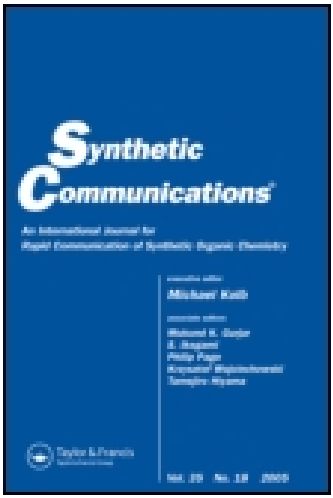

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A Facile Entry to the Caffrane Skeletals : Formal Synthesis of Combretastatin D-2

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A FACILE ENTRY TO THE CAFFRANE SKELETALS : FORMAL SYNTHESIS OF COMBRETASTATIN D-2

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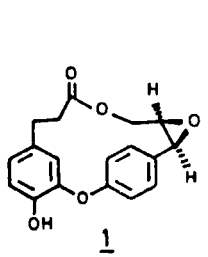
ABSTRACT : Efficient synthesis of Combretastatin D-2, involving a selective reduction of a double bond over a triple bond and a high yielding Ullmann ether formation is described.

Close structural resemblances of Combretastatin D-1[1] (**1**), Combretastatin D-2[2] (**2**), Retipolide-A[3] (**3**), Acerogenins[4] (**4**), Garugamblins[5] (**5**), etc, together with significant biological properties have prompted an extensive synthetic study of these systems. The commonality of the diaryl ether unit involving meta and paracyclophane sub-systems to a broad spectrum of natural products[6] led us into attempting a prototypal synthesis of Combretastatin D-1 & D-2. Combretastatin D-1 (**1**) and D-2 (**2**) have been isolated as trace constituents of the South African tree *Combretum Caffrum* (combretaceae). These unusual 15-membered cytotoxic substances exhibit their antineoplastic activity by inhibiting PS cell line growth.

Combretastatin D-2 (**2**), which is conceived to be an ultimate biosynthetic precursor of Combretastatin D-1 (**1**) was targetted initially[7]. The biosynthetic precedents point towards an initial diaryl ether formation



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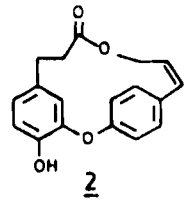

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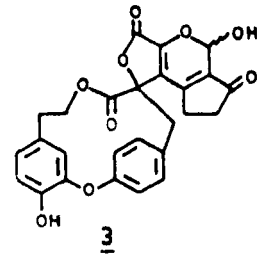

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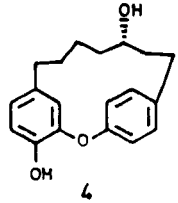

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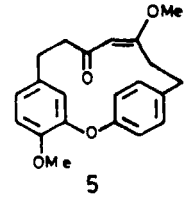

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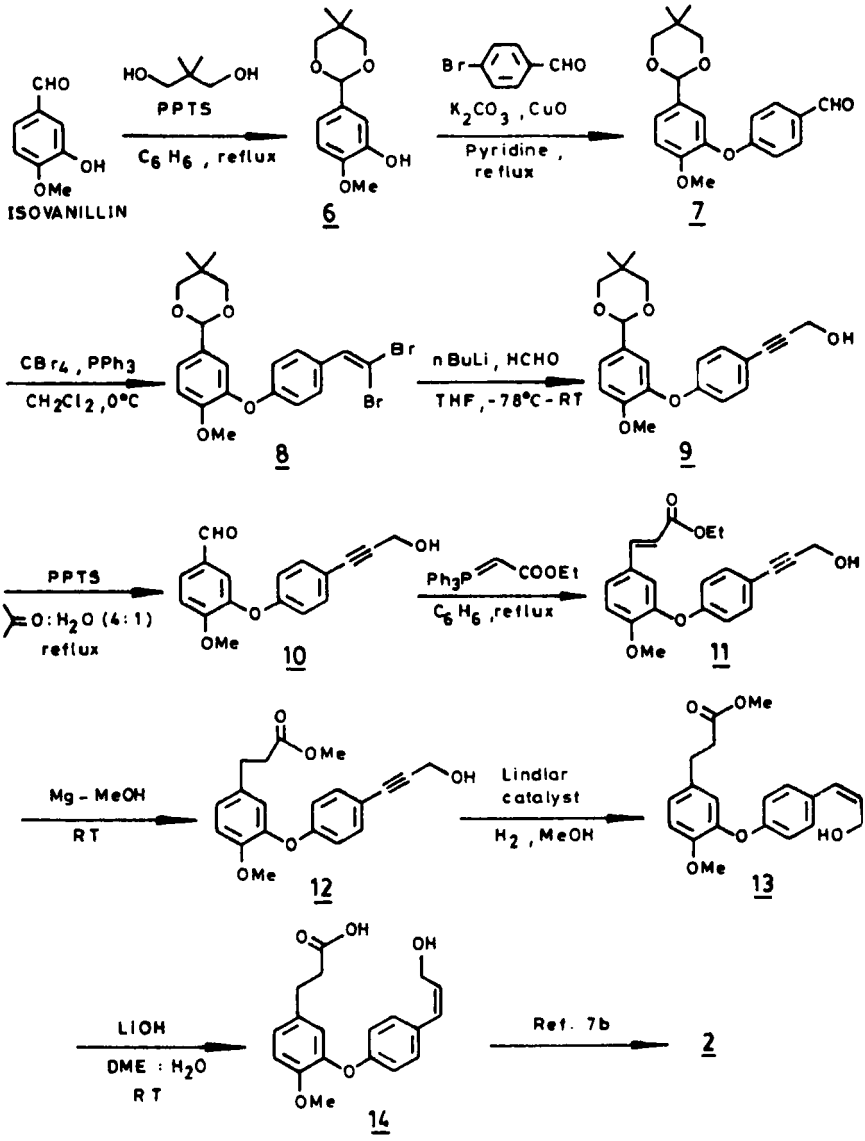
and later a macrolactonization. Following this observation it was proposed to execute the crucial macrolactonization at the final stage.

RESULTS AND DISCUSSION :

The synthesis began with Isovanillin as a convenient starting material. An intermolecular Ullmann ether formation was effected in 93% yield using 4-bromobenzaldehyde and protected isovanillin 6 (Scheme). Treatment of the resulting aldehyde 7 with a modified Wadsworth-Horner-Emmons reagent[8] led to the formation of the (Z)-α,ß-unsaturated ester in over 90% yield in a 13 : 1 ratio in favour of *cis*-isomer. However, further manipulations involving DIBAL-H reduction, deacetalization etc led to extensive isomerization of the *cis* olefin. Hence it was opted for an acetylenic system which could be converted into the desired *cis*-olefin at an appropriate stage. Thus, treatment of the aldehyde 7 with carbon tetrabromide and triphenylphosphine led to



SCHEME

the formation of dibromo olefin **8**. Base induced elimination of the halogens[9] and subsequent *in situ* alkylation led to the formation of the propargylic system **9**. This gave the required carbon framework of the right hand portion. Functionalization of the left hand unit was achieved by deacetalization with PPTS in refluxing aq. acetone. The free aldehyde **10** thus obtained was subjected to Wittig olefination to give **11** in quantitative yield. The selective reduction of the double bond over triple bond was achieved using Mg-MeOH[10] in about 96% yield. This reaction led to an expected ester exchange. Conversion of the acetylenic system **12** to *cis*-olefin **13** over Lindlar catalyst and subsequent hydrolysis gave the seco acid **14** in very high yield. Conversion of the seco acid **14** to Combretastatin D-2 (**2**) has already been described in literature[7b]. Thus, the formal synthesis of Combretastatin D-2 (**2**) is achieved.

EXPERIMENTAL SECTION

General Procedures. NMR spectra were recorded on Varian Gemini 200 instrument in $CDCl_3$ using tetramethylsilane as an internal standard. IR spectra were recorded on Shimadzu IR-470 and Perkin Elmer 283 B instruments. Electron impact mass spectra were recorded on a Finnigan Mat 1210 spectrometer. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected.

5,5-Dimethyl-2-(3-hydroxy-4-methoxyphenyl)-1,3-dioxane [6]

Isovanillin (10g 6.57mmol), 2,2-dimethyl-1,3-propanediol (10.25g 9.85mmol) and Pyridinium-4-toluenesulphonate(4.13g 1.64mmol) were dissolved in 500ml of dry benzene and brought to reflux with continuous removal of water (dean stark). On completion, the reaction

mixture was washed with dilute aq.$NaHCO_3$, water and brine. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The solid obtained was chromatographed over silica gel (eluant : 20% EtOAc:pet.ether) to yield 13.46g (86%) of pure product. mp : 118°C. EIMS (m/e) : 238(M^+). IR (Nujol) : 3415cm^{-1}. ^1H NMR :δ 0.80(s, 3H, -C$\underline{H}_3$), 1.30(s, 3H, -C$\underline{H}_3$), 3.58-3.82(m, 4H, -C$\underline{H}_2$x2), 3.88(s, 3H, -OC$\underline{H}_3$), 5.32(s, 1H, PhC$\underline{H}$-), 5.64(s, 1H, -O$\underline{H}$, D_2O exchg.), 6.83(d, 1H, Ar, J=8Hz), 7.01(dd, 1H, Ar, J=8 & 2Hz), 7.10(d, 1H, Ar, J=2Hz).

5,5-Dimethyl-2-[4-methoxy-3-(4-formylphenoxy)phenyl]-1,3-dioxane [7]

Phenol **6** (5.79g, 2.43mmol), 4-bromobenzaldehyde (3g, 1.62mmol), K_2CO_3 (4.47g, 3.24mmol) and CuO (2.58g, 3.24mmol) were mixed in pyridine (80ml) and refluxed under N_2 overnight. The excess pyridine was removed under reduced pressure and the reaction mixture was diluted with EtOAc (100ml) and filtered through a pad of celite and washed with $CuSO_4$ solution, water and brine. After drying (Na_2SO_4), the organic phase was concentrated and the residue chromatographed (10% acetone:pet.ether) to yield the pure diaryl ether **7** (5.17g, 93%). mp : 76°C. EIMS (m/e) : 342(M^+). IR (KBr) : 1675cm^{-1}. ^1H NMR :δ 0.80(s, 3H, -C$\underline{H}_3$), 1.28(s, 3H, -C$\underline{H}_3$), 3.59-3.85(m, 4H, -C$\underline{H}_2$x2), 3.8(s, 3H, -OC$\underline{H}_3$), 5.36(s, 1H, PhC$\underline{H}$-), 7.0(d, 2H, Ar, J=8Hz), 7.05(d, 1H, Ar, J=8Hz), 7.31(d, 1H, Ar, J=2Hz), 7.41(dd, 1H, Ar, J=8 & 2Hz), 7.82(d, 2H, Ar, J=8Hz), 9.90(s, 1H, -C$\underline{H}$O).

5,5-Dimethyl-2-[4-methoxy-3-(4-(2,2-dibromoethenyl)phenoxy)phenyl]-1,3-dioxane [8]

CBr_4 (4.05g, 12mmol) and PPh_3(6.41g, 24mmol) were dissolved in CH_2Cl_2 and cooled to -10°C (ice-salt) and stirred for 10mins. A solution of the aldehyde **7** (2.09g, 6mmol) in 5ml of CH_2Cl_2 was added dropwise to the reaction mixture and stirred further for 10mins.

Petroleum ether (100ml) was added and stirred for a minute. The liquid phase was decanted and the precipitate was redissolved in CH_2Cl_2 (25ml) and the above process repeated four times. The combined organic extracts were concentrated and chromatographed (10% EtOAc:pet.ether) immediately to afford the dibromo compound **8** (2.22g, 73%). mp : 110°-111°C. EIMS (m/e) : 497(M^+). IR (KBr) : 1600, 1500, 1232, 1020cm^{-1}. ^1H NMR : δ0.78(s, 3H, -C<u>H</u>$_3$), 1.26(s, 3H, -C<u>H</u>$_3$), 3.54-3.78(m, 4H, -C<u>H</u>$_2$x2), 3.80(s, 3H, -OC<u>H</u>$_3$), 5.32(s, 1H, PhC<u>H</u>), 6.90(d, 2H, Ar, J=8.5Hz), 7.00(d, 1H, Ar, J=8.5Hz), 7.21(d, 1H, Ar, J=2.1Hz), 7.34(dd, 1H, Ar, J=8.5 & 2.1Hz), 7.41(s, 1H, PhC<u>H</u>=CBr$_2$), 7.48(d, 2H, Ar, J=8.5Hz).

5,5-Dimethyl-2-{4-methoxy-3-[4-(2-(hydroxymethyl)ethynyl)]phenoxy)phenyl}-1,3-dioxane [9]

To a solution of the dibromo compound **8** (2.22g, 4.47mmol) in dry THF (20ml) was added dropwise at -78°C, under N_2 atmosphere, 1.6M solution of ^{n}BuLi in hexane (5.6ml) and stirred for 0.5h. It was slowly brought to 0°C and paraformaldehyde (0.27g, 8.94mmol) was added. The reaction mixture was allowed to stir at ambient temperature for 6h and quenched with sat.aq. NH_4Cl. It was extracted with EtOAc (2x50ml) and the combined EtOAc extracts were washed with brine. The organic phase was dried (Na_2SO_4), concentrated, and chromatographed (20% EtOAc:pet.ether) to give the propargylic alcohol **9** (1.1g 83%). mp : 110°-111°C. EIMS (m/e) : 368(M^+). IR (Neat) : 3420, 2230cm^{-1}. ^1H NMR : δ 0.78(s, 3H, -C<u>H</u>$_3$), 1.26(s, 3H, -C<u>H</u>$_3$), 1.75(t, 1H, -O<u>H</u> D_2O exchg.), 3.57-3.80(m, 4H, -C<u>H</u>$_2$x2), 3.81(s, 2H, -OC<u>H</u>$_3$), 4.48(d, 2H, -C<u>H</u>$_2$OH, J=6Hz), 5.32(s, 1H, ArC<u>H</u>-), 6.86(d, 2H, Ar, J=8Hz), 7.10(d, 1H, Ar, J=8Hz), 7.20(d, 1H, Ar, J=2Hz), 7.30-7.41(m, 3H, Ar).

4-Methoxy-3-[4-(2-(hydroxymethyl)ethynyl)phenoxy]benzaldehyde [10]

Compound **9** (1g, 2.71mmol) and pyridinium-4-toluenesulphonate (0.17g, 0.68mmol) were dissolved in 80% aq.acetone (20ml) and refluxed for 4h. After cooling to room temperature, aq.$NaHCO_3$ was added and the acetone was removed under reduced pressure and extracted with ethyl acetate (2x20ml). The combined extracts were washed with water, brine and dried (Na_2SO_4). The syrup obtained on concentration was chromatographed to yield the pure aldehyde **10** (0.68g, 89%). mp : 124°-125°C. EIMS (m/e) : 282(M^+). IR (KBr) : 3430, 2232, 1680cm^{-1}. ^1H NMR : δ 1.80(bs, 1H, -OH, D_2O exchg.), 3.81(s, 3H, $-OCH_3$), 4.50(s, 2H, $-CH_2$), 6.90(d, 2H, Ar, J=8.5Hz), 7.13(d, 1H, Ar, J=8.5Hz), 7.41(d, 2H, Ar, J=8.5Hz), 7.52(d, 1H, Ar, J=2.7Hz), 7.72(dd, 1H, Ar, J=8.5 & 2.7Hz), 9.86(s, 1H, -CHO).

(E)Ethyl-4-Methoxy-3-[4-(2-(hydroxymethyl)ethynyl)-phenoxy] cinnamate [11]

The aldehyde **10** (0.5g, 1.77mmol) and (carbethoxymethylene)triphenylphosphorane (0.74g, 2.12mmol) were refluxed for 2h in benzene (10ml). The reaction mixture was concentrated and the residue chromatographed (30% EtOAc:pet.ether) to yield the pure product (0.624g, 100%). mp : 86°C. EIMS (m/e) : 352(M^+). IR (KBr) : 3390, 1695cm^{-1}. ^1H NMR : δ 1.32(t, 3H, $-CH_2CH_3$, J=7.4Hz), 2.06(t, 1H, -OH, J=6.4Hz), 3.85(s, 3H, $-OCH_3$), 4.25(q, 2H, $-CH_2CH_3$, J=7.4Hz), 4.49(d, 2H, $-CH_2OH$, J=6.4Hz), 6.26(d, 1H, CHCOOEt, J=15.95Hz), 6.88(d, 2H, Ar, J=8.5Hz), 7.01(d, 1H, Ar, J=8.5Hz), 7.22(d, 1H, Ar, J=2.1Hz), 7.34(dd, 1H, Ar, J=8.5Hz, 2.1Hz), 7.40(d, 2H, Ar, J=8.5Hz), 7.6(d, 1H, CHCHCOOEt, J=15.95Hz).

Methyl-3-{4-Methoxy-{3-[4-(2-(hydroxymethyl)ethynyl)-phenoxy]phenyl}}propanoate [12]

Compound **11** (0.5g, 1.42mmol) was dissolved in dry MeOH

(5ml) and magnesium (0.2g, 8.5mmol) was added and stirred at 10°C. After 2.5h the excess magnesium was destroyed with dilute 1N HCl and the reaction mixture extracted with EtOAc. The EtOAc layer was washed with water, brine and dried (Na_2SO_4). Concentration under reduced pressure and chromatography afforded the pure product (0.46g, 96%). IR (Neat) : 3420, 2225, 1723cm^{-1}. EIMS (m/e) : 340 (M^+). ^{1}H NMR :δ 1.95(t, 1H, -OH, J=4Hz), 2.59(t, 2H, CH_2COOCH_3), 2.88(t, 2H, $CH_2CH_2COOCH_3$), 3.67(s, 3H, $-COOCH_3$), 3.79(s, 3H, $-OCH_3$), 4.49(d, 2H, $-CH_2OH$, J=4.0Hz), 6.81-7.08(m, 5H, Ar), 7.38(d, 2H, Ar, J=8Hz).

(Z)Methyl-3-{4-methoxy-3-[4-(prop-2-en-1-ol-3-yl)phenoxy]-benzene}propanoate [13]

The acetylenic compound **12** (0.4g, 1.17mmol) was hydrogenated in MeOH (4ml) in the presence of Lindlar catalyst (0.04g) poisoned with quinoline to afford the pure product (0.35g, 87.5%). EIMS (m/e) : 342(M^+). IR (Neat) : 3450, 1722cm^{-1}. ^{1}H NMR :δ 1.55(bs, 1H, -OH), 2.57(t, 2H, $-CH_2CH_2COOEt$, J=8Hz), 2.85(t, 2H, $-CH_2CH_2COOEt$, J=8Hz), 3.64(s, 3H, $-COOCH_3$), 3.81(s, 3H, $-OCH_3$), 4.43(d, 2H, $-CH_2OH$, J=6.35Hz), 5.82(dt, 1H, $-CHCH_2OH$, J=11.73 & 6.35Hz), 6.52(d, 1H, ArCH=CH-, J=11.73), 6.81-7.10(m, 5H, Ar), 7.15(d, 2H, Ar, J=8Hz).

(Z)3-{4-methoxy-3-[4-(prop-2-en-1-ol-3-yl)phenoxy]-benzene}propanoic acid [14]

The compound **13** (0.1g, 0.29mmol) was dissolved in dimethoxyethane (1ml) and 1M solution of LiOH (0.43ml) was added to it. On completion of the reaction (0.5h, t.l.c monitoring) sat. NH_4Cl was added and stirred for 10min and extracted with EtOAc (2x20ml). The combined extracts were washed with water and brine. Evaporation under reduced pressure gave the product in 95% (0.091g) yield. EIMS (m/e) : 328 (M^+). IR (KBr) : 3300, 1695cm^{-1}. ^{1}H NMR :δ 2.62(t, 2H, CH_2COOH, J=7.4Hz), 2.87(t,

2H, $C\underline{H}_2CH_2COOH$, J=7.4Hz), 3.82(s, 2H, $-OC\underline{H}_3$), 4.43(d, $-C\underline{H}_2OH$, J=6.38Hz), 5.82(dt, 1H, $C\underline{H}CH_2OH$, J=11.7Hz, 6.38Hz), 6.53(d, 1H, $ArC\underline{H}CH-$, J=11.7Hz), 6.82-7.03(m, 5H, Ar), 7.16(d, 2H, Ar, J=8.5Hz).

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