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OXIDATIVE ARYL-ARYL, ARYL-BENZYL COUPLING OF LIGNANS-REACTIONS OF PHYLLANTHIN AND HALODERIVATIVES WITH TTFA, DDQ, LI/THF)))) : SYNTHESIS OF DIBENZOCYCLOOCTADIENE SYSTEM AND PHYLTETRALIN

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Abstract: *Treatment of phyllanthin* (**1**) *with TTFA in TFA gives dibenzocyclooctadiene* (**2**) *and phyltetralin* (**3**). *Treatment of* (**1**) *with DDQ in TFA also affords* (**2**) *while with DDQ in acetic acid gives 1-phenylnaphthalenic lignan* (**4**). *Synthesis of halophyllanthins* (**5,6,7**) *and its Ullmann reaction in ultrasonic condition affords reductive dehalogenated product* (**1**) *instead of* (**2**). *Treatment of* (**1**) *with* $POCl_3$ *in TCA gives (+) 3,4-diveratryltetrahydrofuran* (**8**) *and its conversion to* (**9**) *also reported. Treatment of* (**5**) *with TTFA/TFA gives* (**9**).

In continuation of our studies of the oxidations, rearrangements, cyclisation[1,2,3] of lignans with DDQ and recent interest in dibenzocyclooctadiene lignans[4], we now report the reactions of phyllanthin and derived halophyllanthins with TTFA in TFA, DDQ in TFA & CH_3COOH, $POCl_3$ in TCA and attempted intramolecular Ullmann coupling of halophyllanthins employing ultrasound conditions.

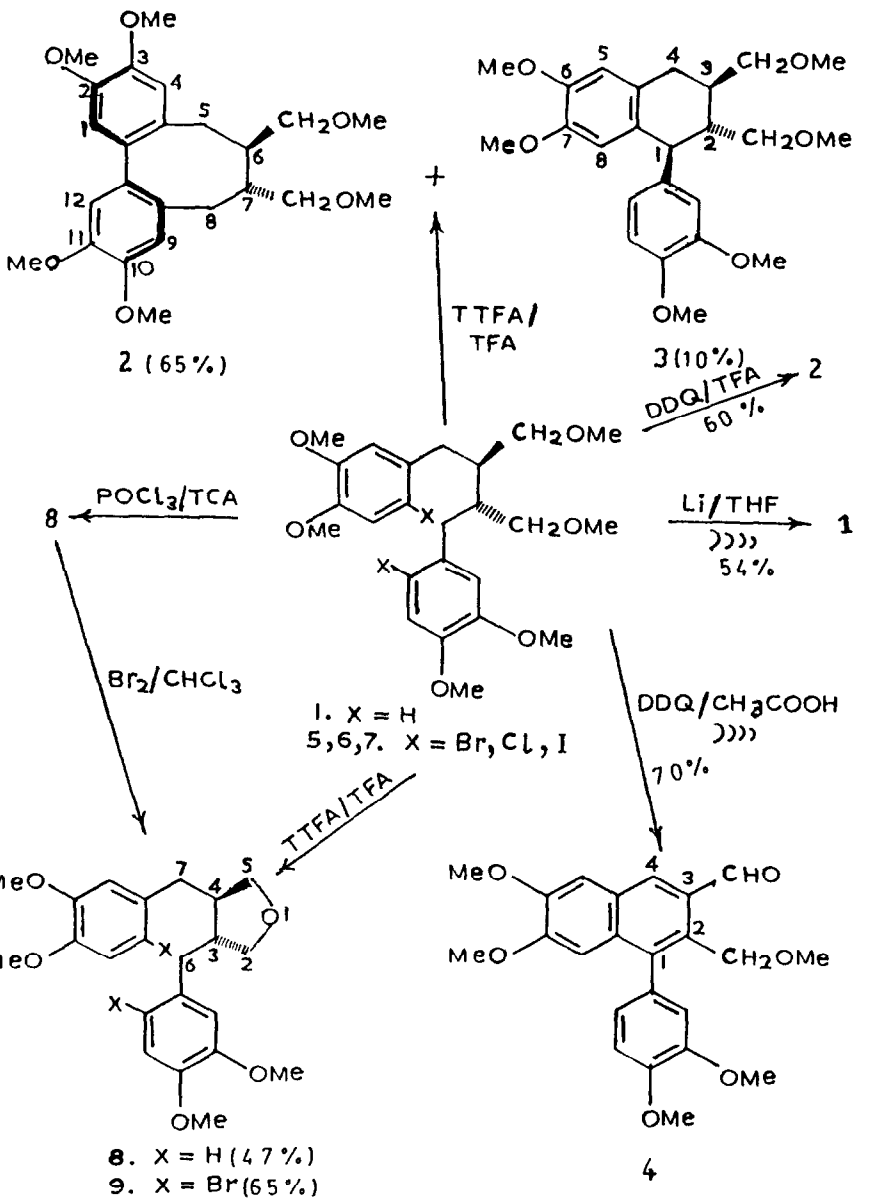
In an effort to effect intramolecular aryl-aryl coupling of diaryl butanes, we prepared the haloderivatives of phyllanthin (**5,6,7**) and studied its reactions with Li/THF in ultrasound[5]. When dibromophyllanthin (**5**) was treated with Li (1eq.) in THF and exposed to ultrasound cleaning bath (37 ± 3) KHz led to a product $C_{24}H_{34}O_6$, m.p. 98°C, M^+418 free of bromine. These observations and its ^1H nmr spectrum clearly pointed the isolation of a reductive dehalogenated compound which was found to be identical in all respects with phyllanthin(**1**)[6]. When the reaction was repeated with diiodo and dichlorophyllanthin, the yielded product, m.p. 98°C was identified also as (**1**). All the three compounds suffered reductive dehalogenation under the conditions studied, instead of introducing aryl-aryl linkages.

Next we turned our attention to study non-phenolic oxidative coupling reagents on phyllanthin (1). When (+) phyllanthin (1) was treated with 1.1 equivalents of TTFA in trifluroacetic acid[7,8,9] dehydrogenation occurred giving a product $C_{24}H_{32}O_6$, M^+ (416,100%) $[\alpha]_D^{29}$-64.96°, m.p. 88°C. A study of its ^1H nmr spectrum clearly indicated the aliphatic part of the structure of starting compound was intact. The only change was noticed in the aromatic region of spectrum, which contained a sharp singlet at δ 6.76 integrating for four protons. Further the ^{13}C nmr spectrum indicated a symmetrical structure since only 11 signals were present. These observations suggested that oxidative coupling of the aromatic rings had occurred leading to the dibenzocyclooctadiene system (2). These deductions were supported by comparison with the work of Chattopadhyay and Rao[10], Pelter and Ward[11] and also by comparision of the above spectra with those of related compounds already reported. The product (2) showed negative cotton effects at 245 and 295 nm indicating that the biphenyl unit in the dibenzocyclooctadiene system possess the absolute configuration shown[10,12,13]. A second product $C_{24}H_{32}O_6$, M^+ (416),$[\alpha]_D^{28}$+16.6°, m.p. 111°C, isomeric to (2) was also obtained. Examination of its ^1H nmr spectrum indicated aryl-benzyl coupling linkage had taken place resulting in aryltetralin structure, fully supported by the presence of a doublet at δ 4.05 doubly benzylic methine proton and a singlet at a high field δ 3.58 for aromatic methoxyl. The spectral data (^1H nmr, mass, IR, UV & mmp) was found to be identical in all respects with phyltetralin (3)[14]. The total synthesis of phyllanthin[15] has previously been reported and this direct oxidative biomimitic conversion constitutes a formal total synthesis of phyltetralin (3).

When (+) phyllanthin (1) was treated with 2 equivalents of DDQ in TFA yielded a product, $C_{24}H_{32}O_6$, M^+ (416, 100%), m.p. 88°C and it was rapidly characterised as the dibenzocyclooctadiene agreeing in all respects with the spectra of (2).

When (+) phyllanthin (1) was treated with 3 equivalants of DDQ in acetic acid gave a single compound (4), $C_{23}H_{24}O_6$, M^+ (396, 10%), m.p. 170-1°C in 70% yield. It readily formed a 2,4-DNP derivative m.p. 196°C. The presence of two singlets at δ 8.37 and 10.45 indicated it to belong to a napthalenic aldehyde system and in fact it was proved to be so by comparision of its spectra (^1H nmr, mass, IR, UV, and mmp) with a compound that has been previously reported by dehydrogenation of phyltetralin with DDQ unequivocally[1]. When this reaction was conducted in ultrasonic conditions the naphthalenic product (4), m.p. 170-1°C formed reducing its time by two fold.

When (+) dibromophyllanthin (5) was treated with 2 equivalents of TTFA in TFA gave a new product, $C_{22}H_{26}O_5Br_2$, m.p. 115°C, $[\alpha]_D^{30}$ + 21°, M^+532, whose ^1H nmr spectrum revealed the absence of two aliphatic methoxyls. Based on ^1H nmr and mass spectrum, formation of a tetrahydrofuran ring was conceived and therefore assigned the structure (9). Incidentally the reaction of phyllanthin (1) for the first time was studied with $POCl_3$ in trichloroacetic acid furnishing a product $C_{22}H_{28}O_5$ m.p. 116°C, $[\alpha]_D^{29}$ + 56°. A study of its ^1H nmr spectrum indicated the absence of aliphatic methoxyls which were originally


OMe
OMe
CH2OMe
CH2OMe
MeO
OMe
2 (65%)
TTFA/
TFA
MeO
CH2OMe
MeO
CH2OMe
OMe
OMe
3 (10%)
DDQ/TFA
60 %
2
OMe
CH2OMe
OMe
CH2OMe
X
X
OMe
OMe
1. X = H
5,6,7. X = Br, Cl, I
POCl3/TCA
8
Li/THF
54%
1
Br2/CHCl3
DDQ/CH3COOH
70%
TTFA/TFA
MeO
MeO
X
X
OMe
OMe
8. X = H (47%)
9. X = Br (65%)
MeO
MeO
CHO
CH2OMe
OMe
OMe
4

present in phyllanthin. Further study of ^1H nmr and analysis, it was characterised as (+) 3,4-diveratryltetrahydrofuran (8) and confirmed its identity with an authentic sample[15] by m.m.p. 116°C, co tlc.

When (+) 3,4-diveratryltetrahydrofuran (8) was treated with bromine in $CHCl_3$ produced the dibromo product. $C_{22}H_{26}O_5Br_2$, m.p. 115°C, $[\alpha]_D^{30}$ + 24°, M^+532, which was found to be identical in all respects with the product (9).

Possible mechanisms for formation of this dibenzocyclooctadiene was well explained by Pelter and Ward[11]. Here in it has been observed for the first time the ability of $POCl_3$ in TCA and TTFA in TFA to demethylate aliphatic methoxyls. It is also the first time the non-phenolic aryl-benzyl coupling effected with TTFA has been noticed.

Experimental

General experimental proceedures: ^1H and ^{13}C nmr spectra were recorded on Jeol JNM EX 90 instrument. IR spectra were recorded on Shimadzu IR 408, UV spectra on Shimadzu UV 260. Mass spectra were recorded on a Jeol D-300 instrument. CD spectra was obtained on Jasco J-20 automatic recording spectropolarimeter. Optical rotations were determined in chloroform with a perkin Elmer 241 MC spectopolarimeter. Melting points are uncorrected. Silica gel-G was used for column chromatography and for tlc.

Preparation of bromophyllanthin (5)

A solution of bromine in $CHCl_3$ (4%) was added dropwise to phyllanthin[16] (1) (100 mg) in $CHCl_3$ (5 ml) with shaking until yellow colour persisted. After 0.5 hrs the solvent was evaporated and the brown residue crystallised from EtOH as colourless needles (5) (100 mg, 73%), m.p. 136°C, R_f 0.45 (pet.ether-EtOAc, 3:1), $[\alpha]_D^{30}$ + 50°(c, 1.00, $CHCl_3$); λ max (CH_3OH) : 209, 285 nm (log ε 4.47, 3.84); ν max(Nujol) : 1602, 1562, 1455, 1380, 1260, 1213, 1160, 1107, 1085, 1025, 1015, 960, 910, 845, 825 cm^{-1}; ^1H nmr ($CDCl_3$,δ) : 2.02 (m, 2H, H-2, H-3), 2.6 (m, 4H, H-1, H-4), 3.4 (s, 6H, $ROCH_3$), 3.45 (s, 4H, CH_2's), 3.8 (s, 6H, $ArOCH_3$), 3.85 (s, 6H, $ArOCH_3$), 6.7 (s, 2H, Ar-H), 6.9 (s, 2H, Ar-H); m/z 578 (15%, M^+), 574 (18%), 434 (10%) 430 (10%), 231 (95%), 229 (100%), 151 (80%).

Preparation of iodophyllanthin (7)

Phyllanthin (1) (100 mg) in EtOH (3 ml) was treated with ICl (0.04 ml) in EtOH (3 ml) and maintained at 70°C for 10 min. water (10ml) was added and the mixture again heated for 5 min. at 80°C, then cooled extracted with ether (3 x 10 ml), dried then evaporated. The residue was crystallised from methanol to yield colourless needles (7) (100 mg, 63%), m.p. 112°C, R_f 0.51 (pet.ether-EtOAc, 3:1),$[\alpha]_D^{30}$ 0° (c, 1.4 $CHCl_3$); λ max (CH_3OH): 210, 283 nm (log ε 4.61, 3.62) νmax (Nujol) : 1599 1512, 1468, 1455, 1450, 1372, 1367, 1255, 1215, 1160, 1107, 1085, 1020, 952, 842, 798 cm^{-1}; ^1H nmr ($CDCl_3$, δ). 2.02

(m, 2H, H-2, H-3), 2.65 (m, 4H, H-1, H-4), 3.4 (s, 6H, $ROCH_3$), 3.45 (s, 4H, CH_2's), 3.8 (s, 6H, $ArOCH_3$), 3.85 (s, 6H, $ArOCH_3$), 6.8 (s, 2H, Ar-H), 7.0 (s, 2H, Ar-H); m/z 670 (2%, M^+), 277 (50%), 151 (80%), 45 (100%).

Preparation of chlorophyllanthin (6)

Phyllanthin (1) (200 mg) was dissolved in 6 ml acetic acid containing sodium acetate (fused, 150 mg). To which iodobenzene dichloride (266 mg) was added and the mixture stirred for 4 hrs. It was then poured into ice water (50 ml) and extracted with $CHCl_3$ (3 x 50 ml). The extract was washed with aqueous $Na_2S_2O_3$ (10%, 40 ml), water (50 ml) and then the solid dried over $MgSO_4$. The solvent was distilled off and the solid crystalised from alcohol gave white crystalline needles (6) (200 mg, 85%), m.p. 125 °C, R_f 0.50 (pet.ether-EtOAc, 3:1), $[\alpha]_D^{28}$ + 20° (c, 1.2, $CHCl_3$); λ max (MeOH): 212, 284 nm (log ε4.78, 3.65); νmax ($CHCl_3$): 1601, 1451, 1390, 1250, 1211, 1145, 1090, 1015, 965, 850, 804 cm^{-1}; ^1H nmr ($CDCl_3$, δ): 2.0-2.2 (m, 2H, H-2, H-3), 2.7-2.8 (m,4H, H-1, H-4), 3.3 (s, 6H, $ROCH_3$), 3.4 (s, 4H, CH_2's), 3.7 (s, 6H, $ArOCH_3$), 3.75 (s, 6H, $ArOCH_3$), 6.6 (s, 2H, Ar-H), 6.7 (s, 2H, Ar-H); m/z 490 (2%, M^+), 486 (6%), 257 (10%), 256 (30%), 187 (15%), 185 (45%), 64 (100%).

Ullmann reactions of bromophyllanthin (5) *assisted by ultrasound technique*

Bromophyllanthin (5) (100 mg) was dissolved in dry THF (20 ml) in a 100 ml flask. To this lithium wire (200 mg) was added and the solution is kept in a ultrasonic cleaning bath (37 ± 3) KHz for 3 hrs. The proudct was isolated and crystallised from ethanol to give a colourless compound (40 mg, 54%), m.p. 98°C, $[\alpha]_D^{28}$ + 13° (c, 1.00, $CHCl_3$), λ max (MeOH): 230, 280 nm (log ε 4.32, 2.11); ν max($CHCl_3$). 1605, 1590, 1520, 1485, 1335, 1275, 1250, 1055, 1040, 955 cm^{-1}; ^1H nmr ($CDCl_3$, δ): 2.04 (m, 2H), 2.64 (d, 4H), 3.26 (s, 6H), 3.32 (m, 4H), 3.76 (s, 6H), 3.80 (s, 6H), 6.5-6.8 (m, 6H); m/z (418, M^+). The spectral data (IR, UV, ^1H nmr, mass) was found to be identical in all respects with phyllanthin (1), m.m.p. 98°C.

Similar reactions were conducted with chloro and iodo phyllanthins, giving product (1), m.m.p. 98°C.

Reaction of phyllanthin (1) *with TTFA in TFA : Isolation of the dibenzocyclooctadiene* (2) *and the phyltetralin* (3)

To a solution of phyllanthin (1) (500 mg) in TFA (6.0 ml) at -10°C was added thallium tris(trifluoroacetate) (1.1 eq.) (750 mg) in one portion. After 0.5 hrs stirring at -10°C, the mixture was quenched with ice water (20 ml) and extracted with EtOAc (50 ml), washed with brine (2x20 ml), dried ($MgSO_4$). Evaporation in vacuo and chromatography of the residue over silica gel eluting with 20% EtOAc-pet.ether gave colourless crystalls of dibenzocyclooctadiene (2) (325 mg, 65%), m.p. 88°C $[\alpha]_D^{29}$ - 64.96 (c, 0.022, $CHCl_3$),

m/z 416 (100%, M^+), 338 (10%) 311 (9%), 298 (15%) 284 (4%), 78 (20%), λ max (CH_3OH); 208, 285 nm (log ε 4.61, 3.94); CD data (CH_3OH): 245 (Δ E 6.42), 295 (Δ E 2.35)nm; ν max ($CHCl_3$): 2990, 2930, 1590, 1480, 1220, 1120, 1100, 1050, 820 cm^{-1}; ^1H nmr ($CDCl_3$, δ): 1.9-2.2 (m, 2H, H-6, H-7), 2.6-2.8 (m, 4H, H-5, H-8), 3.3 (s, 6H, $ROCH_3$), 3.4 (m, 4H, CH_2's),3.9(s, 12H, $ArOCH_3$), 6.76 (s, 4H, Ar-H); ^{13}C nmr ($CDCl_3$, δ): 148.3, 146.8 (C-2, C-3, C-10, C-11), 133.3, 129.2 (C-1a, C-4a, C-8a, C-12a), 112.0, 113.0 (C-1, C-4, C-9, C-12), 42.0 (C-6, C-7), 35.3 (C-5, C-8), 77.0 (CH_2's), 58.8 ($ROCH_3$), 55.9 ($ArOCH_3$); anal.calcd. for $C_{24}H_{32}O_6$ C, 69.20, H, 7.74 found C, 69.65, H, 7.87% and the other product isolated, crystallised from pet.ether as colourless needles (**3**) (50 mg, 10%), m.p. 111°C, $[\alpha]_D^{28}$ +16.6° (c, 0.8, $CHCl_3$); λ max (CH_3OH); 228, 284 nm (log ε 4.16, 3.89); ν max ($CHCl_3$): 1605, 1450, 1360, 1250, 1110, 950 cm^{-1}; ^1H nmr ($CDCl_3$, δ): 1.7-2.0 (m, 2H), 2.80-2.88 (d, 2H), 3.26 (s, 6H), 3.35 (s, 4H), 3.58 (s, 3H), 3.80 (s, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 4.05 (d, 1H), 6.25 (s, 1H), 6.61-6.77 (m, 4H, Ar-H); m/z 416 (85.8%, M^+), anal.calcd. for $C_{24}H_{32}O_6$ C, 69.21, H, 7.75 found C, 68.96 H, 7.74%. The spectral data (IR, UV, ^1H nmr, mass) were found to be identical in all respects with phyltetralin.

Reaction of phyllanthin (1) *with DDQ in TFA : Isolation of the dibenzocyclooctadiene* (2)

A mixture of (1) (100 mg), DDQ (108 mg, 2 eq.) in TFA (3 ml) was stirred at 25° C for 2 hrs. It was diluted with water and extracted with benzene (2 x 25 ml). The solvent layer was washed with $NaHCO_3$, H_2O, NaOH and H_2O. Evaporated and the residue was passed over column of alumina and chromatographed over silica gel eluting with 20% EtOAc-pet.ether gave a compound, which crystallised from pet.ether as colourless crystals of dibenzocyclooctadiene (**2**) (60 mg, 60%), m.p. 88°C.

Reaction of phyllanthin (1) *with DDQ in CH_3COOH : Isolation of the 1-phenylnaphthalenic lignan* (4)

A mixture of phyllanthin (1) (50 mg), DDQ (81 mg, 3 eq.) in HOAc (glacial, 5 ml) was stirred for 90 min. Filtered, the solvent removed in vacuo and the residue chromatographed over silica gel eluting with 20% EtOAc-pet.ether to give a compound, which crystallised from benzene as colourless needles (**4**) (33 mg, 70%), m.p. 170-1°C, R_f 0.42 (pet.ether-EtOAc, 3.2): λ max (MeOH): 233, 260, 280, 340 nm (log ε 4.30, 4.23, 4.25, 3.70); m/z 396 (20%, M^+), 381 (12%), 365 (24%), 364 (100%) 349 (26%), 305 (27%), 261 (25%); ν max ($CHCl_3$); 2950, 1710, 1620, 1500, 1110, 1050, 940 cm^{-1}; ^1H nmr ($CDCl_3$, δ): 3.3 (s, 3H, $ROCH_3$), 3.7 (s, 3H, $ArOCH_3$), 3.8 (s, 3H, $ArOCH_3$), 4.0 (s, 6H, $ArOCH_3$), 4.5-4.55 (d, J = 5Hz, 2H, CH_2's), 6.7-7.0 (m, 4H, Ar-H), 8.3 (s, 1H, H-4), 10.3 (s, 1H, CHO); anal.calcd. for $C_{23}H_{24}O_6$ C, 69.68 H, 6.10 found C, 69.76, H, 6.17%.

The above reaction was completed in 40 min. when placed in ultrasonic cleaning bath (37±3) KHz at 50°C.

Reaction of bromophyllanthin (5) *with TTFA in TFA : Isolation of the tetrahydrofuran* (9)

To a solution of bromophyllanthin (5) (500 mg) in TFA (4.3 ml) at -10°C was added TTFA (500 mg) in one portion. After 0.5 hrs stirring at -10°C, it was worked up. The compound crystallised from ethanol as white needles (9) (300 mg, 65%), m.p. 115°C, R_f 0.52 (pet.ether-EtOAc, 6:4); $[\alpha]_D^{30}$ +21° (c, 1.00, $CHCL_3$); λ max ($CHCl_3$): 225, 265 nm (log ε 4.13, 2.92); νmax ($CHCl_3$): 2920, 1604, 1520, 1440, 1240, 1160, 1040, 840 cm^{-1}; ^1H nmr ($CDCl_3$ δ): 2.4 (m, 2H), 2.6 (d, 4H), 3.5 (m, 4H), 3.8 (s, 12H, $ArOCH_3$), 6.6 (s, 2H, Ar-H), 6.9 (s, 2H, Ar-H); m/z 532 (46%, M^+), 530 (70%), 451 (6%), 449 (6.1%), 372 (5.3%), 370 (16%), 229 (30%), 231 (26%), 151 (100%).

Reaction of phyllanthin (1) *with* $POCl_3$ + *TCA : Isolation of 3,4-diveratryltetrahydrofuran* (8)

Phyllanthin (1) (200 mg) was dissolved in dry benzene (5 ml) and TCA (1 ml) was added. To this mixture $POCl_3$ (1.5 ml) was added slowly by stirring the mixture at 0°C. It was refluxed on steam bath for 6 hours. Benzene was removed in vacuo. After cooling, ice water was added and kept at 0°C for 2 hrs. It was neutralised with cold K_2CO_3 solution (5%) and extracted with EtOAc, dried, evaporated. The residue was crystallised from EtOAc as white needles (8) (88 mg, 47%), m.p. 116°C; $[\alpha]_D^{29}$ + 56° (c, 1.8, $CHCl_3$); λmax ($CHCl_3$): 229, 260 nm (log ε 4.07, 2.73); ν max (KBr): 1585, 1510, 1250, 1150, 1035, 915, 865, 810, 765 cm^{-1}; ^1H nmr ($CDCl_3$, δ): 2.1 (m, 2H), 2.45 (d, 4H), 3.3 (m, 4H), 3.7 (s, 12H, $ArOCH_3$), 6.4-6.7 (m, 6H, Ar-H); m/z (372, M^+) ; anal.calcd. for $C_{22}H_{28}O_5$ requires C, 70.97, H, 7.53,4-O CH_3, 33.34 found C, 70.78, H, 6.89, OCH_3, 34.6%.

Bromination of (+) 3,4-diveratryltetrahydrofuran (8)

A solution of bromine in chloroform (4%) was added dropwise to (8) (80 mg) in chloroform (4 ml) while shaking. After 0.5 hours, the solvent was evaporated and the residue crystallised from alcohol as colourless needles (9) (70 mg, 61%), m.p. 114°C, $[\alpha]_D^{30}$ + 25° (c, 1.9, $CHCl_3$), R_f 0.60 (pet.ether-EtOAc, 3:2). The spectral data (UV, IR, ^1H nmr, mass) were identical in all respects with (9), mm.p. 115°C.

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16. Isolation of phyllanthin and other new lignans from **P.Niruri** will be published in elsewhere.