performed

© 1994 by Organic Preparations and Procedures Inc.

with $LiAlH_4$ (LAH) and led selectively to compounds not epimerized at any of the chiral centers. Although three of these triols were prepared previously,[5,6] no ^1H or ^{13}C NMR spectral data were reported. These data and those of acetylated and dehydrated derivatives are included in this work and can be used for the assignment of configuration at positions 7, 8 and 8' of the cyclolignan skeleton. Most of the compounds obtained have been assayed against several cells lines to determine their anti-neoplasic and antiviral properties.[7,8]

Podophyllotoxone (**2**) was obtained in 84% yield, by oxidation of podophyllotoxin (**1**) with pyridine dichromate in CH_2Cl_2. Reduction of **2** with $NaBH_4$ in ethanol led to a complex mixture of reaction products from which several substances were isolated and identified after treatment with diazomethane. Two of these, **4** and **5**, were products of epimerisation. Two of the remaining compounds were the hydroxy esters **6** and **7**, and the others were the triols **8** and **9**. Hydroxy ester **6**, which was used in the synthesis of junaphthoic acid,[4] displayed an unexpected configuration which was established on the basis of the coupling constants of protons H-7, H-7', H-8 and H-8'. It was concluded that, during borohydride reduction, epimerization occurred both at C-8 and C-8'. The relative configurations of **7** was also determined on the basis of the coupling constants of protons H-7, H-7' and H-8'.[9]

Downloaded At: 08:59 27 January 2011



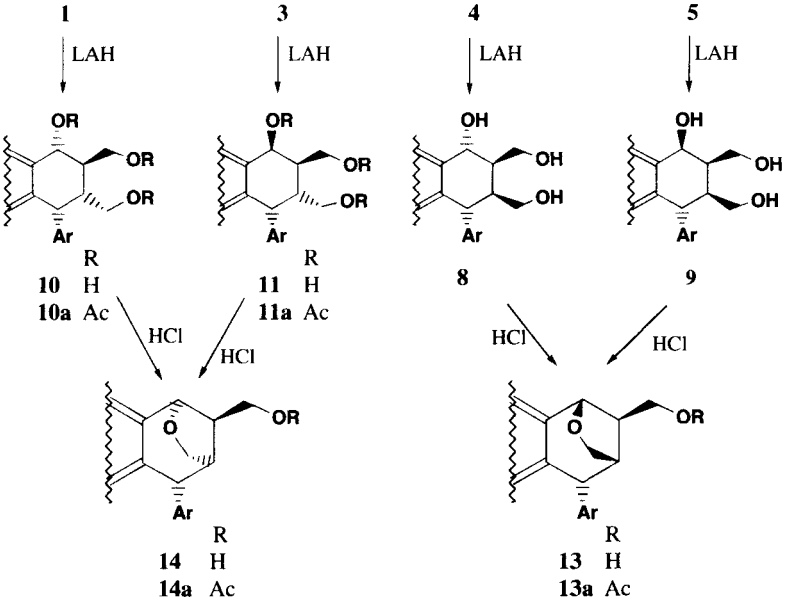
6 **7**

	R_1	R_2
8	OH	H
8a	OAc	Ac
12	OMe	H

	R
9	H
9a	Ac

The relative configurations of triols **8** and **9** was determined by spectral comparison with the reduction products obtained from podophyllotoxin (**1**) and its isomers **3**, **4** and **5** on treatment with LAH. These reactions led selectively to triols **10**, **11**, **8** and **9**, respectively, observing that the product of the reduction of picropodophyllotoxin (**4**), and its acetylated derivative **8a**, were identical to the major product obtained from the $NaBH_4$ reduction of podophyllotoxone (**2**); its physical properties being identical to those described in the literature for picropodophyllol.[6] Additionally, the triol arising from LAH reduction of epipicropodophyllotoxin (**5**) was identical to **9**, what was hitherto unreported. Attempts to crystallize picropodophyllol (**8**) in mixtures of solvents such as MeOH, $CHCl_3$ or CH_2Cl_2 led to its conversion into two substances identified as 7-*O*-methylpicropodophyllol (**12**)[10] and neoanhydropicropodophyllol (**13**).[6]

The formation of **13** can be explained in terms of an intramolecular dehydration affecting the alcoholic groups at positions 7 and 9', possibly motivated by the presence of traces of acid in the solvents used. As a confirmation, the triols **8**, **9**, **10**, and **11** were refluxed in chloroform solution, acidified with a few drops of 2N HCl. Dehydration occurred in all of the cases, giving rise to 7,9'-tetrahydrofuran derivatives (**13** and **14**) with the oxygen bridge in the α or ß orientation depending on the configuration at 8' of the starting triol.



Thus, triols **8** and **9** led to hydroxy ether **13**, and triols **10** and **11** to **14**, whose physical properties were identical to those reported for a compound named anhydropodophyllol by Ayres and Pauwels[6] and more recently called neoanhydropodophyllol by Gensler *et al.*,[11] the latter name is used in the present work. The configuration inversion at C-7 in the cases of triols **8** and **11** was not surprising due to the benzylic character of that position of the molecule. However, it should be noted that NMR spectral data observed for **14** coincide with those reported by our group for a substance isolated from *J. thurifera* and incorrectly identified at the time as the triol podophyllol (**10**).[1d] The previously reported compound was therefore the dehydrated product **14**, probably formed during the work up of the extract.

In view of the complexity of the signals in the ^{1}H NMR spectra of the triols, the corresponding triacetates **8a**, **9a**, **10a** and **11a** were prepared and several two-dimensional NMR experiments (HMQC, COSY and ROESY) performed with **8a** and **11a,** in order to assign unequivocally all the signals in their ^{1}H and ^{13}C NMR spectra.

Downloaded At: 08:59 27 January 2011

TABLE 1. ^{1}H NMR Data for Compounds 7-14a.

H	7	8	8a	9	9a	10	10a
2	6.82, *s*	6.82, *s*	6.82, *s*	7.02, *s*	6.85, *s*	7.08, *s*	6.73, *s*
5	6.36, *s*	6.31, *s*	6.29, *s*	6.36, *s*	6.40, *s*	7.39, *s*	6.45, *s*
7	5.99, *d* (3.5)	4.66, *d* (5.8)	6.00, *d* (3.4)	5.00, *d* (4.3)	6.20, *d* (4.6)	4.81, *d* (7.6)	6.17, *d* (7.8)
8	2.78, *m*	2.38, *m*	2.61, *m*	2.42, *m*	2.40, *m*	2.15, *m*	2.45, *m*
9	4.24, *dd* (11.5;5.9) 3.80, *m*	3.4-3.9, *m*	4.31,*dd* (11.4;5.3) 3.79, *m*	3.6-4.0, *m*	4.30,*dd* (11.0;6.7) 3.75, *m*	3.5-4.1, *m*	4.22,*dd* (11.3;4.6) 3.80, *m*
2', 6'	6.39, *s*	6.33, *s*	6.32, *s*	6.20, *m*	6.16, *s*	6.36, *s*	6.32, *s*
7'	4.31, *d* (10.1)	3.87, *d* (8.2)	3.62, *d* (10.6)	3.6-4.0, *m*	4.08, *d* (7.6)	4.12, *d* (4.1)	4.17, *d* (4.0)
8'	3.42,*dd* (10.5;4.0)	2.28, *m*	2.80, *m*	2.19, *m*	2.69,*m*	2.15, *m*	2.45, *m*
9'		3.4-3.9, *m*	4.14,*dd* (11.3;8.7) 3.98,*dd* (11.3;5.2)	3.6-4.0, *m*	4.35,*dd* (11.2;8.2) 3.97,*dd* (11.2;5.7)	3.5-4.1, *m*	4.03,*dd* (12.0;3.5) 4.14,*dd* (11.0;3.0)
MeO-3',5'	3.80, *s*	3.74, *s*	3.80, *s*	3.77, *s*	3.80, *s*	3.78, *s*	3.73, *s*
MeO-4'	3.83, *s*	3.81, *s*	3.83, *s*	3.83, *s*	3.83, *s*	3.82, *s*	3.79, *s*
O-CH_2-O	5.90, *s*	5.86, *s*	5.90, *s*	5.91, *s* 5.92, *s*	5.95, *s* 5.93, *s*	5.91, *s*	5.92, *s* 5.91, *s*
-OAc	2.12, *s* 2.02, *s*		2.11, *s* 2.03, *s* 2.00, *s*		2.13, *s* 2.09, *s* 2.01, *s*		2.03, *s* 2.03, *s* 2.00, *s*
COOMe	3.65, *s*						

H	11	11a	13	13a	14	14a
2	6.61, *s*	6.94, *s*	6.68, *s*	6.73, *s*	6.63, *s*	6.64, *s*
5	6.35, *s*	6.38, *s*	6.48, *s*	6.50, *s*	6.56, *s*	6.58, *s*
7	4.86, *d* (2.9)	6.26, *d* (3.1)	4.77, *s*	4.70, *s*	4.66, *d* (4.8)	4.69, *d* (4.8)
8	2.58, *m*	2.62, *m*	2.50, *m*	2.48, *m*	2.74, *m*	2.60, *m*
9	3.3-4.0, *m*	4.09,*dd* (11.4;4.8) 3.76, *m*	3.41,*dd* (10.6;5.8) 3.54,*dd* (10.5;8.8)	3.89,*dd* (11.1;6.2) 4.01,*dd* (11.3;9.3)	3.6-3.9, *m*	4.33,*dd* (11.2;6,5) 3.98,*dd* (11.4;8.4)
2', 6'	6.14, *s*	6.12, *s*	6.22, *s*	6.21, *s*	6.36, *s*	6.35, *s*
7'	4.14, *d* (5.3)	4.26, *d* (5.2)	4.09, *d* (1.8)	4.11, *d* (2.5)	4.38, *d* (3.9)	4.38, *d* (2.8)
8'	2.00, *m*	2.70, *m*	2.50, *m*	2.60,*dd*(9.3;6.4)	2.64, *m*	2.79, *m*
9'	3.3-4.0, *m*	4.18,*dd* (11.0;9.3) 4.02,*dd* (11.0;5.5)	4.02,*dd* (8.8;5.9) 3.70, *m*	3.75,*dd* (9.9;8.8) 4.10,*dd* (8.7;6.2)	3.6-3.9, *m*	3.95, *d* (8.8) 3.72,*dd* (9.3)
MeO-3',5'	3.72, *s*	3.73, *s*	3.76, *s*	3.78, *s*	3.79, *s*	3.80, *s*
MeO-4'	3.78, *s*	3.79, *s*	3.82, *s*	3.84, *s*	3.84, *s*	3.85, *s*
O-CH_2-O	5.89, *s* 5.88, *s*	5.92, *s* 5.91, *s*	5.94, *d* (1.2) 5.88, *d* (1.3)	5.96, *d* (1.1) 5.90, *d* (1.2)	5.92, *s* 5.90, *s*	5.94, *s* 5.91, *s*
-OAc	2.03, *s* 2.03, *s* 2.00, *s*	2.03, *s* 2.03, *s* 2.00, *s*	2.03, *s* 2.03, *s* 2.00, *s*	2.00, *s*		2.09, *s*

Downloaded At: 08:59 27 January 2011

TABLE 2. ^{13}C NMR Data for Lignans 7-14a.

C	7	8	8a	9[a]	9a	10[a]	10a	11	11a	13	13a	14	14a
1	124.8	130.6	125.6	130.6	127.7	132.4	127.9	131.1	127.7	129.4	129.0	130.0	129.6
2	109.8	109.7	110.3	108.9	110.0	107.4	107.5	108.5	109.4	110.9	110.8	110.0	110.0
3	148.6	147.6	148.8	146.0	148.2	145.8	147.9	147.9	148.8	147.6	147.8	147.7	147.9
4	146.7	146.6	147.0	145.5	147.2	145.8	147.3	146.8	147.3	146.4	146.5	146.3	146.5
5	109.5	108.4	109.8	107.3	107.9	108.0	108.9	109.5	109.8	107.7	107.7	108.1	108.1
6	132.9	132.0	133.6	133.4	130.4	134.2	132.9	132.8	133.5	133.9	133.9	132.3	131.7
7	70.6	69.8	71.1	67.9	68.8	68.3	71.4	72.5	68.2	78.1	78.0	77.7	77.9
8	39.8	43.3	38.7	40.8	35.6	41.1	38.2	38.2	35.9	44.1	41.1	47.5	43.5
9	61.8	61.9	62.0	58.9	62.0	59.0	62.0	63.4	62.9	62.3	63.8	60.2	62.1
1'	140.2	140.8	140.0	142.1	140.0	137.5	135.9	137.3	136.7	140.4	140.0	139.0	138.6
2'	106.8	106.6	106.4	106.3	106.2	108.3	107.5	107.5	107.7	106.4	106.5	107.0	107.0
3'	153.3	153.2	153.8	152.5	153.4	151.8	153.0	152.8	153.3	153.1	153.2	153.3	153.3
4'	137.3	136.8	137.4	135.9	137.2	135.7	137.2	137.0	137.5	136.9	137.3	137.0	137.2
5'	153.3	153.2	153.8	152.5	153.4	151.8	153.0	152.8	153.3	153.1	153.2	153.3	153.3
6'	106.8	106.6	106.4	106.3	106.2	108.3	107.5	107.5	107.7	106.4	106.5	107.0	107.0
7'	44.0	45.6	46.2	45.5	47.0	45.3	47.0	47.8	47.5	45.0	45.2	43.0	44.7
8'	46.4	44.5	39.0	45.2	42.0	41.1	36.9	36.4	35.2	53.6	53.5	48.2	47.5
9'	173.0	63.0	64.7	60.7	64.6	60.4	64.0	63.7	64.2	71.0	70.7	69.0	68.7
MeO-3',5'	56.2	56.3	56.6	55.8	56.3	55.8	56.1	56.3	56.6	56.2	56.3	56.4	56.4
MeO-4'	60.8	60.9	61.3	59.8	60.9	59.8	60.8	60.8	61.2	60.7	60.7	60.9	60.8
O-CH_2-O	101.3	101.0	101.6	100.4	101.3	100.4	101.2	101.1	101.6	101.0	101.0	101.1	101.1
OAc	170.5		171.2		170.8		171.2		171.2		170.7		170.9
	170.0		170.6				170.9		171.0				
	21.4		21.9		21.2		170.5		170.9		20.7		20.9
	20.7		21.3		20.9		21.3		21.6				
							20.8		21.3				
COOMe	51.9												

a) Spectra obtained in DMSO-d_6

EXPERIMENTAL SECTION

Melting points were determined by heating in an external silicone bath and were uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter in chloroform solution and UV spectra on a Hitachi 100-60 spectrophotometer in ethanol solution. IR spectra were determined on a Beckmann (Acculab VIII) spectrophotometer in chloroform solution. EIMS were runned in a VG-TS-250 spectrometer working at 70 eV. NMR spectra were recorded at 200 MHz for ^1H and 50.3 for ^{13}C in deuterochloroform using TMS as internal reference, on a Bruker WP 200 SY. Chemical shift values are expressed in ppm followed by *multiplicity* and coupling constants (J) in Hz. Flash chromatography was performed on silica gel (Merck No 9385). Analysis was carried out on a Perkin-Elmer 2400 CHN, Elemental Analyzer.

Preparation of Podophyllotoxin Analogs

Podophyllotoxone (**2**).- To a solution of 2.4 g of **1** in 50 mL of dry CH_2Cl_2, were added 3.2 g of pyridine dichromate (PDC). The mixture was kept at room temperature for 3 hrs and the solid was

Downloaded At: 08:59 27 January 2011

collected. Chromatography of the filtrate on SiO_2 yielded 2 g (84%) of **2**[4] by elution with CH_2Cl_2/AcOEt (1:1).

Epipodophyllotoxin (**3**) was obtained in 90% yield by the reaction of **1** with PCl_3 and H_2O according to a reported procedure.[12]

Picropodophyllotoxin (**4**) and *epipicropodophyllotoxin* (**5**) were obtained from **1** and **3**, in 90% and 85% yield respectively, by treatment with 5% KOH/MeOH at room temperature over 1 hr. The reaction mixture was acidified to pH 2 with 2N HCl; the methanol was evaporated and the corresponding "picro-derivative" was extracted with EtOAc.

Reduction of 2 with $NaBH_4$.- A solution of 4 g of $NaBH_4$ in 35 mL of absolute EtOH at 0° was added to 2 g of **2** in 40 mL of EtOH at 35°. The mixture was kept at room temperature for 7 hrs and then poured onto ice: 30% AcOH was added dropwise until no more gas evolved. After extraction with EtOAc and washing with sat. $NaHCO_3$, 1.64 g of a neutral fraction and 350 mg of an acid part were obtained. Crystallization of the neutral part from hexane/CH_2Cl_2 afforded 900 mg of a mixture of **8** (69%) and **9** (6%). They were separated by flash chromatography (Cl_2CH_2/EtOAc 7:3).

Picropodophyllol **8**: mp. 165-170° (CH_2Cl_2/hexane); $[\alpha]^{22}$ (λ, nm): -60.6° (589), -64.7° (578), -74.0° (546), -127.8° (436), -194.9° (365) (c 0.8%, MeOH); UV λ_{max} nm (ε): 215 (22500), 292 (3200); IR (ν_{max}, cm^{-1}): 3600, 3400, 1600, 1510, 1490, 1470, 1430, 1335, 1220, 1130, 1040, 1010, 940, 910 cm^{-1}; MS *m/z* (rel. abond. %): 418 (12) $[M]^+$, 400 (100) $[M-H_2O]^+$, 369 (8) $[M-(H_2O+OCH_3)]^+$, 351 (6) $[M-(2H_2O+OCH_3)]^+$, 339 (34) $[M-(H_2O+OCH_3+OCH_2)]^+$, 324 (9), 307 (10), 224 (9), 201 (11), 181 (14), 173 (18), 153 (11), 115 (15). ^1H NMR: table 1; ^{13}C NMR: table 2.

Anal. Calcd. for $C_{22}H_{26}O_8$: C, 63.15; H, 6.22. Found: C, 63.54; H, 6.02

Triacetate **8a**: $[\alpha]^{22}$ (λ, nm): -28.8° (589), -30.7° (578), -34.8° (546), -59.2° (436), -92.6° (365) (c 0.9%, $CHCl_3$); UV λ_{max} (ε): 206 (21300), 293 (1400); IR: 1740, 1600, 1510, 1490, 1470, 1430, 1375, 1340, 1210, 1135, 1050, 950; ^1H NMR: table 1; ^{13}C NMR: table 2.

Epipicropodophyllol **9**: mp. 196-198° ($CHCl_3$); $[\alpha]^{22}$ (λ, nm): -22.7° (589), -23.8° (578), -27.0° (546), -45.5° (436), -66.1° (365) (c 0.7%, $CHCl_3$); UV λ_{max} (ε): 224 (10600), 292 (3500); IR: 3620, 3400, 1600, 1510, 1490, 1470, 1425, 1335, 1240, 1135, 1050, 1010, 945 cm^{-1}; MS *m/z* (rel. abond. %): 418 (8) $[M]^+$, 400 (100) $[M-H_2O]^+$, 369 (6) $[M-(H_2O+OCH_3)]^+$, 351 (9) $[M-(2H_2O+OCH_3)]^+$, 339 (50) $[M-(H_2O+OCH_3+OCH_2)]^+$, 324 (12), 308 (13), 282 (5), 201 (8), 173 (11), 153 (8), 115 (11). ^1H NMR: table 1; ^{13}C NMR: table 2.

Anal. Calcd. for $C_{22}H_{26}O_8$: C, 63.15; H, 6.22. Found: C, 63.34; H, 6.03

Triacetate **9a**: $[\alpha]^{22}$ (λ, nm): -61.5° (589), -64.1° (578), -73.6° (546), -132.9° (436), (c 0.8%, $CHCl_3$); UV λ_{max} (ε): 212 (31800), 290 (3000); IR: 1735, 1590, 1500, 1480, 1460, 1420, 1370, 1330, 1230, 1130, 1040, 940, 875 cm^{-1}; ^1H NMR: table 1; ^{13}C NMR: table 2.

After several attempts of crystallization in CH_2Cl_2, MeOH, etc, the mother liquours of the above fractionation were flash-chromatographed yielding:

-Neoanhydropicropodophyllol **13** (130 mg): eluted with CH_2Cl_2/EtOAc (2:8). $[\alpha]^{22}$ (λ, nm): +76.7°

Downloaded At: 08:59 27 January 2011

(589), +80.2° (578), +93.1° (546), +175.5° (436), +327.6° (365) (c 0.8%, $CHCl_3$); UV λ_{max} (ε): 212 (20000), 292 (2200); IR: 3620, 1600, 1510, 1480, 1465, 1420, 1380, 1335, 1200, 1130, 1040, 1010, 945, 875 cm^{-1}; MS *m/z* (rel. abond. %): 400 (100) $[M]^+$, 351 (9) $[M-(H_2O+OCH_3)]^+$, 339 (29) $[M-(OCH_3+OCH_2)]^+$, 324 (8), 308 (9), 207 (7), 181 (14), 173 (17), 153 (8), 115 (11). ^1H NMR: table 1; ^{13}C NMR: table 2.

Anal. Calcd. for $C_{22}H_{24}O_7$: C, 66.00; H, 6.00. Found: C, 65.61; H, 6.23

Acetate **13a**: $[\alpha]^{22}$ (λ nm): +58.4° (589), +61.4° (578), +70.9° (546), +133.4° (436) (c 1.3%, $CHCl_3$); UV λ_{max} (ε): 213 (19100), 292 (2600); IR: 1740, 1600, 1510, 1490, 1425, 1380, 1335, 1200, 1130, 1045, 1010, 935, 875 cm^{-1}; ^1H NMR: table 1; ^{13}C NMR: table 2.

- 7-*O*-methylpicropodophyllol **12** (250 mg): eluted with CH_2Cl_2/MeOH (96:4).[10]

- 150 mg of mixture of **8** and **9**.

The acid fraction, once esterified with diazomethane was chromatographed on silica gel, to yield four fractions:

a) 40 mg of hydroxyester **6,** eluted with CH_2Cl_2/EtOAc (8:2)[4]

b) 50 mg of mixture of **4** and **5,** eluted with CH_2Cl_2/EtOAc (1:1)

c) 140 mg of mixture of **8** and **9**, eluted with CH_2Cl_2/MeOH (1:1)

d) 130 mg of a complex mixture eluted with CH_2Cl_2/MeOH (1:1).

Acetylation of fraction d) afforded 50 mg of **13** and 60 mg of *methyl picropodophyllate diacetate* (**7**) by preparative TLC (CH_2Cl_2/AcOEt 6:4): $[\alpha]^{22}$ (λ, nm): -39.6° (589), -41.6° (578), -47.7° (546), -82.8° (436), -129.7° (365) (c 1%, $CHCl_3$); UV λ_{max} (ε): 210 (54800), 214 (13700), 291 (5300); IR: 1740, 1600, 1510, 1490, 1470, 1425, 1370, 1335, 1240, 1130, 1040, 965, 940, 875 cm^{-1}; ^1H NMR: table 1; ^{13}C NMR: table 2.

Downloaded At: 08:59 27 January 2011

Reduction of Lactonic Lignans with $LiAlH_4$

Podophyllol **10**.- A suspension of 83 mg of **1** in dry ether was added to a suspension of 100 mg of LAH, in the same solvent. This was stirred at room temperature under argon for 4 hrs. The excess of hydride was decomposed with wet EtOAc. After drying over Na_2SO_4 and evaporation of the solvent, the organic phase gave 35 mg of triol **10**, wich was purified by crystallization in EtOAc to yield 33 mg of pure triol; mp. 186-188° EtOAc); $[\alpha]^{22}$ (λ, nm): -168.8° (589), -170.0° (578), -204.7° (546), -374.9° (436), -664.5° (365) (c 0.5%, MeOH); UV λ_{max} (ε): 218 (22200), 292 (4700); IR: 3620, 3400, 1600, 1510, 1490, 1470, 1425, 1330, 1240, 1135, 1050, 1010, 945, 880 cm^{-1}; MS *m/z* (rel. abond. %): 418 (31) $[M]^+$, 400 (69) $[M-H_2O]^+$, 382 (41) $[M-2H_2O]^+$, 369 (12) $[M-(H_2O+OCH_3)]^+$, 351 (11) $[M-(2H_2O+OCH_3)]^+$, 339 (43) $[M-(H_2O+OCH_3+OCH_2)]^+$, 327 (18), 321 (17) $[M-(2H_2O+OCH_3+OCH_2)]^+$, 308 (15), 282 (13), 247 (10), 198 (100), 173 (69), 149 (32), 115 (31). ^1H NMR: table 1; ^{13}C NMR: table 2.

Anal. Calcd. for $C_{22}H_{26}O_8$: C, 63.15; H, 6.22. Found: C, 62.84; H, 6.03

Triacetate **10a**: $[\alpha]^{22}$ (λ nm): -70.5° (589), -75.0° (578), -86.1° (546), -156.1° (436) (c 0.6%, $CHCl_3$); UV λ_{max} (ε): 214 (43600), 290 (5300); IR: 1740, 1600, 1500, 1485, 1465, 1420, 1370, 1240, 1130,

1040, 940 cm^{-1}; ^1H NMR: table 1; ^{13}C NMR: table 2.

Proceeding in the same way, the following compounds were obtained:

- 350 mg (69.5 %) of *epipodophyllol* **11** from 500 mg of **3**. $[\alpha]^{22}$ (λ, nm): -109.3° (589), -115.5° (578), -133.0° (546), -246.1° (436), -451.2° (365) (c 1%, $CHCl_3$); UV λ_{max} (ε): 212 (48200), 290 (3400); IR: 3610, 3400, 1600, 1500, 1485, 1470, 1425, 1330, 1230, 1135, 1050, 1010, 945, 875 cm^{-1}; MS *m/z*: (rel. abond. %): 418 (7) $[M]^+$, 400 (100) $[M-H_2O]^+$, 382 (9) $[M-2H_2O]^+$, 369 (5) $[M-(H_2O+OCH_3)]^+$, 351 (6) $[M-(2H_2O+OCH_3)]^+$, 339 (37) $[M-(H_2O+OCH_3+OCH_2)]^+$, 327 (9), 324 (8) $[M-(2H_2O+OCH_3+OCH_2)]^+$, 308 (7), 198 (43), 173 (43), 153 (8), 115 (22). ^1H NMR: table 1; ^{13}C NMR: table 2.

Anal. Calcd. for $C_{22}H_{26}O_8$: C, 63.15; H, 6.22. Found: C, 63.29; H, 6.22

Triacetate **11a**: $[\alpha]^{22}$ (λ, nm): -168.0° (589), -176.9° (578), -203.2° (546), -369.9° (436), -655.9° (365) (c 0.8%, $CHCl_3$); UV λ_{max} (ε): 223 (20700), 292 (4100); IR: 1740, 1590, 1500, 1485, 1465, 1420, 1370, 1335, 1200, 1130, 1040, 950 cm^{-1}; ^1H NMR: table 1; ^{13}C NMR: table 2.

-165 mg of **5** yielded 87 mg (53 %) of *epipicropodophyllol* **9** after crystallization from $CHCl_3$/EtOAc

-25 mg (80 %) of *picropodophyllol* **8** were obtained from 31 mg of **3**.

Dehydration of Triols 8, 9, 10 and 11.

A few drops of 2N HCl were added to a solution of each triol in $CHCl_3$ and heated under reflux for 1 h. After washing with water, drying over Na_2SO_4 and evaporation of the solvent, the organic phase gave the dehydrated product in quantitatively yield.

Triols **8** and **9** led to **13** in 88% and 83% respectively. Triols **10** and **11** led to *neoanhydropodophyllol* **14** in 90% and 84% respectively: mp. 248-256° (MeOH); $[\alpha]^{22}$(λ, nm): 0°; UV λ_{max} (ε): 220 (32000), 292 (5900); IR: 3630, 1600, 1510, 1490, 1470, 1425, 1375, 1335, 1240, 1135, 1050, 1010, 950, 880 cm^{-1}; MS *m/z*: (rel. abond. %): 400 (60) $[M]^+$, 351 (6) $[M-(H_2O+OCH_3)]^+$, 339 (14) $[M-(OCH_3+OCH_2)]^+$, 324 (6), 308 (7), 282 (5), 198 (64), 173 (60), 153 (10), 115 (18), 84 (100). ^1H NMR: table 1; ^{13}C NMR: table 2.

Anal. Calcd. for $C_{22}H_{24}O_7$: C, 66.00; H, 6.00. Found: C, 65.73; H, 5.91

Acetate **14a**: $[\alpha]^{22}$ (λ, nm): 0°; UV λ_{max} (ε): 216 (32200), 292 (4300); IR: 1740, 1600, 1505, 1485, 1465, 1420, 1375, 1335, 1240, 1130, 1045, 1010, 940, 880 cm^{-1}; ^1H NMR: table 1; ^{13}C NMR: table 2.

Acknowledgements.- The authors thank Prof. V. S. Martín, University of La Laguna, Tenerife, Spain, for the 2D NMR experiments and Dr. B. Macías, University of Salamanca, for the elemental analyses. Financial support came from the Spanish DGICYT (project No. 89/394).

REFERENCES

1. a) A. San Feliciano, J. M. Miguel del Corral, M. Gordaliza and M. A. Castro, *Phytochemistry*, **28**, 659 (1989); b) A. San Feliciano, J. M. Miguel del Corral, M. Gordaliza and M. A. Castro, *ibid.*, **29**, 1135 (1990); c) A. San Feliciano, J. M. Miguel del Corral, M. Gordaliza and M. A. Castro, *ibid.*, **30**, 3483 (1991); d) A. San Feliciano, J. M. Miguel del Corral, J. L. López and B. de Pascual-Teresa, *ibid.*, **31**, 267 (1992).

Downloaded At: 08:59 27 January 2011

2. D. C. Ayres and J. D. Loike, *"Lignans: Chemical, Biological and Clinical Properties"*, Ch. 3 and 4, Cambridge University Press, Cambridge, 1990.

3. L. S. Thurston, M. Imakura, D. H. Li, Z. C. Liu, S. Y. Liu, Y. C. Cheng and K. H. Lee, *J. Med. Chem.*, **32**, 604 (1989).

4. A. San Feliciano, J. M. Miguel del Corral, M. Gordaliza and A. Castro, *An. Quim.*, **88**, 256 (1992); *Chem. Abstr.* **118**, 1993, 59480q.

5. N. L. Drake and E. H. Price, *J. Am. Chem. Soc.*, **73**, 201 (1951).

6. D. C. Ayres and P. J. S. Pauwels, *J. Chem. Soc.*, 5025 (1962).

7. A. San Feliciano, M. Gordaliza, J. M. Miguel del Corral, M. A. Castro, M. D. García-Grávalos and P. Ruiz-Lázaro, *Planta Medica*, **59**, 246 (1993); *Chem. Abstr.* **119**, 1993, 151663v.

8. M. Gordaliza, M. A. Castro, M. D. García-Grávalos, P. Ruiz, J. M. Miguel del Corral and A. San Feliciano, *Arch. Pharm. (Weinheim)*, **327**, 175 (1994).

9. E. Pretsch, T. Clerc, J. Seibl and W. Simon, *"Tablas para la Elucidación Estructural de Compuestos Orgánicos por Métodos Espectroscópicos"*, Alhambra, Madrid, 1988.

10. A. San Feliciano, J. M. Miguel del Corral, M. Gordaliza and M. A. Castro, L. J. Morales and J. L. López, *Bull. Soc. Chim. Fr.*, Submitted for publication.

11. W. J. Gensler, C. D. Murthy and M. H. Trammell, *J. Med. Chem.*, **20**, 635 (1977)

12. E. Schreier, *Helv. Chim. Acta*, **47**, 1529 (1964).

(Recieved December 3, 1993; in revised form May 4, 1994)

Downloaded At: 08:59 27 January 2011