ELSEVIER

Carbohydrate Research 301 (1997) 95–109

CARBOHYDRATE RESEARCH

Synthesis of biologically active polyphenolic glycosides (combretastatin and resveratrol series)

Fulvia Orsini *, Francesca Pelizzoni, Barbara Bellini, Giuliana Miglierini

Centro di Studio per le Sostanze Organiche Naturali del CNR, Dipartimento di Chimica Organica e Industriale, via Venezian 21, 20133 Milano, Italy

Received 1 February 1996; accepted in revised form 10 February 1997

Abstract

(*E*)-3-(β-D-Glucopyranosyloxy)-4′,5-dihydroxystilbene (resveratrol 3-β-D-glucoside, piceid), (*Z*)-2′,3′-dihydroxy-3,4,4′,5-tetramethoxystilbene (combretastatin A-1), (*Z*)-3′-hydroxy-3,4,4′,5-tetramethoxystilbene (combretastatin A-4), (*Z*)-2′-hydroxy-3,4,4′,5-tetramethoxystilbene (combretastatin *iso*-A-4), α,β-dihydro-2′,3′-dihydroxy-3,4,4′,5-tetramethoxystilbene (combretastatin B-1), the corresponding glucosides, and related compounds have been synthesized via Wittig reactions followed by glucosylation under phase-transfer catalysis. Most of the compounds synthesized have been tested with respect to biological activity (cytostatic, cytotoxic, antimitotic, neurotoxic, antiplatelet aggregation activity). © 1997 Elsevier Science Ltd.

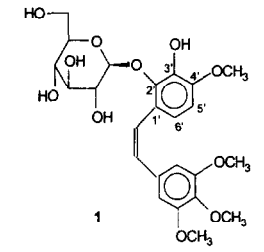
Keywords: Combretastatin glucosides; Resveratrol 3-β-D-glucoside; Piceid; Polyphenolic glucosides

1. Introduction

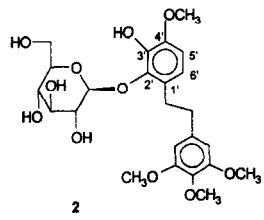
In the course of a systematic investigation on the secondary metabolites from South African plants, we isolated the phenolic glucosides **1–3** which possess biological activity. In particular, the phenolic glucosides **1** (combretastatin A-1 2′-β-D-glucoside) and **2** (combretastatin B-1 2′-β-D-glucoside), isolated from *Combretum kraussi* [1], have shown antimitotic activity [2]. The aglycon of **1**, combretastatin A-1, is a very strong cell-growth and tubulin inhibitor [3]. The phenolic glucoside **3** (resveratrol 3-β-D-glucoside), isolated from *Erythrophleum lasianthum* [4], has shown antiplatelet aggregation activity [4]. The corresponding aglycon, resveratrol, isolated from different sources [5], has shown antiplatelet aggregation activity [5]c, coronary vasodilator action [6]a, and antileukemic [5]d and antifungal activity [6]b. More recently, other stilbenic compounds with substitution patterns similar to **1**, isolated from natural sources, have been reported as antiplatelet aggregation agents [7]a and as environmentally safe, antifouling compounds [7]b,c. Since these compounds are available only in small amounts from natural sources, the synthesis of glucosides **1–3** and related compounds has been undertaken to provide larger quantities for further biological evaluation.

* Corresponding author.

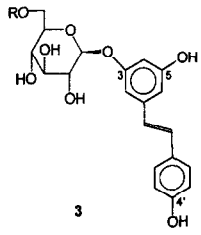
PII S0008-6215(97)00087-6



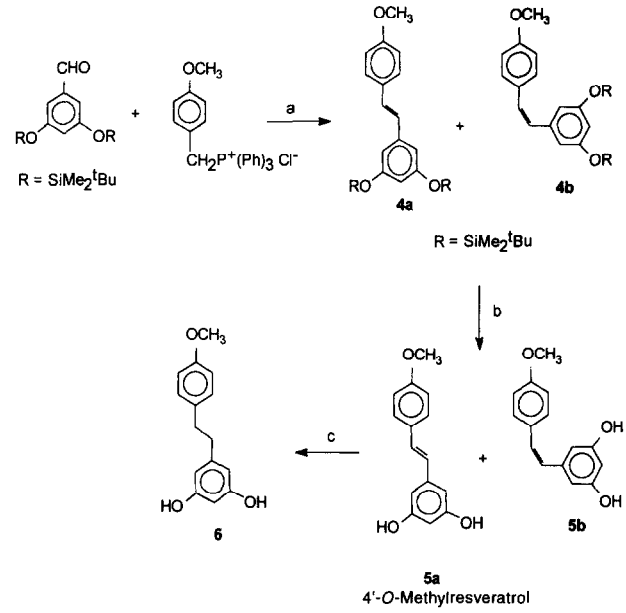
1



2



3



Scheme 1. (a) BuLi, THF, −20 °C. (b) $(n\text{-Bu})_4N^+F^-$, THF. (c) H_2, Pd/C 5%, 5 atm, MeOH, 25 °C.

The synthetic sequence used to synthesize **1** and **2** was also applied to the synthesis of combretastatin A-4 [3], another strong cell-growth and tubulin inhibitor, and *iso*-A-4, and of the corresponding glucosides.

2. Results and discussion

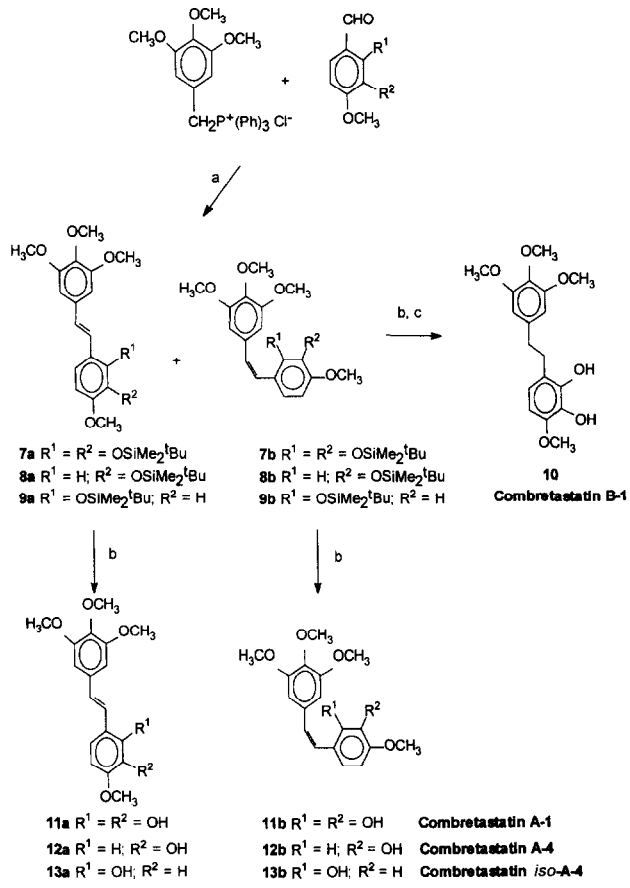
Synthesis of the aglycons and of the glucosides.— In the syntheses of **1** and related compounds, four structural modifications have been considered: (*a*) presence (or not) of the stilbene double bond; (*b*) configuration of the stilbene double bond; (*c*) derivatization of the hydroxyl function at the 4′ position in compound **3**; (*d*) absence of one of the hydroxyl functions at position 2′ or 3′ in **1** (combretastatin A-4 and *iso*-A-4) and **2**.

The stilbene skeleton has been efficiently constructed by Wittig reactions between an aromatic aldehyde and an aromatic phosphonium ylid. In the resveratrol series the best results were obtained by reaction between the phosphonium salt of the commercially available 4-methoxybenzyl chloride and 3,5-bis-(*tert*-butyldimethylsilyloxy)benzaldehyde (Scheme 1) [1]. Protection of the hydroxyl group at position 4′ as the methyl ether had the additional advantage that a methoxy group at the 4′ position is present in several natural bioactive compounds with a stilbene skeleton [8]. Protection of the 3- and 5-hydroxyl groups as *tert*-butyldimethylsilyl ethers could, a priori, afford the target glucoside by treatment with 1-*O*-trimethylsilylglucose derivatives [9]. However, the requirement for an acid promoter made this glucosylation procedure unlikely to be effective because of the presence of the acid-sensitive stilbene double bond [11].

The Wittig product, obtained in 98% yields as a 2.3:1 mixture of the (*Z/E*)-isomers **4b** and **4a** was directly desilylated with tetrabutylammonium fluoride to afford **5a** and **5b**, more easily purified by crystallization or flash chromatography. Additionally, since reduction of the double bond may influence and even improve activity [5]d, the mixture of **4a** and **4b** was hydrogenated to the dihydro-stilbene derivative **6**. Removal of the protective silyl groups could equally well precede or follow the hydrogenation of the stilbene double bond.

(*E*)- and (*Z*)-2′,3′-Di-*O*-(*tert*-butyldimethylsilyl)-combretastatin A-1 (**7a** and **7b**) were synthesized by reaction between the phosphonium salt from 3,4,5-tri-

[1] 3,4′,5-Trihydroxystilbene was previously synthesized from 4-methoxybenzaldehyde and 3,5-dimethoxybenzyltriphenylphosphonium chloride followed by demethylation with pyridinium chloride (41% total yield) [10].



Scheme 2. (a) BuLi, THF, −20 °C. (b) $(n\text{-Bu})_4N^+F^-$, THF. (c) H_2, Pd/C 5%, 5 atm, MeOH, 25 °C.

methoxybenzyl chloride and 2,3-bis-(*tert*-butyldimethylsilyloxy)-4-methoxybenzaldehyde, modifying a literature procedure [2]. Crystallization of the crude Wittig adduct, obtained in 85% yield as a 3:1 *Z/E* mixture, afforded the pure (*Z*)-isomer **7b** (Scheme 2). The mother liquors were either flash-chromatographed, to give the pure **7a** and **7b**, or directly hydrogenated, after removal of the protective silyl groups, to combretastatin B-1 (**10**).

The protective *tert*-butyldimethylsilyl groups in compounds **7a** and **7b** were easily and quantitatively removed with tetrabutylammonium fluoride, and afforded combretastatin A-1 (**11b**) and the corresponding (*E*)-isomer **11a**.

[2] The Wittig reaction is a modification of a synthesis reported in the literature, which used the phosphonium salt from 3,4,5-trimethoxybenzyl bromide [12]. Unlike the corresponding chloride, which is a stable and commercially available product, 3,4,5-trimethoxybenzyl bromide, synthesized in 60% yield from the corresponding alcohol and hydrobromic acid, is unstable and difficult to purify by chromatography or crystallization.

(*Z*)- and (*E*)-3-*O*-(*tert*-Butyldimethylsilyl)combretastatin A-4 (**8b** and **8a**) were obtained in 75% yield (2.6:1 *Z/E* ratio) by reaction of triphenyl(3,4,5-trimethoxybenzyl)phosphonium chloride and 3-*O*-(*tert*-butyldimethylsilyl)isovanillin [3]. Analogously (*E*)- and (*Z*)-2-*O*-(*tert*-butyldimethylsilyl)combretastatin *iso*-A-4 (**9a** and **9b**) were synthesized in 80% yield (2.2:1 *Z/E* ratio) from triphenyl(3,4,5-trimethoxybenzyl)phosphonium chloride and 2-*O*-(*tert*-butyldimethylsilyl)-4-methoxysalicylaldehyde. Removal of the *tert*-butyldimethylsilyl groups in compounds **8** and **9** with tetrabutylammonium fluoride afforded combretastatin A-4 (**12**) and combretastatin *iso*-A-4 (**13**).

The glucosylation, which can be troublesome with phenols because of the very low reactivity of the phenolic moiety as glycosyl acceptor, was tested under a variety of experimental conditions. Additional problems in this case were the protection of the phenolic groups not involved in the glucosylation, mono- versus di-glucosylation (resveratrol), regioselectivity (combretastatins A-1 and B-1), and stereoselectivity (related to the requirement of a β-D-glucoside).

The glucosylation step was first performed on the resveratrol derivative **5a**. Aqueous bases under phase-transfer catalysis gave the best results in terms of yields and convenience (use of a commercially available sugar). Thus refluxing a chloroform solution of **5a**, tetra-*O*-acetyl-α-D-glucopyranosyl bromide, and benzyltriethylammonium chloride with aqueous sodium hydroxide afforded the monoglucoside **14a** (36%), a small amount of diglucoside **15a** (13%), and unreacted aglycon (50%) which could be quite easily separated and recycled. The glucosylation was stereoselective and gave exclusively the β-D-glucopyranoside. The use of non-aqueous bases in dry solvents at room temperature produced sluggish reactions, possibly due to poor solubility of the phenolate ion. Mixtures that were difficult to separate were obtained at higher temperatures. Unsatisfactory results were also obtained using phenyl 2,3,4,6-tetra-*O*-acetyl-α,β-D-glucopyranosyl sulfoxide as glucosyl donor, a procedure recommended for the glycosylation of less reactive substrates such as phenols [14]. A mixture of several unidentified products was ob-

[3] While this manuscript was in preparation a similar synthesis was reported, the only difference being the use of the phosphonium bromide instead of the more stable and commercially available phosphonium chloride [13].

tained, possibly because of the sensitivity of the stilbene double bond to the required acid promoter.

Deacetylation of the glucoside **14a** with sodium methoxide in methanol (see Scheme 3) gave 4′-*O*-methylresveratrol 3-β-D-glucoside (4′-*O*-methylpiceid) in quantitative yield. 4′-*O*-Methylpiceid (**16a**) is a natural product, previously isolated from various sources, which has shown moderate α-D-glucosidase inhibitory activity [7]b. Removal of the protecting methyl group at the 4′ position was carried out under non-acidic conditions to avoid interference of acids with the stilbene double bond. Thus treatment of **16a** with sodium ethanethiolate in dimethylformamide [15] afforded resveratrol 3-β-D-glucoside (**3**, piceid), identical in all respects to an authentic sample.

The combretastatin series presents an additional problem of regioselectivity; the glucosylation step was exhaustively studied on combretastatin B-1 (**10**). Several approaches have been tested which can be summarized as follows: (*1*) the substitution of a leaving group (Br) at the anomeric centre of a glucosyl donor by a phenolate residue of the aglycon in an S_N2 process; (*2*) a promoter-dependent activation of a leaving group (Br [16], $OSiR_3$ [17], $OC(NH)CCl_3$ [18], SO_2R [14], OAc [19]) at the anomeric centre and substitution by the aglycon; (*3*) the use of a glucosylidene carbene [20], generated by thermal decomposition of a D-glucosylidene-derived diazirine, which does not require any promoter-dependent activation.

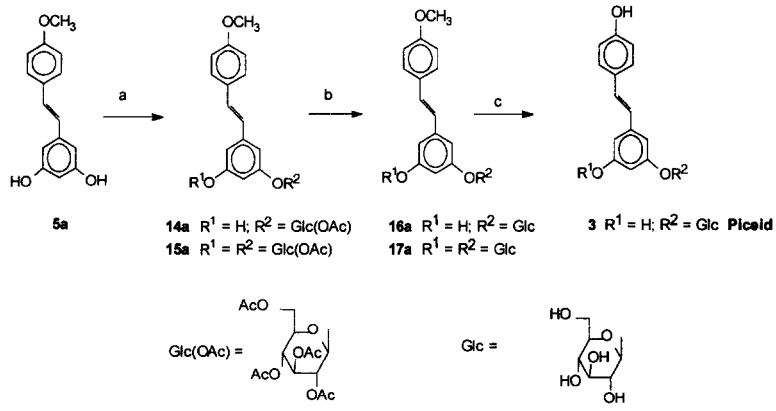
As was found in the resveratrol series, phase-transfer catalysis gave the best results, and proceeded under milder conditions compared with resveratrol. The reaction of combretastatin B-1 with tetra-*O*-acetyl-α-D-glucopyranosyl bromide, performed at 0 °C (to avoid β-elimination in the glucosyl bromide [21]), afforded the monoglucosides **18** and **19** (3.2:1 ratio, 50% total yield) and unreacted aglycon, which could be quite easily separated and recycled. Aqueous bases, if not used under phase-transfer catalysis, were less effective, had to be used in excess, and produced side-products by partial hydrolysis of the protective *O*-acetyl groups. Occasionally the 3′-β-D-glucoside tetraacetate of 2′-*O*-acetylcombretastatin B-1 was detected in significant amounts. O-Acetylation has been already observed as a side-reaction with fully acetylated glycosyl halides, the acetyl group involved originating from the position 2 of the glycosyl halide [16]b [4].

The other approaches were less satisfactory since they required the preparation of functionalized sugar derivatives, dry solvents, and also acid catalysis, without any significant improvement of the yields.

The reaction with 2,3,4,6-tetra-*O*-benzylglucosylidene carbene afforded complex mixtures of regio- and stereo-isomers which, after debenzylation with palladium hydroxide on carbon and cyclohexene as the hydrogen donor [22], were partially separated by flash chromatography. A further drawback of this approach was the preparation of the glucosylidene azirine via a multistep sequence, albeit with high yields.

The results obtained with combretastatin B-1 were then applied to (*Z*)- and (*E*)-combretastatin A-1. Under phase-transfer catalysis, the glucosylation of

[4] Non-nucleophilic bases (lithium diisopropylamide, BuLi, NaH, KH) in dry solvents have been reported to produce sluggish reactions and to afford the 3′-β-D-glucoside with yields increasing with increasing size of the metallic counterion [11].



Scheme 3. (a) $Et_3(PhCH_2)N^+Br^-$, tetra-*O*-acetyl-α-D-glucopyranosyl bromide, NaOH, $CHCl_3$, 60 °C. (b) MeONa, MeOH, 25 °C. (c) EtSNa, DMF.

combretastatin A-1 (**11b**) afforded the monoglucosides **21** (13%) and **22** (37%), and unreacted aglycon (50%). Only monoglucosides were obtained from both combretastatin B-1 and combretastatin A-1. Furthermore, the glucosylation was stereoselective and gave exclusively the β-D-glucoside. The reaction was moderately regioselective and gave a ca. 3:1 mixture of the 3′-β-D-glucoside and 2′-β-D-glucoside, a result of synthetic relevance since the unnatural 3-β-D-glucosides proved to be, in vitro, more active than the corresponding 2-β-D-glucosides.

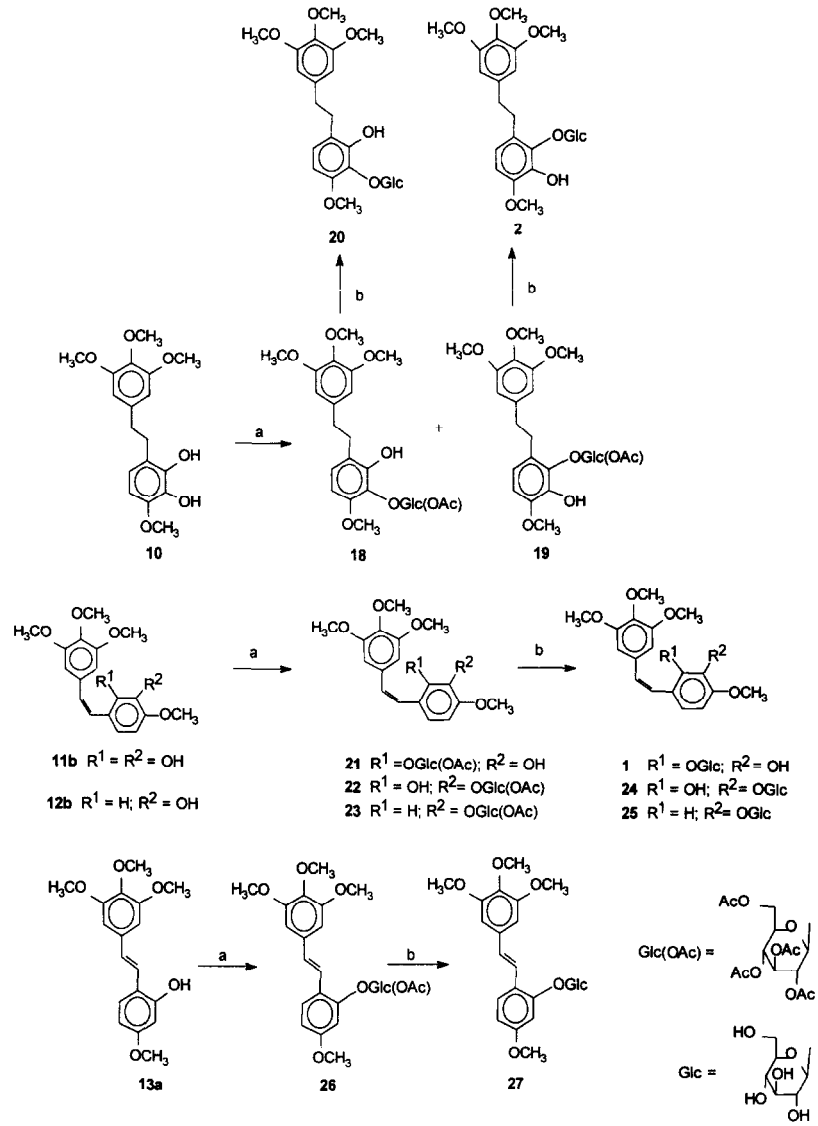
Under the same experimental conditions, combretastatin A-4 (**12b**) gave the glucoside **23** in 50% yield.

The position of the hydroxyl group and the stereochemistry of the double bond influenced the glucosylation yield which rose to 70% in the case of (*E*)-combretastatin *iso*-A-4 (**13a**).

Deacetylation of **18** and **19** with sodium methoxide in methanol quantitatively afforded the 3′-β-D-glucoside **20** and the natural 2′-β-D-glucoside **2**. Under the same experimental conditions, deacetylation of the tetra-*O*-acetyl-glucosides **21**, **22**, **23**, and **26** quantitatively afforded the glucosides **1**, **24**, **25**, and **27** (see Scheme 4).

Biological activities.—Several of the compounds synthesized were tested with respect to different types of biological activities.

(a) Cytostatic and cytotoxic activity. Combretastatin B-1 (**10**), the corresponding 2′-β-D-glucoside **2**, and combretastatin A-1 (**11b**) were tested for in vitro grown inhibition of L1210 mouse leukaemia cells.



Scheme 4. (a) $Et_3(PhCH_2)N^+Br^-$, tetra-*O*-acetyl-α-D-glucopyranosyl bromide, NaOH, $CHCl_3$, 0 °C. (b) MeONa, MeOH, 25 °C.

Combretastatin B-1 showed a lower cytostatic activity (IC_{50} 10 μM) with respect to (*E*)-combretastatin A-1 (**11a**) (IC_{50} 0.6μM). The activity was further reduced, by glucosylation, in the 2′-β-D-glucoside **2** (IC_{50} 20 μM). Both **10** and its 2′-β-D-glucoside also induced a drastic change in the distribution of cells in the various phases of the cell cycles (most cells at the end of the treatment were in late S-G2M phase whereas most control cells were in G1), and induced the appearance of a new tetraploid cell population, an effect already reported for antimitotic agents and other DNA-interacting compounds. They also showed cytotoxic activity [2]a. Combretastatins A-1, B-1, A-4, (*E*)-*iso*-A-4, and the corresponding glucosides (2′- and 3′-β-D-glucosides) were also tested for in vitro cytotoxicity with respect to the B16F10 cancer cell-line. The glucosides were, in general, less active than the corresponding aglycons. The highest activity was observed for combretastatin A-4 (IC_{50} 0.0002 μM), followed by its β-D-glucoside (IC_{50} 0.047 μM). The presence of an additional hydroxyl group in combretastatin A-1 derivatives depressed the cytotoxic activity. Furthermore, the non-natural 3′-β-D-glucoside **24** (IC_{50} 0.15 μM) was five times more active than the natural 2′-D-glucoside **1** (IC_{50} 0.79 μM). Reduction of the stilbene double bond further decreased the cytotoxic activity, as shown by combretastatin B-1 (IC_{50} 1.9 μM), and the 3′- and the 2′-β-D-glucosides (IC_{50} 5.2 and 10 μM, respectively) [5].

(b) Antimitotic activity. Antimitotic activity is related to the ability of a drug to interact with tubulin (the protein connected to the formation of the mitotic spindle) with consequent inhibition of the polymerization/depolymerization of the protein and blocking of the cellular replication. The behaviour with respect to the L1210 cell-line of combretastatin A-1 and B-1 (more active than the corresponding glucosides) resembled that of podofillotoxin and β-peltatin, drugs known to inhibit the polymerization of tubulin [2]a. Combretastatins A-4, A-1, B-1, and their 2′- and 3′-β-D-glucosides were therefore tested in vitro with respect to their ability in promoting tubulin polymerization. Combretastatin A-1, combretastatin A-4 (46% of tubulin disassembly at 100 μM), and to a minor extent combretastatin B-1 (73% of tubulin disassembly at 1 mM) were effective on the microtubule assembly, whilst the corresponding glucosides were inactive. The 2′- and 3′-β-D-glucosides of combretastatin A-1, by contrast, were effective on microtubule disassembly (28 and 14%, respectively, of retained polymerization in the presence of calcium chloride which induces microtubule disassembly), even if less significantly active than taxol [5].

(c) Neurotoxic activity. In order to investigate the hiccuping effect produced by Combretum species and the therapeutic properties of these plants, several compounds were tested with respect to the excitability properties of dorsal root ganglion neurons [23]: α,β-dihydro-3,5-dihydroxy-4′-methoxystilbene (**5a**), (*Z*)- and (*E*)-combretastatins A-1 (**11b** and **11a**), combretastatin B-1 (**10**) and the corresponding 2′,3′-di-*O*-acetyl- and 2′-glucoside derivatives. The dihydrostilbene **5a** proved to be the most active. In the combretastatin series, **10**, **11a**, and **11b** induced, in different degrees, a significant change in the excitability of the sensory neurons, combretastatin B-1 being the most effective compound. The glucoside of combretastatin B-1 was found to be inactive, whereas a 50% loss of activity resulted from acetylation of the phenolic groups in combretastatin B-1. The stereochemistry of the stilbene double bond had no effect on activity since combretastatin A-1 and the corresponding *E*-isomer showed the same behaviour.

The effects were very selective for the outward potassium currents with only minor inhibitions of the other Na^+ and Ca^{2+} ion channels.

(d) Antiplatelet aggregation activity. (*E*)-Resveratrol 3-β-D-glucoside (**3**), tested in vitro on human blood, has shown a significant inhibitory effect on platelet aggregation induced by collagen (IC_{50} 69 μM), adrenalin (IC_{50} 102 μM), and to a minor extent by arachidonic acid (IC_{50} 149 μM) and by ADP (IC_{50} 218 μM) [4].

3. Experimental

Starting materials and procedures.—Triphenylphosphine, benzyltriethylammonium chloride, 4-methoxybenzyl chloride, and 4-hydroxybenzyl alcohol were purchased from Aldrich and were used as received. 3,4,5-Trimethoxybenzyl chloride was purchased from Fluka and used as received. Tetra-*O*-acetyl-α-D-glucopyranosyl bromide was purchased from Sigma and used as received. 2,3-Di-(*tert*-butyldimethylsilyloxy)-4-methoxybenzaldehyde was prepared according to the literature [12]. Reagent grade tetrahydrofuran (THF), 1,2-dimethoxyethane, and pyridine were refluxed over $LiAlH_4$ and dis-

[5] Biological assays were made at Pharmacia Carlo Erba, Milano, Italy.

tilled. Reagent grade CH_2Cl_2 was refluxed over P_2O_5 and distilled. Reagent grade MeOH was refluxed over CaH_2, distilled, refluxed over Mg, distilled, and kept over 3 Å molecular sieves. Reagent grade dimethylformamide (DMF) was distilled at low pressure under N_2 and kept over 4 Å molecular sieves.

^1H NMR spectra were obtained with Varian L-200 and Bruker AC-300 instruments. IR spectra were recorded with a Perkin–Elmer 681 spectrometer and mass spectra with a VG 7070 E9 spectrometer. Melting points were determined with a Büchi 535 apparatus, optical rotations were measured with a Perkin–Elmer 241 polarimeter (*c*, g/mL), and the microanalyses for the new compounds were determined with a Perkin–Elmer 240 Elemental Analyzer. Flash-column chromatography was performed on silica gel (Merck Kieselgel 60, 230–400 mesh ASTM). TLC was carried out on silica gel plates (E. Merck 60 F_{254}); zones were detected visually by ultraviolet irradiation (254 nm) or by spraying with 9:1 MeOH–H_2SO_4 followed by heating at 100 °C.

All reactions were carried out at 25 °C in a dry N_2 atmosphere, using glassware dried by flaming in a stream of dry N_2.

(4-Methoxybenzyl)triphenylphosphonium chloride.—A soln of triphenylphosphine (6.5 g, 25 mmol) in toluene (50 mL) was added to a stirred soln of 4-methoxybenzyl chloride (3.9 g, 25 mmol), and stirring was continued overnight. The phosphonium chloride which separated was collected and crystallized from EtOH–toluene to give colourless prisms: mp 238–240 °C; ^1H NMR ($CDCl_3$): δ 4.66 (s, 3 H, OMe), 5.30 (d, 2 H, *J* 15 Hz, CH_2), 6.68 and 6.98 (d, 4 H, A_2B_2 system, $J_{2,3} = J_{5,6} = 8.5$ Hz, H-2, H-3, H-5, and H-6), 7.45–7.90 (15 H, PPh_3); FABMS: *m/z* 382 ($M^+ - HCl$). Anal. Calcd for $C_{26}H_{24}ClOP$: C, 74.53; H, 5.78. Found: C, 72.86; H, 4.50.

The mother liquor was heated at reflux again and the procedure was repeated until the complete precipitation of the phosphonium salt (total yield 85%).

Triphenyl(3, 4, 5 - trimethoxybenzyl)phosphonium chloride.—The title compound was prepared in 80% yield from triphenylphosphine and 3,4,5-trimethoxybenzyl chloride as described above for (4-methoxybenzyl)triphenylphosphonium chloride: colourless needles; mp 240–242 °C (EtOH–toluene); ^1H NMR ($CDCl_3$): δ 3.45 (s, 6 H, 2 × OMe), 3.70 (s, 3 H, OMe), 5.45 (d, 2 H, *J* 15 Hz, CH_2), 6.41 (bs, 2 H, H-2 and H-6), 7.52–7.78 (m, 15 H, PPh_3); FABMS: *m/z* 442 ($M^+ - HCl$). Anal. Calcd for $C_{28}H_{28}ClO_3P$: C, 70.22; H, 5.89. Found: C, 70.75; H, 6.03.

*3,5-Di-(*tert*-butyldimethylsilyloxy)benzaldehyde.*—*N,N*-Diisopropylethylamine (1.6 mL, 9 mmol) was added to a stirred soln of 3,5-dihydroxybenzaldehyde (0.41 g, 3.0 mmol) in DMF (5 mL) followed by *tert*-butyldimethylsilyl chloride (0.99 g, 6.7 mmol). The reaction mixture was stirred at room temperature for 30 min. Ice was added and the mixture was extracted three times with diethyl ether (3 × 15 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (2 × 10 mL), satd aq NaCl (10 mL), and water (20 mL), and the solvent evaporated under reduced pressure to give the silyl derivative as a chromatographically homogeneous oil (1.0 g, quantitative yield); ^1H NMR ($CDCl_3$): δ 0.20 (s, 12 H, 4 × MeSi), 0.93 (s, 18 H, 2 × ^{t}BuSi), 6.65 (dd, 1 H, $J_{4,2}$ 2.3, $J_{4,6}$ 2.3 Hz, H-4), 6.95 (d, 2 H, H-2 and H-6), 9.85 (s, 1 H, CHO); MS: *m/z* 366 (M^+). Anal. Calcd for $C_{19}H_{34}O_3Si_2$: C, 62.22; H, 9.35. Found: C, 62.45; H, 9.42.

*2-(*tert*-Butyldimethylsilyloxy)-4-methoxybenzaldehyde.*—The title compound was prepared in 85% yield from 2-hydroxy-4-methoxybenzaldehyde as described above for 3,5-di-(*tert*-butyldimethylsilyloxy)benzaldehyde; ^1H NMR ($CDCl_3$): δ 0.25 (s, 6 H, 2 × MeSi), 0.95 (s, 9 H, ^{t}BuSi), 3.8 (s, 3 H, OMe), 6.31 (d, 1 H, $J_{3,5}$ 2.6 Hz, H-3), 6.55 (dd, 2 H, $J_{5,6}$ 8.4 Hz, H-5), 7.75 (d, 1 H, H-6), 9.85 (s, 1 H, CHO); MS: *m/z* 266 (M^+). Anal. Calcd for $C_{14}H_{22}O_3Si$: C, 63.18; H, 8.33. Found: C, 63.40; H, 8.38.

*3-(*tert*-Butyldimethylsilyloxy)-4-methoxybenzaldehyde.*—The title compound was prepared in 83% yield from 3-hydroxy-4-methoxybenzaldehyde as described above for 3,5-di-(*tert*-butyldimethylsilyloxy)benzaldehyde; ^1H NMR ($CDCl_3$): δ 0.15 (s, 6 H, 2 × MeSi), 0.95 (s, 9 H, ^{t}BuSi), 3.95 (s, 3 H, OMe), 6.95 (d, 1 H, $J_{5,6}$ 8.2 Hz, H-5), 7.34 (d, 1 H, $J_{2,6}$ 1.9 Hz, H-2), 7.4 (dd, 1 H, H-6), 9.85 (s, 1 H, CHO); MS: *m/z* 266 (M^+). Anal. Calcd for $C_{14}H_{22}O_3Si$: C, 63.18; H, 8.33. Found: C, 63.30; H, 8.39.

*(*E*)- and (*Z*)-3,5-Di-(*tert*-butyldimethylsilyloxy)-4'-methoxystilbene [(*E*) - and (*Z*) - 3, 5 - di - O - (*tert* - butyldimethylsilyl) - 4' - O - methylresveratrol]* (**4a** *and* **4b**).—Butyllithium (4.5 mL, 1.6 M in hexane, 7.17 mmol) was added dropwise to a suspension of (4-methoxybenzyl)triphenylphosphonium chloride (3.9 g, 7.17 mmol) in THF (110 mL) at 15 °C. The resulting reddish soln was allowed to warm at room temperature and stirred for an additional 30 min. 3,5-Di-(*tert*-butyldimethylsilyloxy)benzaldehyde (2.64 g, 7.17 mmol) was added, and the reaction mixture was stirred for 1 h, diluted with ice-cold

water (2 × 50 mL), and extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed with water (2 × 50 mL), and the solvent was removed under reduced pressure to afford a mixture of (*E*)- and (*Z*)-isomers **4a** and **4b** (*E/Z* 2.3:1). Flash chromatography over silica gel (99:1 hexane–EtOAc) afforded a small amount of pure (*Z*)-isomer **4b** (0.67 g, 1.43 mmol, 20%) and a mixture of (*E*)- and (*Z*)-isomers (2.64 g, 5.6 mmol, 78%). Due to the difficult separation of **4a** and **4b**, the mixture was directly desilylated.

4a (identified in the *E/Z* mixture); ^{1}H NMR ($CDCl_3$): δ 0.2 (s, 12 H, 4 × SiMe), 0.98 (s, 18 H, 2 × ^{t}BuSi), 3.8 (s, 3 H, OMe), 6.21 (dd, 1 H, $J_{4,2} = J_{4,6} = 2.5$ Hz, H-4), 6.59 (d, 1 H, H-2), 6.60 (d, 1 H, H-6), 6.85 (d, 2 H, $J_{3',2'} = J_{5',6'} = 8.8$ Hz, H-3′ and H-5′), 6.90 and 6.93 (AB system, 2 H, *J* 16 Hz, CH=CH), 7.40 (d, 2 H, H-2′ and H-6′).

4b; colourless syrup; ^{1}H NMR ($CDCl_3$): δ 0.10 (s, 12 H, 4 × SiMe), 0.9 (s, 18 H, 2 × ^{t}BuSi), 3.75 (s, 3 H, OCH_3), 6.16 (dd, 1 H, $J_{4,2} = J_{4,6} = 2.2$ Hz, H-4), 6.31 (d, 1 H, H-2), 6.32 (d, 1 H, H-6), 6.45 and 6.48 (AB system, 2 H, *J* 12 Hz, CH=CH), 6.74 and 7.20 (A_2B_2 system, 4 H, $J_{3',2'} = J_{5',6'} = 8.5$ Hz, H-3′, H-5′, H-2′, and H-6′); MS: *m/z* 470 (M^+). Anal. Calcd for: $C_{27}H_{42}O_3Si_2$: C, 68.86; H, 8.99. Found: C, 68.99; H, 9.03.

(E)- and (Z)-3,5-Dihydroxy-4′-methoxystilbene [(E)- and (Z)-4′-O-methylresveratrol] (**5a** *and* **5b**). —To a mixture of **4a** and **4b** (4.6 g, 9.6 mmol) in THF (85 mL) was added tetrabutylammonium fluoride (25 mL of a 1 M soln in THF), and the mixture was stirred at room temperature for 15 min. Ethyl ether was added (50 mL), the soln was washed with water (2 × 30 mL), and the solvent was removed under reduced pressure. The residue was filtered over silica gel to afford a mixture of **5a** and **5b** (2.34 g, quantitative), which was crystallized from $CHCl_3$ and afforded pure (*E*)-isomer **5a** (0.72 g, 2.98 mmol, 31%). The mother liquors (1.62 g) were flash-chromatographed over silica gel (99:1 hexane–EtOAc) and afforded **5a** (0.87 g, 3.58 mmol, 37.3%) and **5b** (0.68 g, 2.58 mmol, 29.6%).

5a; colourless prisms; mp 176–178 °C (EtOAc–hexane); ^{1}H NMR (Me_2SO-d_6): δ 3.79 (s, 3 H, OMe), 6.18 (dd, 1 H, $J_{4,2} = J_{4,6} = 1.5$ Hz, H-4), 6.45 (d, 2 H, H-2 and H-6), 6.93 (d, 2 H, $J_{3',2'} = J_{5',6'} = 9.6$ Hz, H-3′ and H-5′), 6.94 and 6.98 (AB system, 2 H, *J* 16.4 Hz, CH=CH), 7.51 (d, 2 H, H-2′ and H-6′), 9.22 (bs, 2 H, exchanges with D_2O, OH); ^{13}C NMR (Me_2SO-d_6): δ 55.36 (q), 102.06 (d), 2 × 104.63 (d), 113.90 (s), 2 × 114.40 (d), 126.80 (d), 2 × 127.98 (d), 129.84 (d), 139.35 (s), 2 × 158.53 (s), 159.14 (s); MS: *m/z* 242 (M^+). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.35; H, 5.83. Found: C, 74.44; H, 5.90.

5b; colourless syrup; ^{1}H NMR ($CDCl_3$): δ 3.76 (s, 3 H, OMe), 5.68 (bs, 2 H, exchanges with D_2O, OH), 6.19 (dd, 1 H, $J_{4,2} = J_{4,6} = 2.1$ Hz, H-4), 6.31 (d, 2 H, H-2 and H-6), 6.43 and 6.48 (AB system, 2 H, *J* 11.5 Hz, CH=CH), 6.75 (d, 2 H, $J_{3',2'} = J_{5',6'} = 9.5$ Hz, H-3′ and H-5′), 7.19 (d, 2 H, H-2′ and H-6′); ^{13}C NMR ($CDCl_3$): δ 55.86 (q), 102.52 (d), 2 × 109.0 (d), 2 × 114.40 (d), 129.0 (d), 130.37 (s), 2 × 130.95 (d), 131.0 (d), 140.75 (s), 2 × 157.54 (s), 159.37 (s); MS: *m/z*: 242 (M^+). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.35; H, 5.83. Found: C, 74.75; H, 5.98.

α,β-Dihydro-3,5-dihydroxy-4′-methoxystilbene (**6**). —A mixture of the isomers **5a** and **5b** (3.6 mmol) in MeOH (100 mL) was hydrogenated for 12 h at room temperature at 5 atm over 5% Pd-C (0.3 g). The catalyst was filtered off through Celite and washed with MeOH, and the solvent was removed under reduced pressure to give chromatographically homogeneous **6** (silica gel; 7:3 hexane–EtOAc) (0.75 g, 85%); amorphous powder; ^{1}H NMR ($CDCl_3$): δ 3.80 (s, 3 H, OMe), 5.60 (bs, 2 H, exchanges with D_2O, OH), 6.22 (s, 1 H, H-4), 2.7–2.9 (m, 4 H, CH_2CH_2), 6.25 (s, 1 H, H-2), 6.28 (s, 1 H, H-6), 6.83 (d, 2 H, $J_{3',2'} = J_{5',6'} = 8.5$ Hz, H-3′ and H-5′), 7.10 (d, 2 H, H-2′ and H-6′); MS: *m/z* 244 (M^+). Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.73, H, 6.61. Found: C, 73.53; H, 6.53.

*(E)- and (Z)-2′,3′-Di-(*tert*-butyldimethylsilyloxy)-3,4,4′,5-tetramethylstilbene [(E)- and (Z)-2′,3′-di-O-(*tert*-butyldimethylsilyl)combretastatin A-1]* (**7a** *and* **7b**).—The title compounds were prepared from triphenyl(3,4,5-trimethoxybenzyl)phosphonium chloride and 2,3-di-(*tert*-butyldimethylsilyloxy)-4-methoxybenzaldehyde as described above for 3,5-di-(*tert*-butyldimethylsilyloxy)-4′-methoxystilbene. A mixture of (*E*)- and (*Z*)-isomers **7a** and **7b** (85% total yield) in a 1:3 ratio was obtained. The crude product was crystallized from EtOH and gave pure (*Z*)-isomer. The mother liquors were flash-chromatographed (19:1 hexane–EtOAc).

7a; colourless plates (hexane–EtOAc); mp 138–140 °C, lit. 139–140 °C [12]; ^{1}H NMR ($CDCl_3$): δ 0.11 (s, 6 H, 2 × SiMe), 0.13 (s, 6 H, 2 × SiMe), 0.99 (s, 9 H, Si^{t}Bu), 1.09 (s, 9 H, Si^{t}Bu), 3.79 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 3.88 (s, 6 H, 2 × OMe), 6.56 (d, 1 H, $J_{5',6'}$ 8.8 Hz, H-5′), 6.72 (s, 2 H, H-2 and H-6), 6.80 (d, 1 H, *J* 16.4 Hz, CH=CH), 7.20 (d, 1 H, H-6′), 7.31 (d, 1 H, CH=CH); MS: *m/z* 560 (M^+).

7b; colourless needles (hexane–EtOAc); mp 114–116 °C, lit. 117–118 °C [12]; ^{1}H NMR ($CDCl_3$): δ 0.11 (s, 6 H, 2 × SiMe), 0.19 (s, 6 H, 2 × SiMe), 0.99 (s, 9 H, Si^{t}Bu), 1.04 (s, 9 H, Si^{t}Bu), 3.67 (s, 6 H, 2 × OMe), 3.74 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 6.35 and 6.60 (AB system, 2 H, *J* 12.0 Hz, CH=CH), 6.36 (d, 1 H, $J_{5',6'}$ 8.7 Hz, H-5'), 6.62 (s, 2 H, H-2 and H-6), 6.92 (d, 1 H, H-6'); MS: *m/z* 560 (M^+).

(Z)-2',3'-Dihydroxy-3,4,4',5-tetramethoxystilbene [combretastatin A-1] (**11b**).—The derivative **7b** was desilylated as described above for 3,5-dihydroxy-4'-methoxystilbene and afforded pure **11b** in quantitative yield: colourless plates (EtOAc–MeOH); mp 113–115 °C, lit. 114–115 °C [12]; ^{1}H NMR ($CDCl_3$): δ 3.60 (s, 6 H, 2 × OMe), 3.76 (s, 3 H, OMe), 3.77 (s, 3 H, OMe), 5.44 (s, 1 H, exchanges with D_2O, OH), 5.52 (s, 1 H, exchanges with D_2O, OH), 6.31 (d, 1 H, $J_{5',6'}$ 8.6 Hz, H-5'), 6.45 and 6.52 (AB system, 2 H, *J* 12.0 Hz, CH=CH), 6.46 (s, 2 H, H-2, H-6), 6.72 (d, 1 H, H-6'); ^{13}C NMR ($CDCl_3$): δ 56.46 (q), 2 × 56.75 (q), 61.50 (q), 103.50 (d), 2 × 106.49 (d), 118.34 (s), 120.94 (d), 124.65 (d), 130.88 (d), 132.89 (s), 133.80 (s), 137.90 (s), 142.15 (s), 146.91 (s), 2 × 153.40 (s); ^{13}C NMR (Me_2SO-d_6): δ 55.46 (q), 2 × 56.75 (q), 61.50 (q), 103.50 (d), 106.49 (d), 106.49 (d), 118.34 (s), 120.94 (d), 124.65 (d), 130.88 (d), 132.89 (s), 133.80 (s), 137.90 (s), 142.15 (s), 146.91 (s), 153.16 (s), 153.40 (s); MS: *m/z*: 332 (M^+). Anal. Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.06. Found: C, 64.90; H, 6.08.

α,β-Dihydro-2',3'-dihydroxy-3,4,4',5-tetramethoxystilbene [combretastatin B-1] (**10**).—A mixture of (*Z*)- and (*E*)-isomers of combretastatin A-1 (**11a** and **11b**) was hydrogenated as described above for **6** and gave combretastatin B-1 as a chromatographically homogeneous colourless syrup (silica gel; 7:3 hexane–EtOAc) (85% yield); ^{1}H NMR ($CDCl_3$): δ 2.86 (m, 4 H, CH_2CH_2), 3.84 (s, 3 H, OMe), 3.85 (s, 6 H, 2 × OMe), 3.87 (s, 3 H, OMe), 5.47 (bs, 2 H, exchanges with D_2O, OH), 6.40 (d, 1 H, $J_{5',6'}$ 8.5 Hz, H-5'), 6.43 (s, 2 H, H-2 and H-6), 6.60 (d, 1 H, H-6'); ^{13}C NMR ($CDCl_3$): δ 31.77 (t), 36.60 (t), 2 × 55.93 (q), 56.04 (q), 60.77 (q), 102.30 (d), 105.25 (d), 105.27 (d), 120.00 (d), 121.37 (s), 132.13 (s), 135.85 (s), 138.08 (s), 142.00 (s), 145.21 (s), 2 × 152.86 (s); ^{13}C NMR (Me_2SO-d_6): δ 31.59 (t), 36.20 (t), 2 × 55.78 (q), 55.84 (q), 60.04 (q), 102.72 (d), 2 × 105.47 (d), 119.01 (d), 121.43 (s), 133.76 (s), 135.53 (s), 138.02 (s), 143.96 (s), 146.81 (s), 2 × 152.70 (s). MS: *m/z* 334 (M^+). Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63. Found: C, 64.86; H, 6.60.

(E)- and (Z)-3'-(tert-Butyldimethylsilyloxy)-3,4,4',5-tetramethoxystilbene [(E)- and (Z)-3'-(tert-butyldimethylsilyl)combretastatin A-4] (**8a** *and* **8b**).—The title compounds were prepared from 3-(*tert*-butyldimethylsilyloxy)-4-methoxybenzaldehyde according to the Wittig procedure described above for the preparation of **7a** and **7b**. The crude material was purified by flash chromatography (silica gel; 4:1 hexane–EtOAc) and afforded pure **8a** (21%) and **8b** (54%).

8a; colourless syrup; ^{1}H NMR ($CDCl_3$): 0.18 (s, 6 H, 2 × SiMe), 1.02 (s, 9 H, Si^{t}Bu), 3.82 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 3.91 (s, 6 H, 2 × OMe), 6.71 (s, 2 H, H-2 and H-6), 6.83 (d, 1 H, $J_{5',6'}$ 8.4 Hz, H-5'), 6.88 (AB system, 2 H, *J* 16.0 Hz, CH=CH), 7.03 (s, 1 H, H-2'), 7.05 (d, 1 H, H-6'); ^{1}H NMR (C_6D_6): δ 0.28 (s, 6 H, SiMe), 1.18 (s, 9 H, Si^{t}Bu), 3.38 (s, 3 H, OMe), 3.48 (s, 6 H, 2 × OMe), 3.92 (s, 3 H, OMe), 6.65 (d, 1 H, $J_{5',6'}$ 8.6 Hz, H-5'), 6.73 (s, 2 H, H-2 and H-6), 7.13 (AB system, 2 H, *J* 17.0 Hz, CH=CH), 7.14 (dd, 1 H, $J_{6',2'}$ 1.2 Hz, H-6'), 7.42 (d, 1 H, H-2'); MS: *m/z* 430 (M^+).

8b; colourless syrup; ^{1}H NMR ($CDCl_3$): δ 0.05 (s, 6 H, 2 × SiMe), 0.92 (s, 9 H, Si^{t}Bu), 3.69 (s, 6 H, 2 × OMe), 3.77 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), 6.45 (AB system, 2 H, *J* 13.5 Hz, CH=CH), 6.49 (s, 2 H, H-2 and H-6), 6.72 (d, 1 H, $J_{5',6'}$ 8.4 Hz, H-5'), 6.79 (d, 1 H, $J_{2',6'}$ 1.9 Hz, H-2'), 6.85 (dd, 1 H, H-6'); MS: *m/z*: 430 (M^+).

(E)- and (Z)-3-Hydroxy-3,4,4',5-tetramethoxystilbene [(E) and (Z)-combretastatin A-4] (**12a** *and* **12b**).—The silyl derivatives **8a** and **8b** were desilylated according to the procedure described for **7b** and afforded **12a** and **12b** in quantitative yields.

12a; colourless amorphous solid; ^{1}H NMR ($CDCl_3$): δ 3.86 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 3.90 (s, 6 H, 2 × OMe), 5.11 (s, 1 H, exchanges with D_2O, OH), 6.71 (s, 2 H, H-2, H-6), 6.82 (d, 1 H, $J_{5',6'}$ 8.8 Hz, H-5'), 6.88 and 6.94 (AB system, 2 H, *J* 16.3 Hz, CH=CH), 6.97 (dd, 1 H, $J_{6',2'}$ 2.1 Hz, H-6'), 7.14 (d, 1 H, H-2'); ^{13}C NMR ($CDCl_3$): δ 3 × 56.03 (q), 60.85 (q), 103.35 (d), 110.65 (d), 110.75 (d), 111.73 (d), 119.13 (d), 126.94 (d), 127.75 (d), 130.90 (s), 133.28 (s), 137.64 (s), 145.76 (s), 146.41 (s), 2 × 153.29 (s); MS: *m/z* 316 (M^+). Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.38. H, 6.42.

12b; colourless amorphous solid; mp 82–84 °C, lit. 84.5–85.5 °C [3]; ^{1}H NMR ($CDCl_3$): δ 3.70 (s, 6

H, 2 × OMe), 3.87 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 5.51 (s, 1 H, exchanges with D_2O), 6.41 and 6.47 (AB system, 2 H, *J* 12.0 Hz, CH=CH), 6.53 (s, 2 H, H-2 and H-6), 6.73 (d, 1 H, $J_{5',6'}$ 8.4 Hz, H-5'), 6.79 (dd, 1 H, $J_{6',2'}$ 2.0 Hz, H-6'), 6.93 (d, 1 H, H-2'); ^{13}C NMR ($CDCl_3$): δ 3 × 56.57 (q), 61.46 (q), 106.93 (d), 2 × 111.05 (d), 115.73 (d), 121.68 (d), 129.66 (d), 130.05 (d), 131.32 (s), 133.29 (s), 138.50 (s), 145.95 (s), 146.47 (s), 2 × 153.51 (s); MS: *m/z* 316 (M^+). Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.43; H, 6.36.

(E)- and (Z)-2'-(tert-Butyldimethylsilyloxy)-3,4,4',5-tetramethoxystilbene [(E)- and (Z)-2'-O-(tert-butyldimethylsilyl)combretastatin iso-*A-4]* (**9a** *and* **9b**).—The title compounds were prepared from 2-(*tert*-butyldimethylsilyloxy)-4-methoxybenzaldehyde according to the Wittig procedure described above for the preparation of **7a** and **7b**. The crude material was flash-chromatographed (silica gel; 7:3 hexane–EtOAc) and afforded pure **9a** (25%) and **9b** (55%).

9a; colourless oil; ^1H NMR ($CDCl_3$): δ 0.08 (s, 6 H, 2 × SiMe), 0.89 (s, 9 H, Si^{t}Bu), 3.65 (s, 3 H, OMe), 3.79 (s, 3 H, OMe), 3.83 (s, 6 H, 2 × OMe), 6.38 (bs, 1 H, H-3'), 6.39 (d, 1 H, $J_{5',6'}$ 8.7 Hz, H-5'), 6.72 (s, 2 H, H-2 and H-6), 6.84 (d, 1 H, *J* 16.1 Hz, CH=CH), 7.35 (d, 1 H, CH=CH), 7.52 (bd, 1 H, H-6'); MS: *m/z* 430 (M^+).

9b; colourless oil; ^1H NMR ($CDCl_3$): δ 0.09 (s, 6 H, 2 × SiMe), 1.12 (s, 9 H, Si^{t}Bu), 3.35 (s, 6 H, 2 × OMe), 3.67 (s, 3 H, OMe), 3.76 (s, 3 H, OMe), 6.38 (dd, 1 H, $J_{5',6'}$ 8.9 Hz, $J_{5',3'}$ 2.0 H-5'), 6.39 (d, 1 H, *J* 12.0 Hz, CH=CH), 6.40 (d, 1 H, H-3'), 6.52 (s, 2 H, H-2, H-6), 6.56 (d, 1 H, CH=CH), 7.17 (dd, 1 H, H-6'); MS: *m/z* 430 (M^+).

(E)- and (Z)-2'-Hydroxy-3,4,4',5-tetramethoxystilbene [(E)- and (Z)-combretastatin iso-*A-4* (**13a** *and* **13b**).—The silyl derivatives **9a** and **9b** were desilylated according to the procedure described above for **7b** and afforded **13a** and **13b** in quantitative yields.

13a; colourless solid (EtOAc–MeOH); mp 166–168 °C; ^1H NMR ($CDCl_3$): δ 3.80 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 3.91 (s, 6 H, 2 × OMe), 5.24 (s, 1 H, exchanges with D_2O), 6.41 (d, 1 H, $J_{3',5'}$ 2.4 Hz, H-3'), 6.48 (dd, 1 H, $J_{5',6'}$ 8.5 Hz, H-5'), 6.68 (s, 2 H, H-2 and H-6), 6.91 and 7.22 (AB system, 2 H, *J* 16.0 Hz, CH=CH), 7.41 (d, 1 H, H-6'); ^{13}C NMR ($CDCl_3$): δ 55.91 (q), 2 × 56.69 (q), 61.61 (q), 102.46 (d), 2 × 104.00 (d), 107.45 (d), 118.27 (s), 123.30 (d), 128.09 (d), 128.45 (d), 134.68 (s), 137.90 (s), 2 × 153.85 (s), 155.12 (s), 160.84 (s); MS: *m/z* 316 (M^+), 301. Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.43; H, 6.36.

13b; colourless amorphous solid; ^1H NMR ($CDCl_3$): δ 3.53 (s, 6 H, 2 × OMe), 3.75 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), 5.23 (s, 1 H, exchanges with D_2O), 6.49 (s, 1 H, H-3'), 6.52 (s, 2 H, H-2 and H-6), 6.42 and 6.64 (AB system, 2 H, *J* 12.1 Hz, CH=CH), 6.71 (d, 1 H, $J_{5',6'}$ 9.6 Hz, H-5'), 7.12 (d, 1 H, H-6'); MS: *m/z* 316 (M^+), 301. Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.40; H, 6.36.

*Typical glucosylation procedures.—(a) With 2,3,4,6-tetra-*O*-acetyl-α-*D*-glucopyranosyl bromide under phase-transfer catalysis.* A soln of the glucosyl bromide (0.851 g, 2.07 mmol) and benzyltriethylammonium bromide (0.232 g, 0.85 mmol) in $CHCl_3$ (4.5 mL) was added to a soln of **5a** (0.5 g, 2.07 mmol) in 1.25 M NaOH (2.5 mL). The two-phase reaction mixture was vigorously stirred at 60 °C for 5 h. After a second addition of NaOH soln (0.7 mL) and glucosyl bromide (0.4 g), the mixture was stirred at 60 °C for additional 5 h. Ethyl acetate was added and the resulting organic phase was successively washed with water, dried (Na_2SO_4), and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (7:3 hexane–EtOAc) to afford unreacted aglycon **5a** (0.1 g), tetra-*O*-acetyl-3-β-D-glucoside **14a** (0.38 g, 0.66 mmol, 32%), and a small amount of diglucoside **15a** (0.246 g, 0.27 mmol, 13%).

5-Hydroxy-4'-methoxy-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)stilbene (**14a**); amorphous powder; ^1H NMR ($CDCl_3$): δ 1.98 (s, 3 H, OAc), 2.0 (s, 3 H, OAc), 2.01 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 3.78 (s, 3 H, OMe), 4.15 (ddd, 1 H, $J_{5'',4''}$ 8.0, $J_{5'',6''a}$ 6.0, $J_{5'',6''b}$ 3.0 Hz, H-5''), 4.12 (dd, 1 H, $J_{6''a,6''b}$ 12.0 Hz, H-6''a), 4.22 (dd, 1 H, H-6''b), 4.90–5.58 (m, 4 H, H-1'', H-2'', H-3'', and H-4''), 6.42 (dd, 1 H, $J_{4,2}$ 2.6, $J_{4,6}$ 2.6 Hz, H-4), 6.69 (d, 2 H, H-2 and H-6), 6.83 and 7.01 (AB system, 2 H, *J* 15.7 Hz, CH=CH), 6.88 (d, 2 H, $J_{3',2'} = J_{5',6'} = 9.4$ Hz, H-3' and H-5'), 7.42 (d, 2 H, H-2' and H-6'); FABMS: *m/z* 572 (M^+). Anal. Calcd for $C_{29}H_{32}O_{12}$: C, 60.84; H, 5.63. Found: C, 60.98; H, 5.73.

4'-Methoxy-3,5-di-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)stilbene (**15a**); colourless prisms; mp 124–126 °C (molten at 102 °C); $[\alpha]_D$ +2.4° (*c* 0.07, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.04 (s, 6 H, 2 × OAc), 2.06 (s, 6 H, 2 × OAc), 2.08 (s, 6 H, 2 × OAc), 2.10 (s, 6 H, 2 × OAc), 3.83 (s, 3 H, OMe), 3.92 (ddd, 2 H, $J_{5'',4''} = J_{5''',4'''} = 8.8$, $J_{5'',6''b} = J_{5''',6'''b} = 5.2$, $J_{5'',6''a} = J_{5''',6'''a} = 2.5$ Hz, H-5'' and H-5'''), 4.12 (dd, 2 H, $J_{6''a,6''b} = J_{6'''a,6'''b} = 11.3$ Hz, H-6''a and H-6'''a), 4.29 (dd, 2 H, H-6''b and H-6'''b), 5.08–5.39 (m, 8 H,

H-1″, H-1‴, H-2″, H-2‴, H-3″, H-3‴, H-4″, and H-4‴), 6.50 (dd, 1 H, $J_{4,2}$ 2.5, $J_{4,6}$ 2.5 Hz, H-4), 6.82 (d, 2 H, H-2 and H-6), 6.85 and 7.03 (AB system, 2 H, J 16.3 Hz, CH=CH), 6.91 (d, 2 H, $J_{3',2'} = J_{5',6'} = 8.8$ Hz, H-3′ and H-5′), 7.43 (d, 2 H, H-2′ and H-6′); ^{1}H NMR (Me_2SO-d_6): δ 2.00 (s, 6 H, 2 × OAc), 2.05 (s, 6 H, 2 × OAc), 2.07 (s, 6 H, 2 × OAc), 2.08 (s, 6 H, 2 × OAc), 3.82 (s, 3 H, OMe), 4.11 (dd, 2 H, $J_{6''a,6''b} = J_{6'''a,6'''b} = 12.3$, $J_{6''a,5''} = J_{6'''a,5'''} = 2.5$ Hz, H-6a″ and H-6a‴), 4.22 (dd, 2 H, dd, $J_{6''b,5''} = J_{6'''b,5'''} =$ 5.3 Hz, H-6″b and H-6‴b), 4.30 (dd, 2 H $J_{5'',4''} = J_{5''',4'''} = 8.8$ Hz, H-5″b and H-5‴b), 5.02 (dd, 2 H, $J_{4'',3''} = J_{4''',3'''} = 8.8$ Hz, H-4″ and H-4‴), 5.08 (dd, 2 H, dd, $J_{2'',3''} = J_{2''',3'''} = 8.8$, $J_{2'',1''} = J_{2''',1'''} = 7.4$ Hz, H-2″ and H-2‴), 5.43 (dd, 2 H, H-3″ and H-3‴), 5.67 (d, 2 H, H-1″ and H-1‴), 6.51 (dd, 1 H, $J_{4,2} = J_{4,6} =$ 1.8 Hz, H-4), 6.95 (d, 2 H, H-2 and H-6), 6.98 (d, 2 H, $J_{3',2'} = J_{5',6'} = 8.8$ Hz, H-3′ and H-5′), 7.03 and 7.23 (d, 2 H, J 15.8 Hz, CH=CH), 7.56 (d, 2 H, H-2′ and H-6′). ^{13}C NMR (Me_2SO-d_6): δ 8 × 20.29 (q), 55.19 (q), 2 × 61.62 (t), 2 × 68.07 (d), 2 × 70.73 (d), 2 × 70.96 (d), 2 × 72.01 (d), 2 × 96.69 (d), 103.76 (d), 2 × 108.27 (d), 2 × 114.29 (d), 125.22 (d), 2 × 128.05 (d), 129.14 (s), 129.62 (d), 140.10 (s), 2 × 157.33 (s), 159.28 (s), 2 × 169.45 (s), 2 × 169.64 (s), 2 × 169.91 (s), 2 × 170.27 (s); FABMS: m/z 902 (M^+). Anal. Calcd for $C_{43}H_{50}O_{21}$: C, 57.21; H, 5.58. Found: C, 57.14; H, 5.57.

In the combretastatin series, the glucosylation under phase-transfer catalysis was performed as described above for **5a** with the only exception of the temperature which was kept at 0 °C.

Combretastatin B-1 (**10**) gave the starting aglycon (55%), tetra-*O*-acetyl-3-β-D-glucoside **18** (38%), and tetra-*O*-acetyl-2-β-D-glucoside **19** (12%).

α,β-Dihydro-2′-hydroxy-3,4,4′,5-tetramethoxy-3′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)stilbene (**18**); colourless solid (MeOH); mp 135–137 °C; $[\alpha]_D$ +27.0° (*c* 0.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.03 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 2.07 (s, 3 H, OAc), 2.14 (s, 3 H, OAc), 2.77–2.87 (m, 4 H, CH_2CH_2), 3.73 (m, 1 H, H-5″), 3.78 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 3.82 (s, 6 H, 2 × OMe), 4.10 (dd, 1 H, $J_{6''a,6''b}$ 12.4, $J_{6''a,5''}$ 2.6 Hz, H-6″a), 4.30 (dd, 1 H, $J_{6''b,5''}$ 5.3 Hz, H-6″b), 4.86 (dd, 1 H, $J_{1'',2''}$ 5.6, $J_{1'',3''}$ 2.2 Hz, H-1″), 5.12–5.32 (m, 3 H, H-2″, H-3″, and H-4″), 6.38 (s, 2 H, H-2 and H-6), 6.33 and 6.82 (AB system, 2 H, $J_{5',6'}$ 8.6 Hz, H-5′ and H-6′), 6.59 (s, 1 H, exchanges with D_2O, OH); ^{1}H NMR (C_6D_6): δ 1.60 (s, 3 H, OAc), 1.70 (s, 3 H, OAc), 1.72 (s, 3 H, OAc), 1.90 (s, 3 H, OAc), 2.90–3.20 (m, 5 H, H-5″, CH_2CH_2), 3.3 (s, 3 H, OMe), 3.45 (s, 6 H, 2 × OMe), 3.85 (s, 3 H, OMe), 3.86 (dd, 1 H, $J_{6''a,6''b}$ 12.2, $J_{6''a,5''}$ 2.0 Hz, H-6″a), 4.13 (dd, 1 H, $J_{6''b,5''}$ 4.4 Hz, H-6″b), 4.7 (d, 1 H, $J_{1'',2''}$ 8.0 Hz, H-1″), 5.18 (dd, 1 H, $J_{4'',3''} = J_{4'',5''} = 10.0$ Hz, H-4″), 5.38 (dd, 1 H, $J_{3'',2''}$ 10.0 Hz, H-3″), 5.50 (dd, 1 H, H-2″), 6.15 (d, 1 H, $J_{5',6'}$ 8.4 Hz, H-5′), 6.45 (s, 2 H, H-2 and H-6), 6.80 (d, 1 H, H-6′), 7.05 (s, 1 H, exchanges with D_2O, OH); ^{13}C NMR ($CDCl_3$): δ 4 × 21.10 (q), 32.05 (t), 37.05 (t), 56.5 (q), 56.70 (q), 56.71 (q), 61.4 (q), 62.3 (t), 69.0 (d), 71.8 (d), 72.8 (d), 72.9 (d), 103.55 (d), 103.7 (d), 106.3 (d), 106.4 (d), 122.5 (s), 126.7 (d), 133.7 (s), 137.0 (s), 138.6 (s), 149.1 (s), 151.3 (s), 153.6 (s), 153.7 (s), 170.0 (s), 170.7 (s), 171.0 (s), 171.02 (s); FABMS: m/z 664 (M^+). Anal. Calcd for $C_{32}H_{40}O_{15}$: C, 57.83; H, 6.07. Found: C, 57.68; H, 6.26.

α,β-Dihydro-3′-hydroxy-3,4,4′,5-tetramethoxy-2′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)stilbene (**19**); colourless amorphous solid; ^{1}H NMR ($CDCl_3$): δ 1.61 (s, 3 H, OAc), 1.72 (s, 3 H, OAc), 1.74 (s, 6 H, 2 × OAc), 2.92 (m, 2 H, CH_2CH_2), 3.20 (ddd, 1 H, $J_{5'',4''}$ 9.0, $J_{5'',6''b}$ 5.1, $J_{5'',6''a}$ 1.3 Hz, H-5″), 3.35 (s, 3 H, OMe), 3.58 (s, 6 H, 2 × OMe), 3.86 (s, 3 H, OMe), 3.89 (d, 1 H, $J_{6''a,6''b}$ 11.9 Hz, H-6″a), 4.14 (dd, 1 H, H-6″b), 4.82 (d, 1 H, $J_{1'',2''}$ 8.6 Hz, H-1″), 5.22 (dd, 1 H, $J_{3'',2''} = J_{3'',4''} = 9.0$ Hz, H-3″), 5.37 (dd, 1 H, H-4″), 5.56 (dd, 1 H, H-2″), 6.36 (s, 1 H, exchanges with D_2O), 6.42 (d, 1 H, $J_{5',6'}$ 8.6 Hz, H-5′), 6.47 (s, 2 H, H-2 and H-6), 6.60 (d, 1 H, H-6′).

The compound was directly acetylated to give a penta-*O*-acetyl derivative identical in all respects with an authentic sample [1].

(b) With phenyl 2,3,4,6-tetra-O-acetyl-α,β-D-glucopyranosyl sulfoxide. The sulfoxide (2 equiv) [14] in CH_2Cl_2 (1 mL) was added to triflic anhydride (0.6 mL) in CH_2Cl_2 (2 mL) at −78 °C, followed by 2,6-di-*tert*-butyl-4-methylpyridine in CH_2Cl_2 and combretastatin B-1 (**10**) (0.15 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was warmed to −60 °C, stirred for 2 h, allowed to warm to room temperature, and poured into aq $NaHCO_3$. The crude material was flash-chromatographed (silica gel; 3:2 hexane–EtOAc), and afforded **18** (20%) and **19** (10%).

(c) With 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide in the presence of metal triflates. A soln of combretastatin B-1 (**10**) (1 equiv) and *sym*-collidine (1 equiv) in dry CH_2Cl_2 (2 mL) was added to a suspension of glucosyl bromide (1 equiv), Sn(IV) triflate (1 equiv), and molecular sieves 4 Å in dry CH_2Cl_2 (5 mL) at room temperature. The reaction mixture was stirred for 6 h, made neutral by the

addition of aq 5% $NaHCO_3$, and filtered through Celite. The filtrate was diluted with CH_2Cl_2 (5 mL) and washed with water (5 mL), and the solvent removed under reduced pressure. The crude material was flash-chromatographed (silica gel; 3:2 hexane–EtOAc) to afford pure **18** (10%).

No glucosylation products were observed in the presence of silver triflate

*(d) With 2,3,4,6-tetra-*O*-acetyl-α-*D*-glucopyranosyl trichloroacetimidate.* To a soln of combretastatin B-1 (**10**) (0.2 mmol) and the trichloroacetimidate [18] (2 equiv) in CH_2Cl_2 (5 mL) in the dark at −50 °C was added BF_3OEt_2 (0.6 equiv) and the mixture was stirred for 1 h. The resulting soln was diluted with CH_2Cl_2 (5 mL), washed with satd aq $NaHCO_3$ and brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a crude material which was flash-chromatographed (silica gel; 3:2 hexane–EtOAc) to afford pure **18** (34%).

*(e) With 1-azi-2,3,4,6-tetra-*O*-benzyl-1-deoxy-*D*-glucopyranose.* A freshly prepared 0.3 M soln of 1-azi-2,3,4,6-tetra-*O*-benzyl-1-deoxy-D-glucopyranose [20] (1.24 mL) in dry CH_2Cl_2 was added to a mixture of combretastatin B-1 (**10**) (0.4 mmol) and molecular sieves 4 Å in dry CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature and monitored by TLC (silica gel; 4:1 hexane–EtOAc). After all diazirine had disappeared, the mixture was filtered through Celite and the solvent was removed under reduced pressure. The crude material was flash-chromatographed to afford starting material (54%) and a mixture of glucosides (25%) which was directly debenzylated with 20% $Pd(OH)_2$ on carbon (2.5:10 catalyst–substrate by weight), and cyclohexene (0.4 mL) in EtOH (1 mL) [22]. Flash chromatography of the crude material (silica gel; 9:1 $CHCl_3$–MeOH) afforded a mixture of the 2′-β-D-glucoside **2** [1] with the corresponding 2′-α-D-glucoside (total yield 5%, α/β ratio 1:1), and a mixture of the 3′-β-D-glucoside **20** [11] with the corresponding 3′-α-D-glucoside (total yield 10%, α/β ratio 1:2).

Combretastatin B-1 3′-α-D-glucopyranoside (detected in the ^1H NMR spectrum of the mixture); ^1H NMR (Me_2SO-d_6): δ 2.75 (m, 4 H, CH_2CH_2), 3.18 (m, 1 H, H-5″), 3.21–3.68 (m, 5 H, H-2″, H-3″, H-4″, H-6a″, H-6b″), 3.61 (s, 3 H, OMe), 3.63 (s, 6 H, 2 × OMe), 3.66 (s, 3 H, OMe), 4.78 (d, 1 H, $J_{1'',2''}$ 4.0 Hz, H-1″), 6.05 (s, 1 H, exchanges with D_2O), 6.40 (d, 1 H, $J_{5',6'}$ 8.0 Hz, H-5′), 6.47 (s, 2 H, H-2, H-6), 6.82 (d, 1 H, H-6′).

Combretastatin B-1 2′-α-D-glucopyranoside (detected in the ^1H NMR spectrum of the mixture); ^1H NMR (Me_2SO-d_6): δ 2.73 (m, 4 H, CH_2CH_2), 3.12–3.80 (m, 6 H, H-2″, H-3″, H-4″, H-5″, H-6a″, H-6b″), 3.61 (s, 3 H, OMe), 3.73 (s, 9 H, 3 × OMe), 4.93 (d, 1 H, $J_{1'',2''}$ 4.0 Hz, H-1″), 6.10 (s, 1 H, exchanges with D_2O), 6.47 (s, 2 H, H-2, H-6), 6.64 and 6.78 (AB system, 2 H, $J_{5',6'}$ 7.9 Hz, H-5′, H-6′).

*Combretastatin A-1 2′- and 3′-tetra-*O*-acetyl-3-β-*D*-glucosides* (**21** *and* **22**).—Glucosylation of (*Z*)-combretastatin A-1 (**11b**) under phase-transfer catalysis was carried out as described above (*a*) for combretastatin B-1 (**10**). The crude material was flash-chromatographed (silica gel; 3:2 hexane–EtOAc) and afforded **21** (13%) and **22** (37%), and starting aglycon (50%).

(*Z*)-3′-Hydroxy-3,4,4′,5-tetramethoxy-2′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)stilbene (**21**); amorphous solid; $[\alpha]_D$ −5.3° (*c* 0.43, MeOH); ^1H NMR ($CDCl_3$): δ 2.01 (s, 3 H, OAc), 2.03 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 2.11 (s, 3 H, OAc), 3.66 (s, 6 H, 2 × OMe), 3.82 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 3.86 (m, 1 H, H-5″), 4.07 (dd, 1 H, $J_{6''a,6''b}$ 13.0, $J_{6''a,5''}$ 2.2 Hz, H-6″a), 4.29 (dd, 1 H, $J_{6''b,5''}$ 4.8 Hz, H-6″b), 4.97 (d, 1 H, $J_{1'',2''}$ 8.3 Hz, H-1″), 5.05–5.38 (m, 3 H, H-2″, H-3″, and H-4″), 6.35 (s, 1 H, exchanges with D_2O, OH), 6.44 (s, 2 H, H-2 and H-6), 6.40 and 6.55 (AB system, 2 H, *J* 12.5 Hz, CH=CH), 6.56 and 6.78 (AB system, 2 H, $J_{5',6'}$ 8.9 Hz, H-5′ and H-6′); ^{13}C NMR ($CDCl_3$): δ 4 × 21.06 (q), 2 × 56.53 (q), 56.79 (q), 61.43 (q), 62.04 (t), 68.73 (d), 72.01 (d), 72.90 (d), 73.30 (d), 102.88 (d), 2 × 106.95 (d), 109.21 (d), 121.04 (d), 124.55 (s), 125.15 (d), 131.16 (d), 132.75 (s), 134.28 (s), 139.82 (s), 142.42 (s), 148.61 (s), 153.51 (s), 153.52 (s), 169.80 (s), 169.85 (s), 171 (s), 171.03 (s); FABMS: *m/z* 662 (M^+). Anal. Calcd for $C_{32}H_{38}O_{15}$: C, 58.00; H, 5.78. Found: C, 57.76; H, 5.66.

(*Z*)-2′-Hydroxy-3,4,4′,5-tetramethoxy-3′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)stilbene (**22**); colourless plates (MeOH); mp 106–110 °C; $[\alpha]_D$ +8.9° (*c* 0.090, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.03 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 2.08 (s, 3 H, OAc), 2.14 (s, 3 H, OAc), 3.68 (s, 6 H, 2 × OMe), 3.76 (m, 1 H, H-5″), 3.77 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), 4.09 (dd, 1 H, $J_{6''a,6''b}$ 12.2, $J_{6''a,5''}$ 2.2 Hz, H-6″a), 4.31 (dd, 1 H, $J_{6''b,5''}$ 5.3 Hz, H-6″b), 4.82 (dd, 1 H, $J_{1'',2''}$ 7.7, $J_{1'',3''}$ 2.2 Hz, H-1″), 5.10–5.33 (m, 3 H, H-2″, H-3″, and H-4″), 6.30 (d, 1 H, $J_{5',6'}$ 8.6 Hz, H-5′), 6.50 (s, 2 H, H-2 and H-6), 6.45 and 6.6 (AB system, 2 H, *J* 12.0 Hz, CH=CH), 6.71 (s, 1 H, exchanges with D_2O), 7.07 (d, 1 H, H-6′); ^1H NMR (C_6D_6): δ 1.60 (s, 3 H, OAc), 1.70 (s, 3 H, OAc), 1.78 (s, 3 H, OAc), 1.88 (s, 3 H, OAc), 3.0

(m, 1 H, H-5″), 3.8 (bd, 1 H, $J_{6''a,6''b}$ 12.0 Hz, H-6″a), 4.12 (dd, 1 H, $J_{6''b,5''}$ 4.0 Hz, H-6″b), 4.65 (d, 1 H, $J_{1'',2''}$ 8.7 Hz, H-1″), 5.15 (dd, 1 H, $J_{4'',3''} = J_{4'',5''} = 8.7$ Hz, H-4″), 5.38 (dd, 1 H, $J_{3'',2''}$ 8.7 Hz, H-3″), 5.46 (dd, 1 H, H-2″), 5.91 (d, 1 H, $J_{5',6'}$ 9.0 Hz, H-5′), 6.55 (d, 1 H, *J* 12.0 Hz, CH=CH), 6.62 (s, 2 H, H-2 and H-6) 7.02 (d, 1 H, CH=CH), 7.38 (d, 1 H, H-6′); ^{13}C NMR ($CDCl_3$): δ 4 × 21.07 (q), 56.60 (q), 56.61 (q), 56.82 (q), 61.43 (q), 62.25 (t), 69.02 (d), 71.84 (d), 72.90 (d), 73.00 (d), 103.73 (d), 104.43 (d), 2 × 106.98 (d), 118.98 (s), 124.84 (d), 127.20 (d), 130.11 (d), 133.47 (s), 134.48 (s), 138.08 (s), 149.02 (s), 149.24 (s), 153.54 (s), 153.55 (s), 169.94 (s), 170.04 (s), 171.71 (s), 171.12 (s); FABMS: *m/z* 662 (M^+), 332. Anal. Calcd for $C_{32}H_{38}O_{15}$: C, 58.00; H, 5.78. Found: C, 57.76; H, 5.66.

*Combretastatin A-4 tetra-*O*-acetyl-β-*D*-glucoside* (**23**).—Combretastatin A-4 (**12b**) was treated with the glucosyl bromide as described above for combretastatin B-1. Flash chromatography of the crude reaction mixture (silica gel; 4:1 hexane–EtOH) afforded pure **23** (50% yield).

(*Z*)-3,4,4′,5-Tetramethoxy-3′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)stilbene (**23**); colourless syrup; $[\alpha]_D$ +18.0° (*c* 0.11, MeOH); ^{1}H NMR ($CDCl_3$): δ 2.02 (s, 6 H, 2 × OAc), 2.05 (s, 6 H, 2 × OAc), 3.60 (m, 1 H, H-5″), 3.70 (s, 6 H, 2 × OMe), 3.78 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 3.98 (dd, 1 H, $J_{6''a,6''b}$ 12.0, $J_{6''a,5''}$ 2.2 Hz, H-6″a), 4.20 (dd, 1 H, $J_{6''b,5''}$ 5.0 Hz, H-6″b), 4.78 (dd, 1 H, $J_{1'',2''}$ 6.0, $J_{1'',3''}$ 2.0 Hz, H-1″), 5.08–5.30 (m, 3 H, H-2″, H-3″, and H-4″), 6.42 and 6.46 (AB system, 2 H, *J* 12.0 Hz, CH=CH), 6.49 (s, 2 H, H-2 and H-6), 6.76 (d, 1 H, $J_{5',6'}$ 8.0 Hz, H-5′), 6.98 (dd, 1 H, $J_{6',2'}$ 2.0 Hz, H-6′), 7.07 (d, 1 H, H-2′); ^{13}C NMR ($CDCl_3$): δ 4 × 21.0 (q), 2 × 56.80 (q), 56.85 (q), 56.86 (q), 62.2 (t), 69.0 (d), 71.8 (d), 72.1 (d), 73.2 (d), 101.8 (d), 107.0 (d), 113.0 (d), 120.8 (d), 126.0 (d), 129.2 (d), 129.8 (d), 130.5 (s), 133.0 (s), 138.5 (s), 146.0 (s), 150.0 (s), 2 × 153.2 (s), 169.5 (s), 169.7 (s), 170.5 (s), 171.0 (s); FABMS: *m/z* 646 (M^+). Anal. Calcd for $C_{32}H_{38}O_{14}$: C, 59.44; H, 5.92. Found C, 59.80; H, 6.0.

*(E)-3,4,4′,5-Tetramethoxy-2′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)stilbene* (**26**).—(*E*)-Combretastatin *iso*-A-4 (**13a**) was treated with the glucosyl bromide under phase-transfer catalysis as described above for combretastatin B-1 and afforded a 70% yield of **26**; colourless amorphous solid; ^{1}H NMR ($CDCl_3$): δ 1.88 (s, 3 H, OAc), 2.01 (s, 3 H, OAc), 2.05 (s, 3 H, OAc), 2.10 (s, 3 H, OAc), 3.81 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 3.91 (ddd, 1 H, $J_{5'',4''}$ 10.0, $J_{5'',6''b}$ 6.0, $J_{5'',6''a}$ 2.6 Hz, H-5″), 3.93 (s, 6 H, 2 × OMe), 4.22 (dd, 1 H, $J_{6''a,6''b}$ 12.0 Hz, H-6″a), 4.28 (dd, 1 H, H-6″b), 5.01 (d, 1 H, $J_{1'',2''}$ 8.0 Hz, H-1″), 5.14 (dd, 1 H, $J_{4'',3''}$ 10.0 Hz, H-4″), 5.31 (dd, 1 H, $J_{3'',2''}$ 10.0 Hz, H-3″), 5.44 (dd, 1 H, H-2″), 6.61 (dd, 1 H, $J_{5',6'}$ 9.0, $J_{5',3'}$ 2.2 Hz, H-5′), 6.63 (d, 1 H, H-3′), 6.8 (s, 2 H, H-2 and H-6), 6.85 and 7.18 (AB system, 2 H, *J* 17.0 Hz, CH=CH), 7.54 (d, 1 H, H-6′); ^{13}C NMR ($CDCl_3$): δ 4 × 21.0 (q), 56.2 (q), 2 × 57.0 (q), 61.8 (q), 63.0 (t), 69.4 (d), 71.4 (d), 73.2 (d), 73.4 (d), 100.23 (d), 102.88 (d), 2 × 104.06 (d), 108.2 (d), 120.08 (s), 121.8 (d), 127.1 (d), 128.2 (d), 134.1 (s), 138.4 (s), 155.8 (s), 2 × 153.9 (s), 160.8 (s), 169.0 (s), 169.5 (s), 170.0 (s), 171.0 (s); FABMS: *m/z* 646 (M^+). Anal. Calcd for $C_{32}H_{38}O_{14}$: C, 59.44; H, 5.92. Found C, 59.60; H, 5.85.

*(E)-3-(β-D-Glucopyranosyloxy)-5-hydroxy-4′-methoxystilbene (4′-*O*-methylpiceid)* (**16a**).—A 0.2 M soln of methanolic NaOMe (15.2 mL) was added to a soln of **14a** (0.291 g, 0.51 mmol) in MeOH (20 mL). The soln was stirred at room temperature for 2 h, then Dowex 50W-X8 (H^+) resin was added until the pH was neutral. The resin was filtered off and washed with MeOH, and the solvent was evaporated under reduced pressure to afford **16a** [9] in quantitative yield.

16a; colourless needles (EtOH); mp 219–222 °C, lit. 223–224 °C [9]; ^{1}H NMR (Me_2SO-d_6): δ 3.12–3.38 (m, 5 H, H-2″, H-3″, H-4″, H-6″a, and H-6″b), 3.50 (m, 1 H, H-5″), 3.82 (s, 3 H, OMe), 4.57 (t, 1 H, *J* 5.5 Hz, exchanges with D_2O, OH), 4.82 (d, 1 H, $J_{1'',2''}$ 7.1 Hz, H-1″), 4.97 (d, 1 H, *J* 5.0 Hz, exchanges with D_2O, OH), 5.10 (d, 1 H, *J* 4.0 Hz, exchanges with D_2O, OH), 5.22 (d, 1 H, *J* 4.6 Hz, exchanges with D_2O, OH), 6.39 (s, 1 H, H-4), 6.62 (s, 1 H, H-2), 6.78 (s, 1 H, H-6), 6.96 and 7.08 (AB system, 2 H, *J* 16.4 Hz, CH=CH), 6.97 (d, 2 H, $J_{3',2'} = J_{5',6'} = 9.6$ Hz, H-3′ and H-5′), 7.51 (d, 2 H, H-2′, H-6′), 9.40 (bs, 1 H, exchanges with D_2O, OH); ^{13}C NMR (Me_2SO-d_6): 55.67 (q), 61.91 (t), 70.25 (d), 73.65 (d), 76.95 (d), 77.44 (d), 101.14 (d), 103.49 (d), 105.65 (d), 107.70 (d), 2 × 114.72 (d), 126.75 (d), 128.39 (d), 128.40 (d), 128.44 (d), 130.09 (s), 139.78 (s), 158.68 (s), 159.38 (s), 159.57 (s); MS: *m/z* 404 (M^+). Anal. Calcd for $C_{21}H_{24}O_8$: C, 62.37; H, 5.97. Found: C, 62.25; H, 6.01.

(E)-3-(β-D-Glucopyranosyloxy)-4′,5-dihydroxystilbene (resveratrol 3-β-D-glucoside, piceid) (**3**).—A 0.5 M soln of NaSEt in DMF was prepared by adding EtSH (0.93 g, 1.1 mL, 15 mmol) to an ice-cooled and magnetically stirred suspension of NaH (0.4 g of a 60% oil dispersion, 10 mmol) in DMF (20 mL) and

stirring at room temperature for 15 min. Then 4 mL (2 mmol) of this soln were added to **16a** (0.3 g, 0.74 mmol) and the resulting soln was heated in an oil bath at 140 °C. The completion of the reaction was monitored by TLC. After 10 h, the cooled reaction mixture was acidified with 10% HCl and extracted with EtOAc (3 × 10 mL), and with BuOH (2 × 10 mL). The combined organic extracts were washed with water and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a residue which was purified by flash chromatography to give unreacted **16a** (25%) and **3** (60%) which was identical in all respects to an authentic sample [4].

(E)-3,5-Di-(β- D-*glucopyranosyloxy)-4'-methoxystilbene* (**17a**).—The diglucoside **15a** was treated with NaOMe as reported above for **14a** and afforded **17a** in quantitative yield.

17a; colourless syrup; $[\alpha]_D$ −70.0° (*c* 0.03, MeOH); ^{1}H NMR (pyridine-d_5): δ 3.65 (s, 3 H, OMe), 4.3–4.55 (m, 12 H, sugar protons), 5.7 (m, 2 H, m, H-5″ and H-5″a), 6.5 (bs, 8 H, exchanges with D_2O), 6.95 (d, 2 H, $J_{3',2'} = J_{5',6'} = 9.0$ Hz, H-3′ and H-5′), 7.20 (s, 1 H, H-4), 7.22 and 7.25 (AB system, 2 H, *J* 15.0 Hz, CH=CH), 7.32 (s, 2 H, H-2 and H-6), 7.55 (d, 2 H, H-2′ and H-6′); ^{13}C NMR (pyridine-d_5): δ 55.33 (q), 2 × 62.57 (t), 2 × 71.56 (d), 2 × 75.90 (d), 2 × 78.66 (d), 2 × 78.93 (d), 2 × 102.36 (d), 104.77 (d), 2 × 109.00 (d), 2 × 114.72 (d), 126.79 (d), 2 × 128.47 (d), 129.56 (d), 130.49 (s), 140.33 (s), 2 × 160.06 (s); 160.09 (s). FABMS: *m/z* 589 (M^+ + Na), 566 (M^+). Anal. Calcd for $C_{27}H_{34}O_{13}$: C, 57.24; H, 6.05. Found: C, 57.04; H, 6.01.

*Combretastatin A-1 2'-β-*D-*glucoside* (**1**).—Deacetylation of **21** as described above for **14a** afforded **1** (quantitative yields) identical in all respects to an authentic sample of the natural compound [1].

*Combretastatin A-1 3'-β-*D-*glucoside* (**24**).—Combretastatin tetra-*O*-acetyl-3-β-D-glucoside (**22**) was deacetylated with methanolic NaOMe as described above for **14a** and gave **24** in quantitative yield: colourless solid (MeOH); mp 94–96 °C (dec); $[\alpha]_D$ −13.64° (*c* 11.8, MeOH); ^{1}H NMR (Me_2SO-d_6): δ 3.65 (s, 6 H, 2 × OMe), 3.79 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 3.21–3.94 (m, 6 H, H-2″, H-3″, H-4″, H-5″, H-6″a, and H-6″b), 4.50 (d, 1 H, $J_{1'',2''}$ 6.9 Hz, H-1″), 6.42 (d, 1 H, $J_{5',6'}$ 8.8 Hz, H-5′), 6.58 (s, 2 H, H-2 and H-6), 6.38 and 6.58 (AB system, 2 H, *J* 12.0 Hz, CH=CH), 6.92 (d, 1 H, H-6′); ^{13}C NMR (Me_2SO-d_6): δ 2 × 55.97 (q), 56.66 (q), 60.53 (q), 60.87 (t), 69.71 (d), 74.06 (d), 76.21 (d), 77.46 (d), 104.38 (d), 105.91 (d), 106.47 (d), 106.48 (d), 118.25 (s), 125.38 (d), 125.72 (d), 129.31 (d), 132.86 (s), 134.62 (s), 137.04 (s), 148.76 (s), 152.54 (s), 2 × 152.83 (s), 152.84 (s); FABMS: *m/z* 494 (M^+), 332. Anal. Calcd for $C_{24}H_{30}O_{11}$: C, 58.30; H, 6.12. Found: C, 58.40; H, 6.18.

*Combretastatin A-4 β-*D-*glucoside* (**25**).—The tetra-*O*-acetyl-β-D-glucoside **23** was deacetylated with NaOMe as described above for compound **14a** and afforded **25** in quantitative yield; colourless solid; mp 89–91 °C; $[\alpha]_D$ −30.0° (*c* 0.06, MeOH); ^{1}H NMR (Me_2SO-d_6): δ 3.10–3.85 (m, 6 H, H-2″, H-3″, H-4″, H-5″, H-6″a, and H-6″b), 3.63 (s, 6 H, 2 × OMe), 3.71 (s, 3 H, OMe), 3.79 (s, 3 H, OMe), 4.40 (d, 1 H, $J_{1'',2''}$ 6.3 Hz, H-1″), 6.48 and 6.50 (AB system, 2 H, *J* 12.0 Hz, CH=CH), 6.61 (s, 2 H, H-2 and H-6), 6.94 and 6.96 (AB system, 2 H, $J_{5',6'}$ 7.9 Hz, H-5′ and H-6′), 7.08 (s, 1 H, H-2′); ^{13}C NMR (Me_2SO-d_6): δ 3 × 56.40 (q), 60.65 (t), 60.90 (q), 69.57 (d), 73.47 (d), 76.90 (d), 77.02 (d), 101.27 (d), 2 × 106.70 (d), 112.97 (d), 116.21 (d), 123.85 (d), 129.29 (d), 129.30 (s), 129.94 (d), 133.32 (s), 137.05 (s), 146.62 (s), 148.79 (s), 153.31 (s), 153.32 (s); FABMS: *m/z* 478 (M^+). Anal. Calcd for $C_{24}H_{30}O_{10}$: C, 60.24; H, 6.32. Found: C, 60.54; H, 6.37.

(E)-Combretastatin iso-*A-4 β-*D-*glucoside* (**27**).—The tetra-*O*-acetyl-β-D-glucoside **26** was deacetylated with NaOMe as described above for compound **14a** to give **27** (quantitative yield): colourless amorphous solid; $[\alpha]_D$ −57.7° (*c* 0.12, MeOH); ^{1}H NMR (Me_2SO-d_6): δ 3.26–3.72 (m, 6 H, H-2″, H-3″, H-4″, H-5″, H-6″a, and H-6″b), 3.68 (s, 3 H, OMe), 3.73 (s, 3 H, OMe), 3.81 (s, 6 H, 2 × OMe), 4.82 (d, 1 H, *J* 7.9 Hz, H-1″), 6.69 (d, 1 H, $J_{5',6'}$ 8.9 Hz, H-5′), 6.80 (s, 1 H, H-3′), 6.87 (s, 2 H, H-2 and H-6), 7.03 and 7.45 (AB system, 2 H, *J* 16.0 Hz, CH=CH), 7.61 (d, 1 H, H-6′); ^{13}C NMR (Me_2SO-d_6): δ 3 × 56.1 (q), 60.0 (t), 60.1 (q), 69.1 (d), 73.4 (d), 2 × 76.7 (d), 100.1 (d), 2 × 106.2 (d), 112.8 (d), 115.7 (d), 123.9 (s), 128.3 (d), 129.2 (d), 129.6 (s), 132.4 (s), 136.2 (s), 145.8 (d), 147.8 (s), 153.1 (s), 153.2 (s); FABMS: *m/z* 478 (M^+). Anal. Calcd for $C_{24}H_{30}O_{10}$: C, 60.24; H, 6.32. Found: C, 59.90; H, 6.40.

Acknowledgements

Financial support by Consiglio Nazionale delle Ricerche (CNR, Roma) through "Progetto Finalizzato Chimica Fine II", Centro di Studio Per le Sostanze Organiche Naturali (CNR, Milano), MURST "Progetto Nazionale di Ricerca, 40%" is gratefully acknowledged.

References

[1] I. Panzini, F. Pelizzoni, L. Verotta, and C.B. Rogers, *S. Afr. Sci.*, 89 (1993) 324–328.

[2] a) F. Pelizzoni, L. Verotta, C.B. Rogers, M. D' Incalci, G. Balconi, E. Erba, R. Colombo, and B. Pedrotti, *Nat. Prod. Lett.*, 1 (1993) 273–280; b) F. Pelizzoni, R. Colombo, M. D'Incalci, and L. Verotta, Ital. Patent MI92/A 002033 (1992).

[3] G.R. Pettit, S.B. Singh, E. Hamel, C.M. Lin, D.S. Alberts, and D. Garcia-Kendall, *Experientia*, 45 (1989) 209–211.

[4] L. Verotta, B.C. Rogers, A. Talal, A. Cignarella, S. Colli, and L. Puglisi, *Giornale di Chimica delle Sostanze Naturali*, III Convegno Nazionale, Amalfi (SA), 29 maggio-1 giugno, 1994.

[5] a) J.L. Ingham, *Phytochemistry*, 15 (1979) 1791; b) H. Arichi, Y. Kimura, H. Okuda, H. Baba, K. Kozawa, and S. Arichi, *Chem. Pharm. Bull.*, 30 (1982) 1766–1770; c) M.I. Chung, C.M. Teng, K. Cheng, F.-N. Ko, and C.-N. Lin, *Planta Med.*, 58 (1992) 274–275; d) E. Mannila, A. Talvitie, and E. Kolehmainen, *Phytochemistry*, 33 (1993) 813–816.

[6] a) Y. Inamori, M. Kubo, H. Tsujibo, M. Ogawa, Y. Saito, Y. Miki, and S. Takemura, *Chem. Pharm. Bull.*, 35 (1987) 887–890; b) P. Langcake, C.A. Cornford, and R.J. Pryce, *Phytochemistry*, 18 (1979) 1025–1027.

[7] a) C.-C. Chen, *J. Nat. Prod.*, 57 (1994) 1271–1274; b) Yamashita, H. Etho, K. Sakata, H. Ina, and K. Ina, *Agric. Biol. Chem.*, 53 (1989) 2827; c) A. Harada and K. Ina, Patent, Jpn. Kokai Koho JPO2,247, (1995).

[8] I. Kubo and Y. Murai, *J. Nat. Prod.*, 54 (1991) 1115–1118; b) Y. Kashiwada, G.I. Nonaka, and I. Nishioka, *Chem. Pharm. Bull.*, 32 (1984) 3501–3517.

[9] F.L. Tietze, R. Fisher, and H.J. Guder, *Tetrahedron Lett.*, 23 (1982) 4661–4664; E.M. Nashed and C.P.J. Glaudemans, *J. Org. Chem.*, 54 (1989) 6116–6118.

[10] E. Malan, E. Swinny, D. Ferreira, and A.J. Hall, *Phytochemistry*, 27 (1988) 2309–2311; F.W. Bachelor, A.A. Loman, and L.R. Snowdon, *Can. J. Chem.*, 48 (1970) 1554–1557.

[11] F. Pelizzoni, B. Bellini, and G. Miglierini, Ital. Patent MI94/A 000921 (1994).

[12] G.R Pettit, S.B. Singh, M.L. Niven, E. Hamel, and J.M. Schmidt, *J. Nat. Prod.*, 50 (1987) 119–131.

[13] G.R. Pettit, S.B. Singh, M.R. Boyd, E. Hamel, R.K. Pettit, J.M. Schmidt, and F. Hogan, *J. Med. Chem.*, 38 (1995) 1666–1672.

[14] D. Kahne, S. Walker, Y. Cheng, and D. Van Engen, *J. Am. Chem. Soc.*, 111 (1989) 6881–6882.

[15] K. Lal, S. Ghosh, and R.G. Salomon, *J. Org. Chem.*, 52 (1987) 1072–1078; J.I. Fentriel and R.N. Mirrington, *Tetrahedron Lett.*, 16 (1970) 1327–1328.

[16] a) G. Eckborg, B. Kranesie, A.K. Bhattacharjee, P. Kovac, and C.P.J. Glaudemans, *Carbohydr. Res.*, 142 (1985) 203–211; b) T. Ziegler, P. Kovac, and C.P.J. Glaudemans, *Liebigs Ann. Chem.*, (1990) 613–615 and refs. quoted therein.

[17] F.L. Tietze, R. Fisher, and H.J. Guder, *Tetrahedron Lett.*, 23 (1982) 4661–4664.

[18] R.R. Schmidt, and M. Stumpp, *Liebigs Ann. Chem.*, (1983) 1249–1265; R.R. Schmidt and J. Michel, *Angew. Chem. Int. Ed. Engl.*, 19 (1990) 731–732.

[19] E. Bellamy, D. Horton, J. Millet, F. Picart, S. Samreth, and J.B. Chazan, *J. Med. Chem.*, 36 (1993) 898–903.

[20] K. Briner and A. Vasella, *Helv. Chim. Acta*, 73 (1990) 1764–1778; 72 (1989) 1371–1382.

[21] D. Dess, H.P. Kleine, D.W. Wienberg, R.J. Kaufman, and R.S. Sidhu, *Synthesis*, (1981) 883–885.

[22] S. Hanessian, T.J. Liak, and B. Vanasse, *Synthesis*, (1981) 396–397.

[23] E. Guatteo, L. Bianchi, L. Faravelli, L. Verotta, F. Pelizzoni, C.B. Rogers, and E. Wanke, *Br. J. British Pharmacol.*, in press.