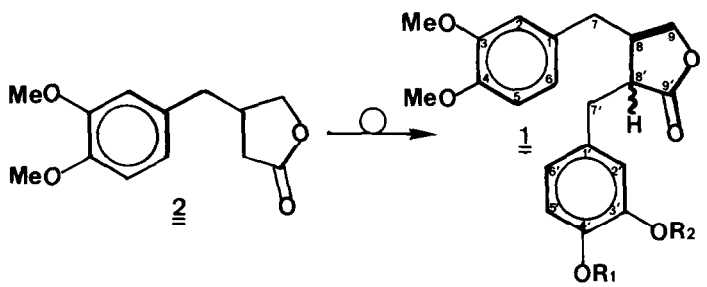
Tetrahedron Letters,Vol.24,No.31,pp 3237-3238,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

Prestegane A, from *Steganotaenia araliacea* Hochst.: The First Natural Dibenzylbutanolide Lignan with a *meta*-Phenol - A Short Synthesis of *cis* and *trans* (±) Arctigenin -

by Mohammed TAAFROUT, Francis ROUESSAC and Jean-Pierre ROBIN*
Laboratoire de Synthèse Organique, E.R.A. - C.N.R.S., Faculté des Sciences,
Route de Laval, 72017 LE MANS CEDEX, FRANCE

Summary : A potential biogenetic precursor of steganes was isolated and its structure 1c was determined using high resolution PMR, total synthesis and comparison with (±) arctigenin resulting from an unequivocal synthesis.

We have recently described six lignans from an antileukemic fraction of the West African variety *Steganotaenia araliacea* Hochst. (1) (2). A careful examination in TLC of the polar chromatographic fraction resulting from our previous work, revealed some closely related compounds. Preparative layer chromatography (Silicagel Merck Si 60, F 254 ; $CHCl_3$-Et_2O 1:1) yielded an amorphous compound which exhibited the following constants :
$[\alpha]_D^{21}$ = -31° (C 0,39, $CHCl_3$) ; IR ($CHCl_3$) 1770 (ν lactonic C=O), 3500 (ν phenolic OH) cm^{-1}
M^+ calcd for $C_{21}H_{24}O_6$ 372.1573, found 372.1578 ; the PMR data (3) showed that it was a dibenzylbutanolide lignan identical or closely related to arctigenin 1a (4)



	H-8'	R_1	R_2
1a	β	H	Me
1b	α	H	Me
1c	β	Me	H

In view of conflicting data concerning the aliphatic hydrogen assignments of the latter in PMR (5), we synthesized it using two independent short sequences from the known β-veratryl γ-butyrolactone 2 as a common precursor. For the first route, 2 was submitted to alkylidenation by O-benzyl vanillin according to a Stobbe-like reaction (MeONa/C_6H_6, r.t., 120 mn ; 10 % H_2SO_4, r.t., 60 mn) followed by hydrogenation-debenzylation (Pd-C/AcOEt, 12 h) to give *cis* (±) arctigenin 1b in a 43 % overall yield. This lactone 2 was quantitatively isomerized (KOH/MeOH, r.t.; 4 days,refluxing AcOH, 2 h) into the more stable lactone *trans* (±) arctigenin 1.

Alternatively, a direct condensation of O-benzyl vanillyl bromide (in THF-HMPT) on the anion of 2 (LDA/THF, -78°, 2 h) followed by deprotection (Pd-C/AcOEt, 12 h) resulted in the same above *trans* lactone 1a in a 68 % overall yield from 2.

Still, our unknown lignan cleanly differed from both of these structures 1a and 1b. Furthermore, alternate irradiations of every benzylic methylen protons at 400 MHz, gave a clear enhancement with sharpening of the corresponding pair of ortho-aromatic protons, which

eliminated any substituents at C-2, C-6, C-2' and C-6'. Observation of the fragment at m/e 194 allowed to place phenol on the lignan (C_6-C_3) moiety attached to the carbonyl side as in arctigenin 1a (6). At this stage, only lacton 1c could be considered. Finally the structure of this new lignan was unequivocally proved with the help of the same direct synthetic previous sequence using O-benzyl isovanillyl bromide instead of O-benzyl vanillyl bromide (7).

According to these data, we named 1c (-) prestegane A as a possible biogenetic precursor of lignans of the stegane group (8).

REFERENCES AND NOTES

1. (a) M. TAAFROUT, F. ROUESSAC et J.P. ROBIN, Tetrahedron Lett., 24, 197 (1983).
   (b) M. TAAFROUT, F. ROUESSAC and J.P. ROBIN, Tetrahedron Lett., in press.
2. Including the four lignans formerly discovered in a sample of other origin : S.M. KUPCHAN, R.W. BRITTON, M.F. ZIEGLER,C.J. GILMORE, R.J. RESTIVO and R.F. BRYAN, J. Am. Chem. Soc., 95, 1335 (1973). This paper is dedicated to memory of the late S. Morris KUPCHAN.
3. 250 MHz PMR (δ, $CDCl_3$) 6.78 (d, 1H, $J_{5'-6'}$ = 8.2 Hz) H-5' ; 6.77 (d, 1H, J_{5-6} = 8.2 Hz) H-5 ; 6.75 (d, 1H, $J_{2'-6'}$ = 2.1 Hz) H-2' ; 6.63 (dd, 1H, $J_{6'-2'}$ = 2.1 Hz) H-6' ; 6.58 (dd, 1H, J_{6-5} = 8.2 Hz, J_{6-2} = 2.1 Hz) H-6 ; 6.50 (d, 1H, J_{2-6} = 2.1 Hz) H-2 ; 5.6 (broad s, 1H) phenol ; 4.11 (dd, 1H, J_{9b-9a} = 9 Hz, J_{9b-8} = 8 Hz) H-9b ; 3.91 (dd, 1H, J_{9a-9b} = 9 Hz, J_{9a-8} = 7 Hz) H-9a ; 3.90, 3.84 and 3.83 (9H, 3s) 3 OMe ; 3.00 (dd, 1H, $J_{7'b-8'}$ = 4.8 Hz, $J_{7'b-7'a}$ = 14 Hz) H-7'b ;2.83 (dd, 1H, $J_{7'a-7'b}$ = 14 Hz, $J_{7'a-8'}$ = 6.2 Hz) H-7'a ; 2.61 (dd, 1H, J_{7b-7a} = 13.5 Hz, J_{7b-8} = 5.4 Hz) H-7b ; 2.54 (m, 2H) H-8 and H-8' ; 2.48 (dd, 1H, J_{7a-7b} = 13.5 Hz, J_{7a-8} = 7.8 Hz) H-7a.
4. For an explanation of the numbering system, see : O.R. GOTTLIEB, Fortschr. Chem. Org. Naturst., 35, 1 (1978).
5. Nevertheless, the following references are in agreement with the present findings :
   (a) J.E.T. CORRLE, G.H. GREEN, E. RITCHIE and W.C. TAYLOR, Aust. J. Chem., 23, 133 (1970).
   (b) R.W. MILLER, J.L. MCLAUGHLIN, R.G. POWELL, R.D. PLATTNER, D. WEISLEDER and C.R. SMITH jr, J. Nat. Prod., 45 (1) (1982).
6. P.B. MCDONIEL and J.R. COLE, J. Pharm. Sci., 61, 1992 (1972).
7. To give pure amorphous (±)-1c in a 70 % overall yield from 2. 90 MHz-PMR and IR ($CHCl_3$) spectra of natural and synthetic samples of 1c were strictly superimposable. Rf's in TLC using five solvant systems were identical.
8. The only example of a biogenetic precursor with such a substitution have been described in a diarylbutane type lignan : Y. IKEYA, H. TAGUCHI and I. YOSIOKA, Chem. Pharm. Bull., 26 (2) 682 (1978).

ACKNOWLEDGEMENTS

These data are the results of screening performed under the auspices of the Developmental Therapeutics program, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland.

This research is supported by funds from the "Ligue Française contre le Cancer, Association d'Hygiène Sociale, Le Mans, France". We are grateful to the Institut Universitaire de Technologie in Le Mans for its technical support.

(Received in France 28 March 1983)