Total Synthesis of Combretastatins D

Elias A. Couladouros,* Ioanna C. Soufli, Vassilios I. Moutsos, and Raj K. Chadha

Abstract: The 15-membered caffrane ring of the natural product group of combretastatins D is synthesized in high yield with suitably functionalized saturated seco acids. The key step is a Mitsunobu-type macrolactonization. A common synthon is used for the construction of both combretastatins. The synthesis of combretastatin D-2 is completed by the use of Sammuelson's dehydroxylation protocol. The asymmetric epoxide of combretastatin D-1 is constructed in two separate operations: one asymmetric center is fixed at an early stage of the synthetic route by Sharpless AD of a *trans*-styrene derivative, inducing the intramolecular formation of the asymmetric epoxide at the final stages. The synthesis of the title compounds is accomplished in high overall yields (37% for D-1 and 41% for D-2, 9 steps in both cases). X-ray crystallographic analysis of the (*S*)-(+)-acetylmandelic ester of (−)-combretastatin D-1 verified its revised structure.

Keywords: asymmetric synthesis · combretastatins · lactones · macrocycles · natural products · total synthesis

Introduction

Combretastatins A and B (**1**–**3**; Figure 1) are biosynthetically related stilbene and dihydrostilbene secondary metabolites isolated from the South African folk medical tree *Combretum caffrum*.[1] They inhibit both the growth of the murine P-388 lymphocytic leukemia cell line (PS system) and tubulin polymerization.[2] Structure–activity-relationship and molecular modeling studies have shown that their mode of action is closely related to that of colchicine **4**, podophyllotoxins **5**, and steganacins **6** (Figure 1).[3] The structural simplicity of combretastatins A and B and their important biological activity make them very attractive leads for the development of new drugs.[4] Recently, a further series of biaryl derivatives with significant activity against the PS system was isolated in trace amounts from the same tree:[5] combretastatin D-1 (**7**, 2.3×10^{-4}%, ED_{50} 3.3 μg mL^{-1}) and combretastatin D-2 (**8**, 7.5×10^{-6}%, ED_{50} 5.2 μg mL^{-1}). The most prominent structural feature of combretastatins D is the caffrane ring, a 15-member biaryl ether macrolactone. The relative spatial arrangement of the aromatic rings in caffranes is similar to that of their carbon analogues **1**–**6**. Moreover, their characteristic meta- and paracyclophane subunits are reminiscent of a growing class of potent antitumor antibiotics including bouvardins,[6] RA

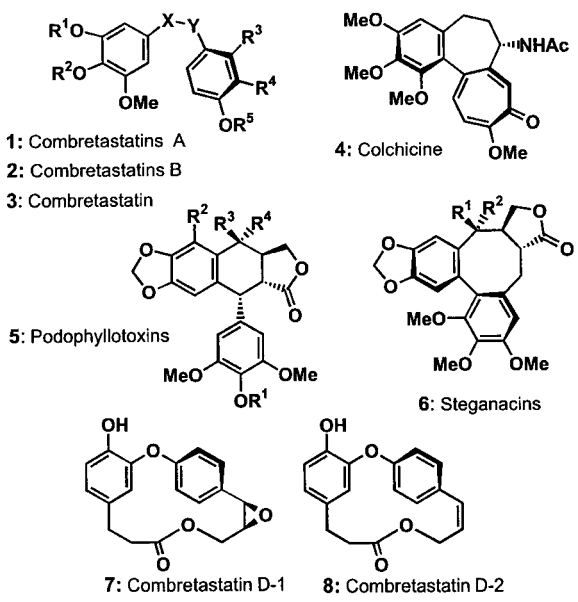

Figure 1. Some naturally occurring biaryl tubulin polymerization inhibitors. **1**: X, Y = CH_2; R^1, R^2 = H, Me, -CH_2O-; R^3, R^4 = H, OH, OMe; R^5 = H, Me. **2:** X, Y = CH=CH; R^1, R^2 = H, Me, -CH_2O-; R^3, R^4 = H, OH, OMe; R^5 = H, Me. **3:** X, Y = H, OH; R^1, R^2, R^5 = Me; R^3 = H, R^4 = OH. **5:** R^1 = H, Me; R^2 = H, OH; R^3, R^4 = H, OH, glycoside; **6:** R^1, R^2 = H, OAc, -O-.

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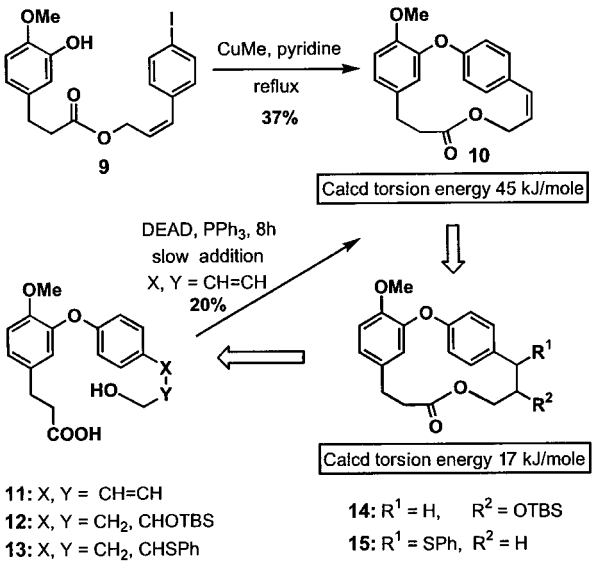
I–IV,[7] K-13,[8] OF-4949,[9] and piperazinomycin.[10] Consequently, because of their interesting structure, important biological activity, and scarcity in nature, caffranes have been popular synthetic targets in recent years.[11]

We would like to present herein a convergent and efficient total synthesis of both combretastatin D-1 and combretastatin D-2 by a common synthetic pathway. This work led to the unambiguous confirmation of the revised absolute configuration of (−)-combretastatin D-1.

The main synthetic obstacles associated with the construction of the caffrane ring are formation of the biaryl ether and the 15-member macrocyclic ring. Many methodologies for the formation of biaryl ethers have been developed,[12] especially after the isolation of the vancomycin and ristocetin families of antibiotics. However, the classic Ullman procedure remains popular because it utilizes less elaborate precursors.[13] Thus, Boger et al.[11a] succeeded in solving both synthetic problems in one step by applying a modified Ullman protocol to intermediate **9** to prepare **10** (Scheme 1). On the other hand, Desphande and Gokhale[11b] opted for a more conservative approach towards **10**: working with seco acid **11**, prepared from an Ullman coupling of the two aromatic subunits, they achieved a Mitsunobu-type[14] macrolactonization (Scheme 1) under very dilute conditions.[15] Both strategies were low-yielding, requiring carefully controlled reaction conditions. We attributed this to the extra strain associated with an unsaturated vs. saturated medium-size ring. Indeed, after Monte Carlo minimization[16] the calculated torsion energies for macrocycles **14** and **10** were found to be 17 and 45 kJ mol^{-1}, respectively. Therefore, we opted to work with monosubstituted saturated ring precursors like **12** or **13**, which should lead to macrolide intermediates **14** and **15** by a less energy-demanding cyclization. Consequently, macrolactonization will precede double-bond formation (in the case of combretastatin D-2) or epoxide formation (in the case of combretastatin D-1).



Scheme 1. Synthetic and retrosynthetic approaches to macrolactone **10**.

Abstract in Greek:

Ο 15-μελής καφρανικός δακτύλιος των κομπρεταστατινών D, συντίθεται σε υψηλή απόδοση με την χρήση κατάλληλα υποκατεστημένων κεκορεσμένων *seco* οξέων. Το κρίσιμο στάδιο είναι η μακρολακτονοποίηση κατά Mitsunobu. Η παρασκευή αμφοτέρων των κομπρεταστατινών επιτυγχάνεται με την χρήση ενός κοινού ενδιαμέσου. Η σύνθεση της κομπρεταστατίνης D-2 ολοκληρώνεται με την εφαρμογή της μεθόδου αποϋδροξυλίωσης κατά Sammuelson. Το ασύμμετρο εποξείδιο της κομπρεταστατίνης D-1 οικοδομείται σε δύο ξεχωριστές διεργασίες. Το ένα ασύμμετρο κέντρο τοποθετείται στα πρώτα στάδια της σύνθεσης, με εφαρμογή της μεθόδου AD του Sharpless σε ένα παράγωγο *trans* στυρενίου, το οποίο, στα τελικά στάδια, επάγει τον ενδομοριακό σχηματισμό του ασύμμετρου εποξειδίου. Η σύνθεση αμφοτέρων των φυσικών προϊόντων ολοκληρώνεται σε υψηλές ολικές αποδόσεις (37% - 9 στάδια - για την D-1 και 41% - 9 στάδια - για την D-2). Η κρυσταλλογραφική ανάλυση με ακτίνες X του μανδελικού εστέρα της (−)-κομπρεταστατίνης D-1 επιβεβαιώνει την αναθεωρημένη της δομή.

Results and Discussion

In order to explore the feasibility of our strategy we planned to synthesize several seco acids bearing a saturated side chain suitably substituted to allow eventual formation of the double bond. Two such precursors were envisioned: a) benzylsulfide **26** (Scheme 2), which after macrolactonization and oxidation should readily eliminate in an E_2 fashion; and b) the hydroxylated analogue **29** (Scheme 3), which should also tend to eliminate easily after macrolactonization and deprotection. Both pathways should lead to the styrene moiety of target compound **8**. This approach towards the total synthesis of combretastatin D-2 is depicted in detail in Schemes 2 and 3.

The Wittig-type elongation of commercially available *p*-bromobenzaldehyde **16** by means of Ph_3P=CHCOOEt afforded conjugated ester **17**. DIBAL (diisobutyl aluminium) reduction of this ester furnished allylic alcohol **18**, which was protected either as a silyl ether **19**, a benzyl ether **20**, or a pivaloate ester **21**. Epoxidation of **20** using *m*-CPBA (3-chloroperoxybenzoic acid) and regioselective ring opening with DIBAL[17] afforded, after silylation with TBSCl, the desired oxygenated synthon **22**. We were now ready to prepare the designed seco acids and try our strategy. Ullman-type coupling of arylbromide **19** with phenol **23**[18] afforded diaryl ether **25** in high yield after desilylation and ester hydrolysis. The attempted electrophilic addition of thiophenol to the double bond of **25** resulted in messy reactions that furnished many products, according to TLC analysis. However, prolonged reaction times afforded, in moderate yield, a main product that upon spectroscopic analysis proved to be 3-[3-((4-formyl)phenoxy)-4-methoxyphenyl]propanoic acid. Eventually, the sulfide approach was abandoned and a

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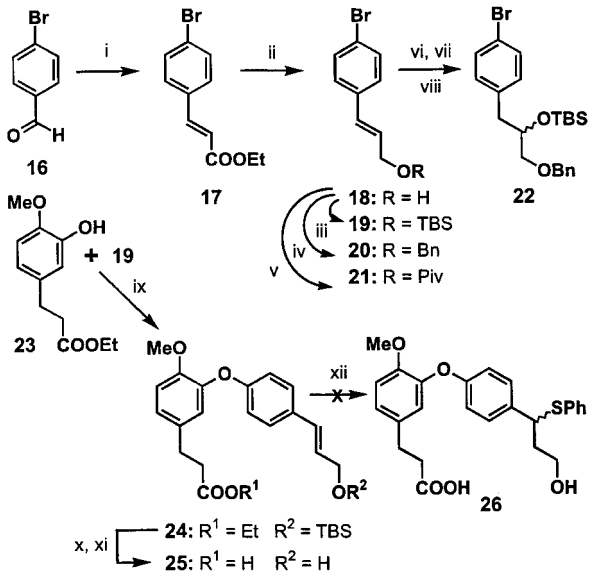
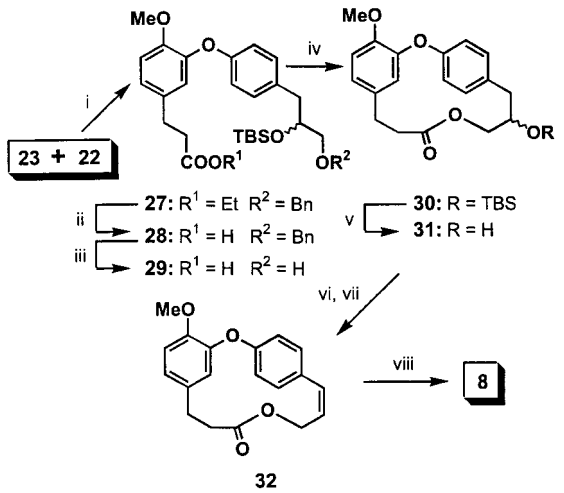


Scheme 2. Attempts to prepare seco acid **26**. Reagents and conditions: i) 1.2 equiv $Ph_3P{=}CHCOOEt$, benzene, 25 °C, 30 min, 93 %; ii) 2.1 equiv DIBAL, CH_2Cl_2, −78 °C, 20 min, 97 %; iii) 1.2 equiv TBSCl, 1.4 equiv imidazole, DMF, 25 °C, 3 h, 97 %; iv) 1.1 equiv NaH, THF, 0 →25 °C, 30 min, then 1.2 equiv BnBr, cat. Bu_4NI, 3 h, 25 °C, 94 %; v) 1.7 equiv PivCl, pyridine, DMF, 0 →25 °C, 6 h, 87 %; vi) 1.5 equiv *m*-CPBA, CH_2Cl_2, 25 °C, 4 h, 82 %; vii) 1.1 equiv DIBAL, toluene, 0 °C, 30 min, 86 %; viii) 1.1 equiv TBSCl, 1.3 equiv imidazole, DMF, 25 °C, 3 h, 97 %; ix) 2 equiv $CuBr \cdot Me_2S$, 6 equiv K_2CO_3, pyridine, 6 h, 140 °C, 78 %; x) 2.5 equiv TBAF, THF, 25 °C, 3 h, 96 %; xi) LiOH 3 N:THF:MeOH 1:1:1, 0 →25 °C, 2 h, 92 %; xii) 3 equiv PhSH, AcOEt, 25 °C, 5 h. TBS = *tert*-butyldimethylsilyl, Bn = benzyl, Piv = pivaloyl, TBAF = tetrabutylammonium fluoride.

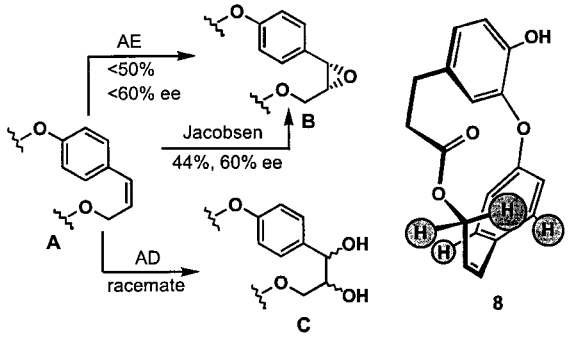


Scheme 3. Formal synthesis of combretastatin D-2 (**8**). Reagents and conditions: i) 2 equiv $CuBr \cdot Me_2S$, 0.7 equiv **22**, 6 equiv K_2CO_3, pyridine, 6 h, 140 °C, 92 %; ii) LiOH 3 N:THF:MeOH 1:1:1, 0 →25 °C, 2 h, 94 %; iii) H_2, Pd/C 10 %, AcOEt, 25 °C, 4 h, 100 %; iv) 9 equiv DEAD, 8.8 equiv Ph_3P, toluene 2.5 mM final concentration, 45 °C, 7 h addition, 91 %; v) 1.2 equiv TBAF, THF, 25 °C, 0.5 h, 94 %; vi) 2 equiv I_2, 2 equiv Ph_3P, 3 equiv imidazole, toluene, 80 °C, 30 min, 95 %; vii) 10 equiv KF, DMSO 0.15 M, 115 °C, 4 h, 87 %; viii) 1 equiv BI_3, 1.2 equiv *N,N*-dimethylaniline, benzene, 0 →25 °C, 17 %.

hydroxylated seco acid was targeted as an alternative synthon (compound **29**, Scheme 3). Ullman coupling of **23** and **22** and subsequent deprotection of the terminal carboxylic and hydroxyl functionalities afforded the saturated seco acid **29**. This substrate proved very efficient for macrolactonization. Indeed, by applying modified Mitsunobu-type conditions[14,15] we achieved cyclization in 91 % yield when the reaction was performed at 40–45 °C with slow addition of the seco acid into the reaction mixture for a 7 h period (final concentration 2.5 mM). Under these reaction conditions, no dimer formation was observed. It is noteworthy that the yield of the cyclization of the related unsaturated seco acid reported in the literature[11b] was only 20 %, though the addition was carried out over a 24 h period and the final concentration was 0.5 mM. Subsequent desilylation, promoted by fluoride anions, afforded alcohol **31** in 94 % yield. Following publication of our preliminary results[11c] Rychnovsky et al.[11d] also disclosed an efficient macrolactonization of a saturated seco acid.

All efforts to induce a smooth and direct elimination of water from alcohol **31** failed (CSA (camphorsulfonic acid), TsOH, $CuSO_4$/silica gel or H_2SO_4).[19] Elimination was very slow and, consequently, several by-products due to decomposition of the lactone were usually detected in the reaction mixtures. The same disappointing results also followed our trials to induce elimination of the corresponding methylsulfonate ester by heating it with NaI in HMPA (hexamethyl phosphoramide), or by treatment with *t*BuOK or DBU (1,8-diazabicyclo[5.4.0]undec-7-ene).[19] Finally, the double bond was formed in high yield by a two-step protocol. Thus, the hydroxyl group was first replaced by iodine (Sammuelson's conditions).[20] Subsequent dehydrohalogenation in refluxing DMF in the presence of excess KF afforded methyl combretastatin D-2 (**32**) in 83 % yield for the two steps. Combretastatin D-2 (**8**) was finally prepared after demethylation of **32** in 17 % yield following Boger's procedure.[11a]

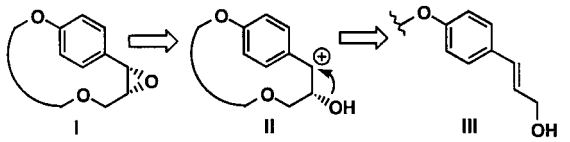
Having established an efficient route to the caffrane ring, we focused our efforts on the construction of (−)-combretastatin D-1. The additional synthetic problem associated with this target is the introduction of an asymmetric epoxide onto a *cis*-styrene derivative. It is well known that Sharpless asymmetric epoxidation (AE) gives very poor chemical yields and *ee*'s on *cis*-styrene substrates.[21] Therefore, this method cannot be applied for the corresponding seco acid (*cis*-allylic alcohol **A**, Scheme 4). In addition, Rychnovsky and Hwang[11e] have shown that Sharpless asymmetric dihydroxylation of combretastatin D-2 with AD-mix-α[22] yields a completely racemic mixture (**A** to **C**). To make things worse, Jacobsen's ((*S,S*)-salen)Mn catalyst derived from 1,2-diami-



Scheme 4. Asymmetric additions on *cis*-styrene substrates.

nocyclohexane, which has been successfully applied with many (*Z*)-styrenes,[23] gives very disappointing *ee*'s when applied to **A**[11e] (**A** to **B**). From the minimized structure of **8** both faces of the double bond seem to have almost the same steric environment. Therefore, the above experimental results are not surprising.

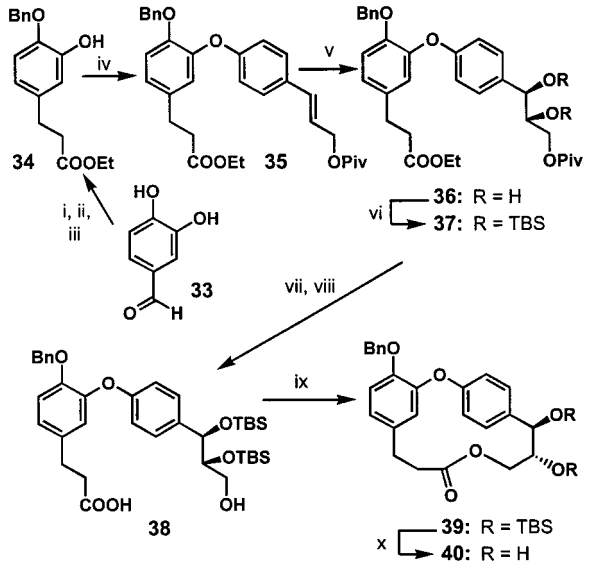
In order to circumvent these problems we designed a different plan, which was based on the concept depicted in Scheme 5. Instead of fixing both asymmetric centers of



Scheme 5. Retrosynthesis for the construction of the asymmetric epoxide **I**.

target **I**, we simplified the problem by targeting a precursor with only one asymmetric center fixed. Specifically, we decided to form the desired epoxide via the optically active alcohol cation **II**. This intermediate should be formed if a good leaving group was present at the benzylic position. By this approach, the chirality of the alcohol will govern that of the epoxide. The advantage is that we may now work on a *trans*-styrene alcohol **III** where both Sharpless's asymmetric procedures (AE, AD) are known to proceed with high *ee*'s.

In detail, our final synthetic scheme began with an Ullman coupling of the monobenzylated catechol derivative **34** with aryl bromide **21** (Scheme 6). Intermediate **34** was prepared



Scheme 6. Construction of the common key intermediate **40**. Reagents and conditions: i) DMF, excess K_2CO_3, 60 °C, 4 h then 1.1 equiv BnBr, 25 °C, 12 h, 76 %; ii) benzene, $Ph_3P{=}CHCOOEt$, 25 °C, 24 h, 93 %; iii) H_2, Pd/C 5 %, benzene, 25 °C, 5 h, 97 %; iv) 2 equiv $CuBr \cdot Me_2S$, 0.7 equiv **21**, 6 equiv K_2CO_3, pyridine, 6 h, 140 °C, 78 %; v) 3 equiv $K_3[Fe(CN)_6]$, 3 equiv K_2CO_3, 0.01 equiv $K_2[OsO_2(OH)_4]$, 0.25 equiv $(DHQD)_2PHAL$, *t*BuOH: H_2O 1:1, 0 °C, 12 h, 87 %; vi) 2.2 equiv TBSCl, 2.4 equiv imidazole, DMF, 25 °C, 3 h, 97 %; vii) LiOH 3 N:THF:MeOH 1:1:1, 0 → 25 °C, 2 h, 94 %; viii) 1.1 equiv DIBAL, CH_2Cl_2, −78 °C, 10 min, 96 %; ix) 9 equiv DEAD, 8.8 equiv Ph_3P, toluene 2.5 mM final concentration, 45 °C, 6 h addition, 81 %; x) 2.5 equiv TBAF, THF, 25 °C, 30 min, 94 %.

from commercially available aldehyde **33** by selective benzylation, Wittig-type carbon elongation and reduction of the double bond under controlled conditions. The benzyl group of starting material **34** was chosen as the ideal one to survive throughout the entire reaction sequence and yet to be easily removed at the final step in the presence of either the epoxide or the double bond. Introduction of asymmetry on biaryl ether **35** was achieved by means of the well-known Sharpless catalyst $(DHQD)_2PHAL$ (hydroquinidine 1,4-phthalazinediyl diether) for asymmetric dihydroxylation. The (3*R*,4*R*) configuration of diol **36** depicted was expected, based on literature precedent.[22] The ^1H NMR spectrum of diol **36** recorded with $[Eu(hfc)_3]$ as a chiral shift reagent gave no extra signals, indicating an optical purity of more than 95 %. Reaction of diol **36** with TBSCl proceeded in high yield to afford fully protected intermediate **37**. Subsequent hydrolysis of the ester functionality with LiOH and reductive cleavage of the pivaloate ester with DIBAL afforded seco acid **38**. Macrolactonization of this saturated disubstituted seco acid was again very efficient under the same protocol previously used for the synthesis of combretastatin D-1. Thus, after desilylation, macrolactone **40** was synthesized in 76 % yield for the two steps.

Intermediate **40** was the ideal substrate for performing the final stages of both syntheses (that is, restoration of the double bond or the epoxide functionalities of the natural products, Scheme 7). Following Sammuelson's protocol for 1,2-diol dehydroxylation,[24] diol **40** was easily transformed into the corresponding olefin **42** with triiodoimidazole and Ph_3P. Subsequent selective cleavage of the benzylic ether under Lewis acid catalysis with $AlCl_3$ afforded **8** in high overall yield (35 % based on **21**). The same product was observed from the reverse order of operations. Thus hydrogenolysis of benzyl ether **40** yielded quantitatively triol **41**, which was subsequently treated with triiodoimidazole and Ph_3P to afford target compound **8** in a very clean reaction and in high overall yield (41 % based on **21**). It should be emphasized here that the use of tetrachloroethylene instead of methylene chloride as a solvent was crucial for the effective dehydroxylation of diols **40** and **41**.

Finally, in order to restore the epoxide functionality of (−)-combretastatin D-1, we decided to use the well-known diol cyclodehydration protocol, which is usually promoted by the use of phosphoranes and oxyphosphonium salts.[25,26] The exact mechanism of this transformation is not always clear. However, it is believed that during the preparation of styrene oxides, the cyclodehydration proceeds through the formation of the more stable carbocation at the benzylic position,[26] which in our case should be intermediate **43** (Scheme 7, path A). Since substrate **40** has no free rotation between C3 and C4, the epoxide **45** should be formed in high enantiomeric purity. Thus, after heating diol **40** with excess diethyl azodicarboxylate (DEAD) and Ph_3P at 145 °C for 40 min followed by hydrogenolysis of the benzyl group, (−)-combretastatin D-1 (**7**) was obtained in high overall chemical yield (83 % after crystallization[27]). The reported optical rotation of natural **7** is $[\alpha]_D = -100$ ($c = 0.015$ in $CHCl_3$) while the optical rotation of synthetic **7** was $[\alpha]_D = -96$ ($c = 0.015$ in $CHCl_3$), implying an optical purity of 96 % of the synthetic

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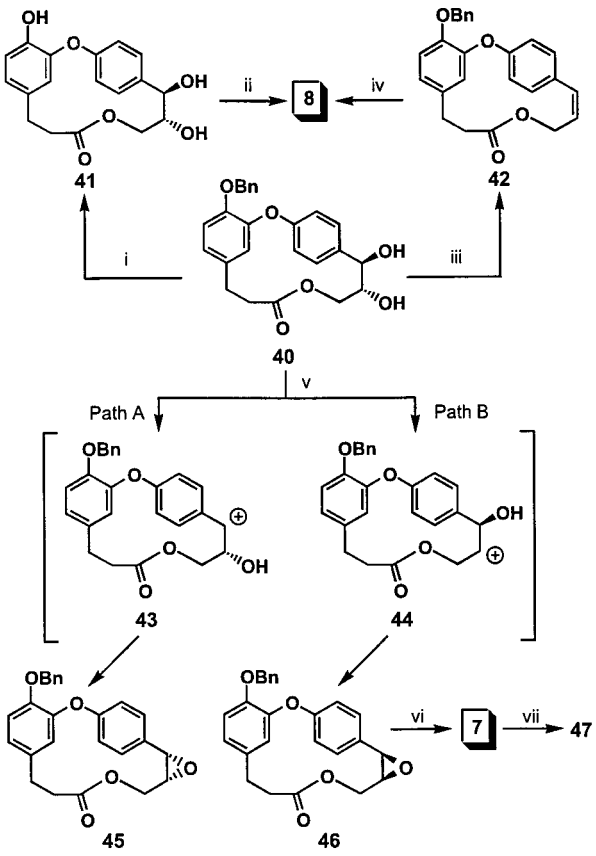

Scheme 7. Total syntheses of natural combretastatins D-1 (**7**) and D-2 (**8**). Reagents and conditions: i) Pd/C 10%, AcOEt, 25°C, 5 h, 98%; ii) $Cl_2C{=}CCl_2$, Ph_3P, TII, imidazole, 140°C, 30 min, 94%; iii) $Cl_2C{=}CCl_2$, Ph_3P, TII, imidazole, 140°C, 30 min, 92%; iv) $AlCl_3$, CH_2Cl_2, 25°C, 30 min, 85% (based on 20% recovered starting material); v) 4 equiv DEAD, 4 equiv Ph_3P, DMF, 145°C, 40 min, 87%; vi) H_2, Pd/C 10%, AcOEt, 25°C, 3 h, 95%; vii) 1.4 equiv (*S*)-(+)-*O*-acetylmandelic acid, 1.4 equiv DCC, 0.3 equiv DMAP, 25°C, 3 h, 90%. TII = triiodoimidazole, DMAP = 4-dimethylaminopyridine.

material. The high optical purity of the synthetic compound suggests that the reaction proceeds by a unique pathway (either A or B). If both the original assignment of naturally occuring (−)-combretastatin D-1 and the expected mechanism for the cyclodehydration were correct, synthetic (−)-combretastatin would have the configuration of compound **45**. In order to verify the suggested mechanism and fully elucidate the absolute configuration of the natural product, X-ray crystallographic analysis of the (*S*)-(+)-*O*-acetyl mandelic ester **47** of synthetic (−)-combretastatin (**7**) was performed (Figure 2). To our surprise, the observed configuration was that of compound **46**, indicating that both the proposed mechanism and the original assignment of (−)-combretastatin[5a] were wrong. These findings agree with the revised configuration, already proposed by Rychnovsky et al.[11e] In addition, since the configuration of the benzylic hydroxyl governs the stereochemistry of the resultant epoxide, the reaction should proceed via intermediate **44** (path B) and consequently no benzylic carbocation should formed. As Professor Rychnovsky suggests[28] a reasonable explanation is that the angle of the orbitals of the benzylic cation would be in

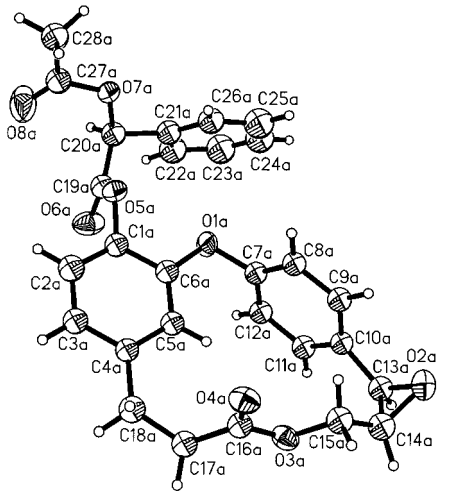

Figure 2. ORTEP view of the (*S*)-(+)-*O*-acetylmandelic ester **47** of synthetic (−)-combretastatin D-1 (**7**).

a disfavored alignment, perpendicular to the aromatic ring π system, making the formation of such a cation energetically unfavorable. Supporting this hypothesis is the fact that this dehydration reaction requires very high temperatures to proceed, while at lower temperatures formation of by-products predominates.

Thus, although we targeted the wrong isomer, we achieved a synthesis of the natural compound thanks to this unusual dehydration mechanism in the epoxide formation and an incorrect stereochemical assignment originally reported for the natural product.

Conclusion

To summarize, we have developed an effective route for the synthesis of the title compounds and a concise synthetic plan which can be utilized to rapidly prepare a variety of related analogues. In addition, the absolute configuration of naturally occurring (−)-combretastatin D-1 has been unambiguously verified.

Experimental Section

General techniques: Melting points were determined on a Buchi apparatus and are uncorrected. NMR spectra were recorded on Bruker AMX-500, AM-250, or AM-200 instruments with Me_4Si or $CHCl_3$ (in $CDCl_3$) as internal standard; signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). IR spectra were recorded on Perkin Elmer 283 B or Nicolet 750 FT spectrophotometers. Optical rotations were recorded with a Perkin Elmer 241 polarimeter at 25°C. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) or electrospray conditions.

All reactions were monitored by thin-layer chromatography (TLC) carried out on E. Merck silica gel precoated plates with UV light, *p*-anisaldehyde or 7% ethanolic phosphomolybdic acid and heat as developing agents. E. Merck silica gel (60, particle size 0.032–0.063 mm) was used for flash column chromatography. Dry THF was distilled from sodium/benzophenone, methylene chloride from calcium hydride and benzene and toluene from sodium. All reagents were obtained from Aldrich and Merck. All

reactions were carried out under argon. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogenous materials, unless otherwise stated.

X-Ray crystallography: A colorless, platelike crystal of compound **47** was obtained after slow evaporation of a methylene chloride/acetone solution. Crystal data were collected with a Rigaku AFC6R diffractometer equipped with a copper rotating anode and a highly oriented graphite monochromator. A constant scan speed of 8° min^{-1} in ω was used; the weak reflections [$I < 5\sigma(I)$] were rescanned a maximum of 6 times and the counts accumulated to assure good counting statistics. The intensities of three check reflections measured after every 200 reflections did not change significantly over 75 h X-ray exposure. Unit cell dimensions and standard deviations were obtained by least-squares fit to 25 reflections ($50 < 2\theta < 80°$). The data were corrected for Lorentz and polarization effects and also for absorption by a ψ-scan method. The structure was solved by direct methods with SHELXS86. Nitrogen and oxygen atoms were refined anisotropically and carbon atoms isotropically by the full-matrix least-squares method. The function minimized was $\Sigma w(|F_o| - |F_c|^2)$. Hydrogen atoms were included in the ideal positions with a fixed isotropic U value of 0.08 Å^2. A weighting scheme of the form $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$ where $a = 0.0901$ and $b = 1.62$ was used. (P is defined as $(\mathrm{Max}(F_o^2,0) + 2F_c^2)/3$). An extinction correction was also applied to the data. All calculations were performed on a Silicon Graphics Personal Iris 4D/35 and an IBM-compatible PC using programs TEXSAN (data reduction) and SHELXL-93 (refinement) and SHELXTL-PC (plotting). Cell parameters and other relevant data: crystal size: 0.16 × 0.12 × 0.08 mm; crystal system: triclinic; space group: $P\bar{1}$; unit cell dimensions: $a = 9.411(2)$, $b = 9.984(1)$, $c = 13.479(1)$ Å, $\alpha = 100.21(1)°$, $\beta = 93.22(1)°$, $\gamma = 91.45(1)°$; T: 296(2) K; λ: 1.54178 Å; V: 1243.7(3) Å^3; Z: 2; $F(000)$: 514; ρ (calculated): 1.309 Mg m^{-3}; absorption coefficient: 0.800 mm^{-1}; absorption correction (transmission factors): 0.85–0.98; θ range for data collection: 3.34 to 60.52°, scan type: $2\theta - \theta$; scan width: $1.837 + 0.140\tan\theta$: scan time/background time 2:1; index ranges: $-10 \le h \le 10$, $-11 \le k \le 0$, $-14 \le l \le 15$; reflections collected: 4035, independent reflections: 3950 ($R_{int} = 0.0473$); refinement method: full-matrix least-squares on F^2; data/restraints/parameters: 3950/0/368; goodness-of-fit on F^2 (S): 1.269; final R indices [$I > 2\sigma(I)$]: $R1 = 0.0827$, $wR2 = 0.2083$; R indices (all data): $R1 = 0.1466$, $wR2 = 0.2732$; $R1 = (\Sigma||F_o| - |F_c||/\Sigma|F_o|)$, $wR2 = \Sigma w(F_o^2 - F_c^2)^2/\Sigma w[(F_o^2)^2]^{1/2}$, $S = [\Sigma w(F_o^2 - F_c^2)^2/(n-p)]^{1/2}$; Flack's absolute structure parameter: 0.6(6); largest diff. peak and hole: 0.317 and −0.355 e Å^{-3}. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-10047. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: Int. code +44 1223 336-033; e-mail: deposit@ccdc.cam.ac.uk).

Ethyl 3-(4-bromophenyl)-2(*E*)-propenoate (**17**): A solution of *p*-bromobenzaldehyde (6.2 g, 33 mmol) and $Ph_3P{=}CHCOOEt$ (13.9 g, 40 mmol) in benzene (10 mL) was stirred at 25 °C for 30 min. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5–15% EtOAc in hexane) afforded compound **17** (7.9 g, 93%) as a colorless oil: $R_f = 0.50$ (silica gel, 10% EtOAc in hexane); IR (neat): $\tilde{\nu} = 2970$, 1705, 1630, 1580, 1478, 1305, 1168, 1063, 807 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.61$ (d, $J = 16.5$ Hz, 1H, Ar*CH*=CH), 7.52 (d, $J = 8.5$ Hz, 2H, Ar), 7.38 (d, $J = 8.5$ Hz, 2H, Ar), 6.42 (d, $J = 16.5$ Hz, 1H, ArCH=*CH*), 4.27 (q, $J = 7.0$ Hz, 2H, CH_2CH_3), 1.33 (t, $J = 7.0$ Hz, 3H, CH_2CH_3); FAB HRMS (NBA): calcd for $C_{11}H_{11}O_2Br$ $[M+H]^+$ 255.0021; found $m/e = 255.0030$.

3-(4-Bromophenyl)-2(*E*)-propenol (**18**): A solution of **17** (7.0 g, 27 mmol) in CH_2Cl_2 (120 mL) was cooled to −78 °C and treated with DIBAL-H (57 mL, 1.0 M in hexane) dropwise over 10 min. After the mixture had been stirred at −78 °C for 10 min, the reaction mixture was quenched with MeOH (7 mL) and subsequently treated with saturated sodium/potassium tartrate while stirred at 25 °C for 15 min. EtOAc was added to the reaction mixture and the organic layer was washed with 1N HCl, saturated $NaHCO_3$, and brine, then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford white crystals of alcohol **18** (5.6 g, 97%). M.p. 68–69 °C; $R_f = 0.18$ (silica gel, 20% EtOAc in hexane); FT-IR (thin film): $\tilde{\nu} = 3319$, 1485, 1398, 1090, 917, 841 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.43$ (d, $J = 8.5$ Hz, 2H, Ar), 7.23 (d, $J = 8.5$ Hz, 2H, Ar), 6.55 (d, $J = 15.4$ Hz, 1H, Ar*CH*=CH), 6.33 (dt, $J = 15.4$, 5.4 Hz, 1H, ArCH=*CH*), 4.31 (d, $J = 5.4$ Hz, 2H, CH_2), 1.90 (s, 1H, OH); FAB HRMS (NBA): calcd for C_9H_9OBr $[M-H]^+$ 210.9759; found $m/e = 210.9766$.

***O*-(*tert*-Butyldimethylsilyl)-3-(4-bromophenyl)-2(*E*)-propenol** (**19**): A solution of alcohol **18** (1.8 g, 8.4 mmol), TBDMSCl (1.5 g, 10 mmol) and imidazole (0.8 g, 11.75 mmol) in DMF (7 mL) was stirred at 25 °C for 3 h. Ethyl acetate was added to the reaction mixture and the organic layer was washed with H_2O and saturated NaCl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5–10% ethyl acetate/hexanes) yielded 2.65 g (8.1 mmol, 97%) of **19** as a colorless oil: $R_f = 0.6$ (silica gel, 10% EtOAc in hexane); FT-IR (neat): $\tilde{\nu} = 2924$, 2853, 1469, 1247, 1122, 836 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.44$ (d, $J = 8.4$ Hz, 2H, Ar), 7.24 (d, $J = 8.4$ Hz, 2H, Ar), 6.55 (d, $J = 15.8$ Hz, 1H, Ar*CH*=CH), 6.33 (dt, $J = 15.8$, 5.0 Hz, 1H, ArCH=*CH*), 4.31 (d, $J = 5.0$ Hz, 2H, CH_2), 0.95 (s, 9H, Si*t*Bu), 0.1 (s, 6H, $Si(CH_3)_2$); FAB HRMS (NBA): calcd for $C_{15}H_{23}OSiBr$ $[M-H]^+$ 325.0623; found $m/e = 325.0635$.

***O*-Benzyl-3-(4-bromophenyl)-2(*E*)-propenol** (**20**): A solution of alcohol **18** (1.3 g, 6.1 mmol) in THF (10 mL) was treated with NaH (0.16 g, 6.7 mmol) at 0 °C. The reaction was allowed to reach 25 °C and stirred for additional 30 min. Then BnBr (0.88 mL, 7.32 mmol) and Bu_4NI (0.11 g, 0.3 mmol) were added and stirred at 25 °C for 3 h. Ethyl acetate was added and the organic layer was washed with saturated NH_4Cl, H_2O, and saturated NaCl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5–10% ethyl acetate/hexanes) yielded 1.7 g (5.7 mmol, 94%) of **20** as a colorless oil: $R_f = 0.57$ (silica gel, 10% EtOAc in hexane); FT-IR (neat): $\tilde{\nu} = 2853$, 1588, 1490, 1074, 738 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.34-7.12$ (band, 9H, Ar), 6.47 (d, $J = 15.8$ Hz, 1H, Ar*CH*=CH), 6.21 (dt, $J = 15.8$, 5.7 Hz, 1H, ArCH=*CH*), 4.47 (s, 2H, OCH_2Ph), 4.07 (dd, $J = 5.7$, 1.4 Hz, 2H, CH_2OBn); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 138.1$, 135.6, 131.6, 131.3, 131.0, 128.7, 128.4, 127.9, 127.8, 127.7, 127.6, 126.9, 121.3, 72.3, 70.5; FAB HRMS (NBA): calcd for $C_{16}H_{15}OBr$ $[M+Cs]^+$ 434.9361; found $m/e = 434.9375$.

***O*-Pivaloyl-3-(4-bromophenyl)-2(*E*)-propenol** (**21**): A solution of alcohol **18** (1.5 g, 7.0 mmol) in DMF (7 mL) and pyridine (3 mL) was treated with pivaloyl chloride (1.5 mL, 12.2 mmol) at 0 °C. The reaction was allowed to reach 25 °C and stirred for a further 6 h. Ethyl acetate was added and the organic layer was washed with 1N HCl, H_2O, saturated Na_2CO_3, H_2O, and saturated NaCl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5–10% ethyl acetate/hexanes) yielded 1.8 g (6.1 mmol, 87%) of a colorless oil: $R_f = 0.78$ (silica gel, 10% EtOAc in hexane); IR (neat): $\tilde{\nu} = 2960$, 1720, 1584, 1475, 1273, 1140, 1063, 957 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.43$ (d, $J = 8.8$ Hz, 2H, Ar), 7.24 (d, $J = 8.8$ Hz, 2H, Ar), 6.57 (d, $J = 16.0$ Hz, 1H, Ar*CH*=CH), 6.26 (dt, $J = 16.0$, 6.4 Hz, 1H, ArCH=*CH*), 4.70 (d, $J = 6.4$ Hz, 2H, CH_2), 1.22 (s, 9H, Piv); FAB HRMS (NBA): calcd for $C_{14}H_{17}O_2Br$ $[M]^+$ 296.0412; found $m/e = 296.0419$.

***O*-Benzyl-3-(4-bromophenyl)-2,3-epoxypropanol**: A solution of benzyl ether **20** (1.5 g, 4.95 mmol) in CH_2Cl_2 (20 mL) was treated with *m*-CPBA (1.28 g, 7.4 mmol) at 25 °C for 4 h. Ethyl acetate was added to the reaction mixture, and the organic layer was washed with saturated KI, $Na_2S_2O_5$, H_2O, and saturated NaCl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 10–20% ethyl acetate/hexanes) yielded 1.3 g (4.05 mmol, 82%) of the epoxide as a colorless oil: $R_f = 0.33$ (silica gel, 10% EtOAc in hexane); FT-IR (neat): $\tilde{\nu} = 2859$, 1598, 1490, 1452, 1360, 1101, 1009 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.38$ (d, $J = 8.5$ Hz, 2H, Ar), 7.28 (m, 5H, Ar), 7.06 (d, $J = 8.5$ Hz, 2H, Ar), 4.54 (d, $J = 5$ Hz, 2H, OCH_2Ph), 3.76 (dd, $J = 3$, 11.5 Hz, 1H, CH_2OBn), 3.69 (d, $J = 2$ Hz, 1H, C-3), 3.55 (dd, $J = 11.5$, 5.5 Hz, 1H, CH_2OBn), 3.11 (m, 1H, C-2); FAB HRMS (NBA): calcd for $C_{16}H_{15}O_2Br$ $[M+Cs]^+$ 450.9310; found $m/e = 450.9314$.

***O*-Benzyl-3-(4-bromophenyl)-2-hydroxypropanol**: A solution of the above epoxide (1.2 g, 3.76 mmol) in toluene (20 mL) was cooled to 0 °C and treated with DIBAL-H (4.2 mL, 1.0 M in hexane) dropwise over 5 min. After the mixture had been stirred at 0 °C for 10 min the reaction mixture was quenched with MeOH (1 mL). The reaction mixture was then treated with saturated sodium/potassium tartrate and stirred at 25 °C for 15 min. EtOAc was added and the organic layer was washed with 1N HCl, saturated $NaHCO_3$, and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography

0947-6539/98/0401-0038 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 1

(silica gel, 30–40% ethyl acetate/hexanes) yielded 1.04 g (3.2 mmol, 86%) of the alcohol as a colorless oil: $R_f = 0.29$ (silica gel, 20% EtOAc in hexane); FT-IR (neat): $\tilde{\nu} = 3420$, 3028, 2856, 1488, 1453, 1104, 1075, 730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.32$ (d, $J = 8.5$ Hz, 2H, Ar), 7.25 (m, 5H, OCH_2Ph), 7.0 (d, $J = 8.0$ Hz, 2H, Ar), 4.45 (d, $J = 4$ Hz, 2H, OCH_2Ph), 3.91 (m, 1H, $CHOH$), 3.41 (dd, $J = 9.5$, 3.5 Hz, 1H, CH_2OBn), 3.29 (dd, $J = 9.5$, 7.0 Hz, 1H, CH_2OBn), 2.67 (d, $J = 7.0$ Hz, 2H, $ArCH_2$), 2.38 (br, 1H, OH); FAB HRMS (NBA): calcd for $C_{16}H_{17}O_2Br$ $[M+Cs]^+$ 452.9466; found $m/e = 452.9469$.

***O*-Benzyl-3-(4-bromophenyl)-2-(*tert*-butyldimethylsilyloxy)propanol (22)**: A solution of the above alcohol (0.9 g, 2.8 mmol), TBDMS-Cl (0.55 g, 3.6 mmol), and imidazole (0.25 g, 3.64 mmol) in DMF (3 mL) was stirred at 25 °C for 3 h. Ethyl acetate was added to the reaction mixture and the organic layer was washed with H_2O and saturated NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 10–20% ethyl acetate/hexanes) yielded 1.18 g (2.7 mmol, 97%) of compound **22** as a colorless oil. $R_f = 0.68$ (silica gel, 10% EtOAc in hexane); FT-IR (neat): $\tilde{\nu} = 2924$, 2853, 1490, 1258, 1106, 830, 776 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 7.54$ (d, $J = 8.4$ Hz, 2H, Ar), 7.50 (s, 5H, OCH_2Ph), 7.23 (d, $J = 8.4$ Hz, 2H, Ar), 4.73 (s, 2H, OCH_2Ph), 4.19 (m, 1H, $CHOTBS$), 3.57 (dd, $J = 9.4$, 5.1 Hz, 1H, CH_2OBn), 3.49 (dd, $J = 9.4$, 6.0 Hz, 1H, CH_2OBn), 3.07 (dd, $J = 13.2$, 4.4 Hz, 1H, $ArCH_2$), 2.81 (dd, $J = 13.2$, 5.3 Hz, 1H, $ArCH_2$), 1.04 (s, 9H, Si*t*Bu), 0.15 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 138.2$, 137.7, 131.6, 131.1, 131.0, 128.3, 127.6, 127.5, 119.8, 73.7, 73.3, 72.2, 40.5, 25.7, 17.9, 3.4,3.3, 3.0, 2.9, 2.8; FAB HRMS (NBA): calcd for $C_{22}H_{31}O_2SiBr$ $[M-H]^+$ 433.1198; found $m/e = 433.1181$.

Ethyl 3-[3-[4-(3-*tert*-butyldimethylsilyloxy-2*E*-propenyl)]phenoxy-4-methoxyphenyl]propanoate (24): A solution of ethyl 3-(3-hydroxy-4-methoxy)-phenyl propanoate (**23**) (0.7 g, 3.12 mmol), silyl ether **19** (0.98 g, 3.0 mmol), K_2CO_3 (2.58 g, 18.7 mmol) and $CuBr \cdot Me_2S$ (1.28 g, 6.2 mmol) in dry pyridine (10 mL) was stirred at 140 °C for 6 h in an autoclave. After the reaction mixture had cooled down, ethyl acetate was added, and the organic layer was washed with 1N HCl and saturated NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% ethyl acetate/hexanes) gave 1.10 g of the biaryl ether (2.34 mmol, 78%) as a colorless oil. $R_f = 0.73$ (silica gel, 30% EtOAc in hexane); IR (neat): $\tilde{\nu} = 1730$, 1500, 1270 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.32$ (m, 2H, Ar), 7.12 (d, $J = 7.2$ Hz, 1H, Ar), 6.60–6.99 (band, 4H, Ar), 6.53 (d, $J = 15.7$ Hz, 1H, ArCH=CH), 6.33 (dt, $J = 15.7$, 5.7 Hz, 1H, ArCH=CH), 4.34 (d, $J = 5.0$ Hz, 2H, CH_2OTBS), 4.10 (q, $J = 7.1$ Hz, 2H, CH_2CH_3), 3.81 (s, 3H, ArOCH_3), 2.85 (t, $J = 7.7$ Hz, 2H, ArCH_2CH_2), 2.52 (t, $J = 7.7$ Hz, 2H, $ArCH_2CH_2$), 1.22 (t, $J = 7.1$ Hz, 3H, CH_2CH_3), 0.95 (s, 9H, Si*t*Bu), 0.12 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$).

Ethyl 3-[3-[4-(3-hydroxy-2*E*-propenyl)]phenoxy-4-methoxyphenyl]propanoate: A solution of the above ester (0.9 g, 1.9 mmol) in THF (10 mL) was treated with TBAF (2 mL, ≈1M in THF) at 25 °C for 3 h. Ethyl acetate was added to the reaction mixture and the organic layer was washed with H_2O and saturated NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 0.64 g (1.8 mmol, 94%) of the alcohol as a pale yellow oil, which was used without further purification. $R_f = 0.13$ (silica gel, 30% EtOAc in hexane).

3-[3-[4-(3-hydroxy-2*E*-propenyl)]phenoxy-4-methoxyphenyl]propanoic acid (25): The above aryl ether (0.6 g, 1.69 mmol) was dissolved in THF (5 mL)/MeOH (5 mL). The mixture was cooled in an ice-water bath and 3N LiOH (5 mL) was added dropwise. The reaction mixture was allowed to warm slowly to 25 °C and after 2 h was acidified with 1N HCl and extracted with ethyl acetate. The organic layer was washed with water and saturated NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a white solid (0.51 g, 1.55 mmol, 92%). $R_f = 0.21$ (silica gel, 30% EtOAc and 2% CH_3COOH in hexane); FT-IR (thin film): $\tilde{\nu} = 1696$, 1506, 1225, 1128 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.31$ (d, $J = 8.4$ Hz, 2H, Ar), 6.95–6.82 (band, 5H, Ar), 6.58 (d, $J = 16.2$ Hz, 1H, ArCH=CH), 6.26 (dt, $J = 16.2$, 6.1 Hz, 1H, ArCH=CH), 4.30 (d, $J = 6.4$ Hz, 2H, CH_2OH), 3.81 (s, 3H, ArOCH_3), 2.87 (t, $J = 7.2$ Hz, 2H, ArCH_2CH_2), 2.62 (t, $J = 7.2$ Hz, 2H, $ArCH_2CH_2$); FAB HRMS (NBA): calcd for $C_{19}H_{20}O_5$ $[M]^+$ 328.1311; found $m/e = 328.1302$.

3-[3-((4-formyl)phenoxy)-4-methoxyphenyl]propanoic acid: A solution of the above acid (0.20 g, 0.61 mmol) in AcOEt (13 mL) was treated with PhSH (1 mL, 9.7 mmol) at 25 °C for 3 h. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 30% ethyl acetate/hexanes) gave 0.10 g (0.35 mmol, 57%) of pale yellow crystals. M.p. 110–114 °C; $R_f = 0.53$ (silica gel, 30% EtOAc and 2% CH_3COOH in hexane); FT-IR (thin film): $\tilde{\nu} = 1690$, 1598, 1512, 1274, 1155 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 9.85$ (s, 1H, CHO), 7.78 (d, $J = 8.6$ Hz, 2H, Ar), 7.08–6.92 (band, 5H, Ar), 3.75 (s, 3H, OCH_3), 2.88 (t, $J = 7.6$ Hz, 2H, ArCH_2CH_2), 2.63 (t, $J = 7.6$ Hz, 2H, $ArCH_2CH_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 190.9$, 178.5, 163.5, 150.0, 142.6, 133.4, 131.9, 130.7, 125.9, 122.4, 116.1, 113.1, 55.9, 35.5, 29.5; FAB HRMS (NBA): calcd for $C_{17}H_{16}O_5$ $[M]^+$ 300.0998; found $m/e = 300.0992$.

Ethyl 3-[3-[4-(3-benzyloxy-2-*tert*-butyldimethylsilyloxypropyl)]phenoxy-4-methoxyphenyl]propanoate (27): A solution of ethyl 3-(3-hydroxy-4-methoxy)phenyl propanoate (**23**) (0.7 g, 3.12 mmol), silyl ether **22** (0.9 g, 2.08 mmol), K_2CO_3 (0.86 g, 6.24 mmol) and $CuBr \cdot Me_2S$ (0.85 g, 4.16 mmol) in dry pyridine (7 mL) was stirred at 140 °C for 6 h in an autoclave. Ethyl acetate was added to the cooled reaction mixture and the organic layer was washed with 1N HCl and saturated NaCl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5–15% ethyl acetate/hexanes) gave 1.1 g (1.91 mmol, 92%) of biaryl ether **27** as a colorless oil: $R_f = 0.65$ (silica gel, 20% EtOAc in hexane); FT-IR (neat): $\tilde{\nu} = 2953$, 2856, 1734, 1505, 1270, 1230, 1121, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.58$–6.97 (band, 12 H, Ar), 4.76 (s, 2H, OCH_2Ph), 4.31 (q, $J = 7.5$ Hz, 2H, CH_2CH_3), 4.19 (m, 1H, $CHOTBS$), 4.03 (s, 3H, OCH_3), 3.65 (dd, $J = 9.5$, 5.0 Hz, 1H, CH_2OBn), 3.60 (dd, $J = 9.5$, 6.0 Hz, 1H, CH_2OBn), 3.14 (dd, $J = 13.5$, 4.5 Hz, 1H, $ArCH_2CHOTBS$), 3.04 (t, $J = 8.0$ Hz, 2H, $ArCH_2CH_2$), 2.86 (dd, $J = 13.5$, 8.0 Hz, 1H, $ArCH_2CHOTBS$), 2.74 (t, $J = 8.0$ Hz, 2H, $ArCH_2CH_2$), 1.42 (t, $J = 7.5$ Hz, 3H, CH_2CH_3), 1.04 (s, 9H, Si*t*Bu), 0.14 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$); FAB HRMS (NBA): calcd for $C_{34}H_{46}O_6Si$ $[M+Na]^+$ 601.2961; found $m/e = 601.2954$.

3-[3-[4-(3-benzyloxy-2-(*tert*-butyldimethylsilyloxy)propyl)]phenoxy-4-methoxyphenyl]propanoic acid (28): The above aryl ether (1.0 g, 1.72 mmol) was dissolved in THF (7 mL)/MeOH (7 mL); the mixture was cooled in an ice-water bath and 3N LiOH (7 mL) was added dropwise. The reaction mixture was allowed to warm slowly to 25 °C and after 2 h was acidified with 1N HCl and extracted with ethyl acetate. The organic layer was washed with water and saturated NaCl, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the acid as a colorless oil 0.89 g (1.6 mmol, 94%), which was used without further purification. $R_f = 0.36$ (silica gel, 20% EtOAc and 2% CH_3COOH in hexane); IR (neat): $\tilde{\nu} = 3035$, 2920, 2860, 1710, 1505, 1270, 1225, 1125, 830 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 7.56$–6.75 (band, 12H, Ar), 4.75 (s, 2H, OCH_2Ph), 4.18 (m, 1H, $CHOTBS$), 4.02 (s, 3H, OCH_3), 3.62 (m, 2H, CH_2OBn), 3.14 (dd, $J = 13.4$, 4.5 Hz, 1H, $ArCH_2CHOTBS$), 3.03 (t, $J = 7.6$ Hz, 2H, $ArCH_2CH_2$), 2.85 (dd, $J = 13.4$, 8.0 Hz, 1H, $ArCH_2CHOTBS$), 2.79 (t, $J = 7.6$ Hz, 2H, $ArCH_2CH_2$), 1.03 (s, 9H, Si*t*Bu), 0.14 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$); FAB HRMS (NBA): calcd for $C_{32}H_{42}O_6Si$ $[M+Cs]^+$ 683.1805; found $m/e = 683.1825$.

3-[3-[4-(3-hydroxy-2-*tert*-butyldimethylsilyloxypropyl)]phenoxy-4-methoxyphenyl]propanoic acid (29): A solution of compound **28** (0.8 g, 1.45 mmol) and Pd/C (10%, 80 mg) in EtOAc (40 mL) was stirred at 25 °C under hydrogen for 4 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure to give 0.67 g (1.45 mmol, 100%) of compound **29** as a colorless oil. $R_f = 0.16$ (silica gel, 20% EtOAc and 2% CH_3COOH in hexane); IR (neat): $\tilde{\nu} = 2940$, 2920, 1705, 1600, 1578, 1494, 825 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.19$–6.75 (band, 7H, Ar), 3.90 (m, 1H, $CHOTBS$), 3.81 (s, 3H, OCH_3), 3.46 (m, 2H, CH_2OH), 2.81 (t, $J = 8.5$ Hz 2H, $ArCH_2CH_2$), 2.59 (t, $J = 8.5$ Hz, 2H, $ArCH_2CH_2$), 0.90 (s, 9H, Si*t*Bu), 0.05 (s, 3H, $SiCH_3$), −0.10 (s, 3H, $SiCH_3$); FAB HRMS (NBA): calcd for $C_{25}H_{36}O_6Si$ $[M+Na]^+$ 483.2179; found $m/e = 483.2189$.

4-Methoxy-13-(*tert*-butyldimethylsilyloxy)-2,11-dioxatricyclo[13.2.2.1^{3,7}]eicosa-1(18),3,5,7(20),1(19),16-hexaen-10-one (30): A solution of **28** (0.23 g, 0.505 mmol) in toluene (50 mL) and benzene (3 mL) was prepared. DEAD (0.48 mL, 3.0 mmol) was added to a solution of PPh_3 (0.78 g, 2.97 mmol) in dry toluene (200 mL) under N_2 at 25 °C. The temperature was increased to 45 °C and half of the solution of **28** was added dropwise over 3.5 h, while the reaction mixture was stirred vigorously. Second portions of PPh_3 (0.39 g, 1.48 mmol) and DEAD (0.24 mL, 1.5 mmol) were added and the remaining **28** was added over 3.5 h. The reaction mixture was stirred for another 8 h and concentrated under reduced pressure to give a red oil. Purification by

flash column chromatography (silica gel, 10–25%, ethyl acetate/hexanes) gave 0.20 g of macrolactone **30** (0.459 mmol, 91%) as a white solid. M.p. 153–155 °C; R_f = 0.26 (silica gel, 10% EtOAc in hexane); FT-IR (thin film): $\tilde{\nu}$ = 2924, 1739, 1582, 1225, 1085, 830 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21–7.08 (band, 2H, C-6, C-18), 6.94 (dd, J = 8.0, 3.0 Hz, 1H, C-7), 6.86 (dd, J = 8.0, 2.5 Hz, 1H, C-19), 6.67 (d, J = 8.0 Hz, 1H, C-12), 6.52 (dd, J = 8.3, 2.1 Hz, 1H, C-13), 5.11 (d, J = 2.8 Hz, 1H, C-20), 4.31 (dd, J = 11.5, 7.0 Hz, 1H, C-2b), 3.95 (m, 1H, C-3), 3.80 (s, 3H, ArOCH_3), 3.51 (d, J = 11.5 Hz, 1H, C-2a), 3.12 (dd, J = 11.9, 5.9 Hz, 1H, C-4), 2.95 (dd, J = 17.1, 11.9 Hz, 1H, C-15b), 2.53–2.44 (band, 2H, C-4, C-15a), 2.26 (dd, J = 17.1, 7.3 Hz, 1H, C-16), 2.01 (dd, J = 17.1, 11.9 Hz, 1H, C-16), 0.79 (s, 9H, *t*BuSi), 0.04 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$); FAB HRMS (NBA): calcd for $C_{25}H_{34}O_5Si$ [M+Cs]$^+$ 575.1230; found m/e = 575.1248.

4-Methoxy-13-hydroxy-2,11-dioxatricyclo[13.2.2.1^{3,7}]eicosa-1(18),3,5,7-(20),1(19),16-hexaen-10-one (**31**): A solution of compound **30** (150 mg, 0.34 mmol) in THF (8 mL) was treated with TBAF (0.4 mL, ≈ 1M in THF) at 25 °C for 30 min. Ethyl acetate was added to the reaction mixture and the organic layer was washed with H_2O and saturated NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 30–50% ethyl acetate/hexanes) yielded 105 mg (0.32 mmol, 94%) of **31** as a white amorphous solid: R_f = 0.14 (silica gel, 30% EtOAc in hexane); FT-IR (thin film): $\tilde{\nu}$ = 2925, 1734, 1585, 1522, 1264, 1219, 1133, 755 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.32 (m, 2H, C-6, C-18), 7.09, (m, 2H, C-7, C-19), 6.78 (d, J = 7.7 Hz, 1H, C-12), 6.62 (dd, J = 8.3, 1.8 Hz, 1H, C-13), 5.26 (d, J = 1.3 Hz, 1H, C-20), 4.32 (dd, J = 11.5, 6.7 Hz, 1H, C-2b), 4.22 (m, 1H, C-3), 3.95 (s, 3H, ArOCH_3), 3.91 (d, J = 11.5 Hz, 1H, C-2a), 3.22 (dd, J = 12.5, 3.8 Hz, 1H, C-4b), 2.95 (dd, J = 16.0, 9.6 Hz, 1H, C-15b), 2.80–2.62 (band, 2H, C-4a, C-15a), 2.41–2.12 (band, 2H, C-16), 2.10 (s, 1H, OH); FAB HRMS (NBA): calcd for $C_{19}H_{20}O_5$ [M]$^+$ 328.1311; found m/e = 328.1323.

4-Methoxy-13-iodo-2,11-dioxatricyclo[13.2.2.1^{3,7}]eicosa-1(18),3,5,7(20),1-(19),16-hexaen-10-one: A solution of alcohol **31** (95 mg, 0.29 mmol), PPh_3 (152 mg, 0.58 mmol), I_2 (147 mg, 0.58 mmol) and imidazole (59 mg, 0.87 mmol) in toluene (7 mL) was stirred at 80 °C for 30 min. Ethyl acetate was added to the reaction mixture and the organic layer was washed with H_2O and saturated NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Small column filtration (silica gel) yielded 120 mg (0.275 mmol, 95%) of the iodide as a white amorphous solid [R_f = 0.38 (silica gel, 10% EtOAc in hexane)], which was used without further purification.

Combretastatin D-2 methyl ether (**32**): A solution of the above iodide (110 mg, 0.25 mmol) and KF (145 mg, 2.5 mmol) in DMSO (2 mL) was stirred at 115 °C for 4 h. Ethyl acetate was added to the reaction mixture and the organic layer was washed with H_2O and saturated NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 10–25% ethyl acetate/hexanes) yielded 67 mg (0.22 mmol, 87%) of methoxy combretastatin D-2 as a white solid. M.p. 130–132 °C; R_f = 0.31 (silica gel, 10% EtOAc in hexane); FT-IR (thin film): $\tilde{\nu}$ = 1734, 1522, 1210, 1150, 1127, 749 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.34 (d, J = 8.3 Hz, 1H, C-6), 7.28 (d, J = 9.5 Hz, 1H, C-18), 7.12–7.08 (band, 3H, C-4, C-19, C-7), 6.83 (d, J = 6.9 Hz, 1H, C-12), 6.68 (dd, J = 1.3, 6.9 Hz, 1H, C-13), 6.08 (dt, J = 9.2, 5.6 Hz, 1H, C-3), 5.11 (d, J = 1.6 Hz, 1H, C-20), 4.65 (d, J = 5.6 Hz, 2H, C-2), 3.94 (s, 3H, ArOCH_3), 2.89 (t, J = 4.4 Hz, 2H, C-15), 2.29 (t, J = 4.4 Hz, 2H, C-16); FAB HRMS (NBA): calcd for $C_{19}H_{18}O_4$ [M]$^+$ 310.1205; found m/e = 310.1212.

3-Hydroxy-4-benzyloxybenzaldehyde: A solution of 3,4-dihydroxybenzaldehyde **33** (7.0 g, 0.050 mol) and K_2CO_3 (6.1 g, 0.044 mol) in DMF (60 mL) was stirred at 60 °C for 4 h. Then BnBr (6.5 mL, 0.055 mol) was added and the reaction mixture was stirred at 25 °C for another 12 h. Ethyl acetate was added to the reaction mixture and the organic layer was washed with saturated NH_4Cl, H_2O, and saturated NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 30/50% ethyl acetate/hexanes) yielded 8.6 g (0.038 mol, 76%) of the monoprotected compound as a white crystalline solid. M.p. 109–112 °C; R_f = 0.72 (silica gel, 50% EtOAc in hexane); FT-IR (KBr): $\tilde{\nu}$ = 3200, 2580, 1720, 1680, 1610, 1520, 1290, 1115, 1010, 740 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.70 (s, 1H, CHO), 7.30 (m, 6H, Ar), 6.90 (d, J = 8 Hz, 1H, Ar), 5.69 (s, 1H, OH), 5.08 (s, 2H, OCH_2Ph); FAB HRMS (NBA): calcd for $C_{14}H_{12}O_3$ [M+H]$^+$ 229.0865; found m/e = 229.0860.

Ethyl 3-(3-hydroxy-4-benzyloxy)phenyl-2(*E*)-propenoate: A solution of 3-hydroxy-4-benzyloxybenzaldehyde (6.7 g, 0.029 mol) and Ph_3P=CHCOOEt (12.4 g, 0.035 mol) in benzene (18 mL) was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 25–35% EtOAc in hexane) afforded 8.0 g (0.027 mol, 93%) of the ester as white crystals. M.p. 80–85 °C; R_f = 0.46 (silica gel, 30% EtOAc in hexane); FT-IR (KBr): $\tilde{\nu}$ = 3480, 3005, 2900, 1705, 1610, 1505, 1290, 985 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.62 (d, J = 15.6 Hz, 1H, ArCH=CH), 7.40 (s, 5H, Ar), 7.15 (d, J = 1.9 Hz, 1H, Ar), 6.99 (dd, J = 8.2, 1.9 Hz, 1H, Ar), 6.89 (d, J = 8.2 Hz, 1H, Ar), 6.28 (d, J = 15.6 Hz, 1H, ArCH=CH), 5.75 (s, 1H, OH), 5.12 (s, 2H, OCH_2Ph), 4.24 (q, J = 7.0 Hz, 2H, CH_2CH_3), 1.32 (t, J = 7.0 Hz, 2H, CH_2CH_3); FAB HRMS (NBA): calcd for $C_{18}H_{18}O_4$ [M+H]$^+$ 299.1283; found m/e = 299.1289

Ethyl 3-(3-hydroxy-4-benzyloxy)phenylpropanoate (**34**): A solution of the above ester (5.0 g, 16.7 mmol) and Pd/C (5%, 250 mg) in benzene (40 mL) was stirred at 25 °C under hydrogen for 5 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure to give 4.88 g of **34** (16.2 mmol, 97%) as a colorless oil. R_f = 0.59 (silica gel, 20% EtOAc in hexane); IR (neat): $\tilde{\nu}$ = 3520, 2965, 1715, 1582, 1500, 1265, 1008, 735 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40 (m, 5H, Ar), 6.86 (d, J = 6.1 Hz, 1H, Ar), 6.83 (s, 1H, Ar), 6.68 (dd, J = 6.1, 2.2 Hz, 1H, Ar), 5.87 (s, 1H, OH), 5.09 (s, 2H, OCH_2Ph), 4.15 (q, J = 7.2 Hz, 2H, CH_2CH_3), 2.89 (t, J = 7.7 Hz, 2H, ArCH_2CH$_2$), 2.60 (t, J = 7.7 Hz, 2H, ArCH$_2CH_2$), 1.25 (t, J = 7.2 Hz, 3H, CH_2CH_3); FAB HRMS (NBA) calcd for $C_{18}H_{20}O_4$ [M]$^+$ 300.1362; found m/e = 300.1367.

Ethyl 3-[3-[4-(3-pivaloyloxy-2*E*-propenyl)]phenoxy-4-benzyloxyphenyl]-propanoate (**35**): A solution of compound **34** (2.3 g, 7.6 mmol), aryl bromide **21** (1.6 g, 5.0 mmol), K_2CO_3 (2.1 g, 15.2 mmol) and CuBr·Me_2S (2.1 g, 10.2 mmol) in dry pyridine was stirred at 140 °C for 6 h in an autoclave. Ethyl acetate was added to the cooled reaction mixture and the organic layer was washed with 1N HCl and saturated NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 10–20% ethyl acetate/hexanes) yielded 1.95 g of **35** (3.9 mmol, 78%) as a colorless oil. R_f = 0.53 (silica gel, 15% EtOAc in hexane); FT-IR (neat): $\tilde{\nu}$ = 3028, 1722, 1505, 1213, 755 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.43–6.81 (band, 12H, Ar), 6.62 (d, J = 16.5 Hz, 1H, ArCH=CH), 6.20 (dt, J = 16.5, 5.9 Hz, 1H, ArCH=CH), 5.05 (s, 2H, OCH_2Ph), 4.71 (d, J = 5.9 Hz, 2H, CH_2OPiv), 4.12 (q, J = 6.9 Hz, 2H, CH_2CH_3), 2.88 (t, J = 8.0 Hz, 2H, ArCH_2CH$_2$), 2.58 (t, J = 8.0 Hz, 2H, ArCH$_2CH_2$), 1.25 (m, 12H, C(CH_3)$_3$ and CH_2CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.2, 172.5, 159.9, 150.4, 146.4, 135.8, 134.8, 132.1, 130.1, 129.8, 129.4, 129.3, 129.2, 128.5, 126.3, 123.5, 123.4, 118.3, 116.8, 72.6, 66.6, 61.8, 37.42, 31.6, 28.7, 15.7; FAB HRMS (NBA): calcd for $C_{32}H_{36}O_6$ [M+Cs]$^+$ 649.1566; found m/e = 649.1576.

Ethyl 3-[3-[4-(1*R*,2*R*)-(1,2-dihydroxy-3-pivaloyloxy)propyl]phenoxy-4-benzyloxyphenyl]propanoate (**36**): A solution of $K_3Fe(CN)_6$ (1.0 g, 3 mmol), K_2CO_3 (0.42 g, 3 mmol) and $(DHQD)_2PHAL$ (193 mg, 0.25 mmol) in *t*BuOH:H_2O (1:1) was stirred at 25 °C for 40 min. After addition of $K_2Os_2(OH)_4$ (3.7 mg, 0.01 mmol) the mixture was cooled to 0 °C; $CH_3SO_2NH_2$ (190 mg, 0.2 mmol) was added and stirred for 10 min. Finally olefin **35** (0.50 g, 1 mmol) was added and the reaction mixture was stirred vigorously at 0 °C for 12 h. After addition of Na_2SO_3 the mixture was allowed to warm to 25 °C and ethyl acetate was added. The organic layer was washed with saturated NH_4Cl and saturated NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 50–60% ethyl acetate/hexanes) afforded 0.48 g (0.87 mmol, 87%) of compound **36** as a white amorphous solid. R_f = 0.12 (silica gel, 30% EtOAc in hexane); $[\alpha]_D$ = −4.5 (c = 0.078 in acetone); FT-IR (thin film): $\tilde{\nu}$ = 2970, 1728, 1608, 1511, 1276, 1167, 1127, 1041, 743 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.25 (m, 7H, Ar), 6.90 (m, 5H, Ar), 5.08 (s, 2H, OCH_2Ph), 4.61 (d, J = 7.2 Hz, 1H, ArCHOTBS), 4.22–3.86 (band, 5H, CHOTBS, CH_2OPiv, and CH_2CH_3), 2.87 (t, J = 7.5 Hz, 2H, ArCH_2CH$_2$), 2.57 (t, J = 7.5 Hz, 2H, ArCH$_2CH_2$), 1.25 (m, 12H, C(CH_3)$_3$ and CH_2CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 180.5, 174.3, 160.0, 150.5, 146.4, 138.4, 135.9, 135.2, 76.0, 75.6, 72.5, 66.7, 62.0, 37.5, 31.7, 28.8; FAB HRMS (NBA): calcd for $C_{32}H_{38}O_8$ [M+Cs]$^+$ 683.1621; found m/e = 683.1633.

Ethyl 3-[3-[4-(1*R*,2*R*)-(1,2-di-*tert*-butyldimethylsilyloxy-3-pivaloyloxy)-propyl]phenoxy-4-benzyloxyphenyl]propanoate (**37**): A solution of diol **4**

0947-6539/98/0401-0040 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 1

(0.4 g, 0.73 mmol), TBDMSCl (242 mg, 1.6 mmol), and imidazole (119 mg, 1.75 mmol) in DMF was stirred at 25 °C for 3 h. Ethyl acetate was added to the reaction mixture, and the organic layer was washed with H_2O and saturated NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5–15% ethyl acetate/hexanes) yielded 0.55 g (0.71 mmol, 97%) of **37** as a colorless oil. $R_f = 0.50$ (silica gel, 10% EtOAc in hexane); $[\alpha]_D = -14$ ($c = 0.012$ in $CHCl_3$), FT-IR (neat): $\tilde{\nu} = 2959$, 2856, 1734, 1505, 1156, 841 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.23$ (m, 7H, Ar), 6.88 (m, 5H, Ar), 5.05 (s, 2H, O*CH*$_2$Ph), 4.72 (d, $J = 4.5$ Hz, 1H, Ar*CH*OTBS), 4.23 (dd, $J = 4.5$, 11.1 Hz, 1H, *CH*$_2$OPiv), 4.10 (q, $J = 7.3$ Hz, 2H, *CH*$_2$CH$_3$), 3.87 (m, 1H, *CH*OTBS), 3.65 (dd, $J = 6.5$, 11.1 Hz, 1H, *CH*$_2$OPiv), 2.85 (t, $J = 8.0$ Hz, 2H, Ar*CH*$_2$), 2.55 (t, $J = 8.0$ Hz, 2H, ArCH$_2$*CH*$_2$), 1.2 (m, 12H, C(CH$_3$)$_3$ and CH$_2$*CH*$_3$), 0.90 (s, 9H, Si*t*Bu), 0.89 (s, 9H, Si*t*Bu), 0.05 (s, 3H, SiCH$_3$), 0.03 (s, 3H, SiCH$_3$), −0.08 (s, 3H, SiCH$_3$), −0.10 (s, 3H, SiCH$_3$); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 179.9$, 174.3, 159.0, 150.5, 147.0, 138.6, 136.5, 135.8, 76.2, 72.6, 67.1, 61.9, 40.3, 37.5, 32.5, 31.7, 28.9, 27.4, 19.8, 19.6, 15.8; FAB HRMS (NBA): calcd for $C_{44}H_{66}O_8Si_2$ $[M+Cs]^+$ 911.3351; found $m/e =$ 911.3368.

3-[3-[4-(1*R*,2*R*)-(1,2-Di-*tert*-butyldimethylsilyloxy-3-hydroxy)propyl]phenoxy-4-benzyloxyphenyl]propanoic acid (**38**): Compound **37** (0.5 g, 0.64 mmol) was dissolved in THF (10 mL)/MeOH (10 mL). The mixture was cooled in an ice-water bath and 3N LiOH (10 mL) was added dropwise. The reaction mixture was allowed to warm slowly to 25 °C and after 2 h was acidified with 3N HCl and extracted with ethyl acetate. The organic layer was washed with water and saturated NaCl, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the respective acid as a colorless oil [$R_f = 0.29$ (silica gel, 30% EtOAc in hexane)] which was diluted with anhydrous CH_2Cl_2 and cooled to −78 °C. DIBAL-H (1M solution in cyclohexane, 0.7 mL, 0.7 mmol) was added dropwise over 10 min. MeOH was added and the reaction mixture was then treated with saturated sodium/potassium tartrate and stirred at 25 °C for 15 min. EtOAc was added to the reaction mixture and the organic layer was washed with 1N HCl, saturated $NaHCO_3$, and brine, then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 40–50% ethyl acetate/hexanes) yielded 385 mg (0.58 mmol, 90%) of **38** as a colorless oil: $R_f = 0.57$ (silica gel, 20% EtOAc and 5% CH_3COOH in hexane); FT-IR (neat): $\tilde{\nu} = 2924$, 2859, 1707, 1501, 1263, 1214, 830 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta =$ 9.81 (s, 1H, COOH), 7.25 (m, 7 H, Ar), 6.90 (m, 5H, Ar), 5.08 (s, 2H, O*CH*$_2$Ph), 4.77 (d, $J = 5.0$ Hz, 1H, Ar*CH*OTBS), 3.87 (m, 1H, CH$_2$*CH*OTBS), 3.60 (br, 1H, OH), 3.54 (dd, $J = 5.7$, 11.2 Hz, 1H, *CH*$_2$OH), 3.65 (dd, $J = 4.5$, 11.2 Hz, 1H, *CH*$_2$OH), 2.86 (t, $J = 7.3$ Hz, 2H, Ar*CH*$_2$CH$_2$), 2.58 (t, $J = 7.3$ Hz, 2H, ArCH$_2$*CH*$_2$), 0.90 (s, 18H, Si*t*Bu), 0.08 (s, 3H, SiCH$_3$), 0.05, (s, 3H, SiCH$_3$), 0.03 (s, 3H, SiCH$_3$), −0.07 (s, 3H, SiCH$_3$); FAB HRMS (NBA): calcd for $C_{37}H_{54}O_7Si_2$ $[M+Cs]^+$ 799.2462; found $m/e =$ 799.2478.

(13*R*,14*R*)-4-Benzyloxy-13,14-(di-*tert*-butyldimethylsilyloxy)-2,11-dioxatricyclo[13.2.2.1^{3,7}]eicosa-1(18),3,5,7(20),1(19),16-hexaen-10-one (**39**): A solution of **38** (250 mg, 0.37 mmol) in toluene (50 mL) was prepared. DEAD (0.35 mL, 2.22 mmol) was added to a solution of PPh_3 (0.58 g, 2.20 mmol) in dry toluene (200 mL) under N_2 at 25 °C. The temperature was increased to 45 °C and half of the solution of **39** was added dropwise over 3 h while the reaction mixture was stirred vigorously. Second portions of PPh_3 (0.29 g, 1.10 mmol) and DEAD (0.18 mL, 1.11 mmol) were added and the remaining **38** was added over 3 h. The reaction mixture was stirred for another 8 h period and concentrated under reduced pressure, affording a red viscous oil. Purification by flash column chromatography (silica gel, 10–20% ethyl acetate/hexanes) gave 194 mg (0.30 mmol, 81%) of the macrolide as a white amorphous solid. $R_f = 0.75$ (silica gel, 20% EtOAc in hexane); $[\alpha]_D = -51$ ($c = 0.080$ in $CHCl_3$); FT-IR (thin film): $\tilde{\nu} = 2959$, 2930, 2856, 1740, 1516, 1259, 1121, 829 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta =$ 7.62 (dd, $J = 8.1$, 2.1 Hz, 1H, C-6), 7.51 (dd, $J = 8.1$, 2.4 Hz, 1H, C-18), 7.43–7.26 (band, 5H, OCH$_2$*Ph*), 7.12 (dd, $J = 8.3$, 2.6 Hz, 1H, C-7), 6.98 (dd, $J =$ 8.3, 2.4 Hz, 1H, C-19), 6.84 (d, $J = 8.3$ Hz, 1H, C-12), 6.59 (dd, $J = 8.3$, 1.9 Hz, 1H, C-13), 5.31 (d, $J = 1.9$ Hz, 1H, C-20), 5.20 (s, 2H, O*CH*$_2$Ph), 4.58 (d, $J = 8.4$ Hz, 1H, C-4), 4.15 (m, 1H, C-3), 3.88 (dd, $J = 9.6$, 6.4 Hz, 1H, C-2), 3.70 (d, $J = 9.6$ Hz, 1H, C-2), 3.00 (dd, $J = 16.0$, 9.6 Hz, 1H, C-15), 2.65 (dd, $J = 16.0$, 8.8 Hz, 1H, C-15), 2.41–2.10 (band, 2H, C-16), 0.94 (s, 9H, Si*t*Bu), 0.88 (s, 9H, Si*t*Bu), 0.20 (s, 3H, SiCH$_3$), 0.12 (s, 3H, SiCH$_3$), 0.80 (s, 3H, SiCH$_3$), −0.50 (s, 3H, SiCH$_3$); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 174.9, 157.7, 153.5, 146.7, 139.3, 135.3, 131.0, 80.4, 77.7, 73.4, 68.9, 33.9, 28.5, 27.5, 27.5, 19.7, 19.6; FAB HRMS (NBA): calcd for $C_{37}H_{52}O_6Si_2$ $[M+Cs]^+$ 781.2357; found $m/e =$ 781.2387.

(13*R*,14*R*)-4-Benzyloxy-13,14-dihydroxy-2,11-dioxatricyclo[13.2.2.1^{3,7}]-eicosa-1(18),3,5,7(20),1(19),16-hexaen-10-one (**40**): A solution of the above macrolide (170 mg, 0.26 mmol) in THF (8 mL) was treated with TBAF (0.8 mL, ≈1M in THF) at 25 °C for 3 h. Ethyl acetate was added to the reaction mixture and the organic layer was washed with H_2O and saturated NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 60–90% ethyl acetate/hexanes) yielded 103 mg (0.24 mmol, 94%) of compound **40** as a white solid. M.p. 185–188 °C; $[\alpha]_D = -37$ ($c = 0.030$ in acetone); $R_f = 0.15$ (silica gel, 50% EtOAc in hexane); FT-IR (thin film): $\tilde{\nu} = 1730$, 1516, 1430, 1224, 778 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.63$ (d, $J = 8.0$ Hz, 1H, C-6), 7.51–7.18 (band, 7H, C-18, C-7 and OCH$_2$*Ph*), 7.01 (d, $J = 8.0$ Hz, 1H, C-19), 6.82 (d, $J = 8.0$ Hz, 1H, C-12), 6.59 (d, $J = 8.0$ Hz, 1H, C-13), 5.22 (s, 3H, C-20 and O*CH*$_2$Ph overlapped), 4.60 (d, $J = 8.8$ Hz, 1H, C-4), 4.35 (dd, $J = 9.6$, 7.0 Hz, 1H, C-3), 3.92 (m, 1H, C-2), 3.70 (d, $J =$ 11.8 Hz, 1H, C-2), 3.15–2.05 (band, 4H, C-15 and C-16); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 174.4$, 158.6, 153.4, 137.5, 135.1, 132.4, 80.1, 77.3, 73.2, 67.6, 33.9, 28.4; FAB MS (NBA): calcd for $C_{25}H_{24}O_6$ $[M+Na]^+$ 443; found $m/e = 443$.

(13*R*,14*R*)-4-Hydroxy-13,14-dihydroxy-2,11-dioxatricyclo[13.2.2.1^{3,7}]eicosa-1(18),3,5,7(20),1(19),16-hexaen-10-one (**41**): A solution of diol **40** (20 mg, 0.047 mmol) and Pd/C (10%, 4 mg) in EtOAc (7 mL) was stirred at 25 °C under hydrogen for 5 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure to give 15 mg (0.046 mmol, 98%) of triol **41** as a white amorphous solid: $R_f = 0.13$ (silica gel, 60% EtOAc in hexane); $[\alpha]_D = -35.5$ ($c = 0.040$ in MeOH); IR (KBr): $\tilde{\nu} = 3430$, 3296, 2912, 1708, 1597, 1518, 1438, 1359, 1291, 1230, 1164, 1104, 1029, 981, 872 cm^{-1}; ^1H NMR (600 MHz, CD_3OD): $\delta = 7.54$ (dd, $J = 8.4$, 2.1 Hz, 1H, C-6), 7.26 (dd, $J = 8.2$, 2.1 Hz, 1H, C-18), 7.04 (dd, $J = 8.4$, 2.4 Hz, 1H, C-7), 6.85 (dd, $J = 8.2$, 2.4 Hz, 1H, C-19), 6.61 (dd, $J = 8.2$, 1.5 Hz, 1H, C-12), 6.44 (dd, $J = 8.2$, 2.0 Hz, 1H, C-13), 5.16 (s 1H, C-20), 4.38 (d, $J = 8.4$ Hz, 1H, C-4), 4.13 (dd, $J = 11.8$, 7.5 Hz, 1H, C-2a), 3.71 (dd, $J = 8.4$, 7.5 Hz, 1H, C-3), 3.48 (d, $J = 11.8$ Hz, 1H, C-2b), 2.84 (dd, $J = 16.7$, 12.0 Hz, 1H, C-15a), 2.45 (dd, $J = 16.7$, 7.3 Hz, 1H, C-15b), 2.32 (dd, $J =$ 16.9, 7.3 Hz, 1H, C-16a), 2.00 (ddd, $J = 16.9$, 12.0, 1.1 Hz, 1H, C-16b); ^{13}C NMR (150 MHz, CD_3OD): $\delta = 174.7$, 157.8, 151.0, 144.4, 138.6, 132.9, 131.0, 129.6, 123.9, 122.3, 117.0, 114.4, 79.3, 76.4, 68.7, 33.5, 27.8; FAB HRMS (NBA): calcd for $C_{18}H_{18}O_6$ $[M+Na]^+$ 353.1001; found $m/e = 353.1016$.

Combretastatin D-2 (from **41**): A solution of triol **41** (3.8 mg, 0.0115 mmol), PPh_3 (12.1 mg, 0.0461 mmol), imidazole (1.57 mg, 0.0231 mmol) and triiodoimidazole (8.18 mg, 0.0183 mmol) in tetrachloroethylene (0.40 mL) was stirred at 140 °C for 0.5 h. After the reaction mixture was cooled down, EtOAc was added and the organic layer was washed with saturated $Na_2S_2O_3$, H_2O, and saturated NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% ethyl acetate/hexanes) yielded 3.4 mg (0.0108 mmol, 94%) of combretastatin D-2. $R_f = 0.30$ (silica gel, 20% EtOAc in hexane); IR (neat): $\tilde{\nu} = 3440$, 1725, 1520, 1500, 1440, 1210, 1185, 1110 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.30–7.02$ (band, 5H, Ar, C-4), 6.78 (d, $J = 8.0$ Hz, 1H, C-12), 6.57 (dd, $J = 8.0$, 2.0 Hz, 1H, C-13), 6.00 (dt, $J = 11.0$, 7.0 Hz, 1H, C-3), 5.43 (br, 1H, OH), 4.99 (d, $J =$ 2.0 Hz, 1H, C-20), 4.58 (d, $J = 6.5$ Hz, 2H, C-2), 2.80 (t, $J = 5.5$ Hz, 2H, C-15), 2.23 (t, $J = 5.5$ Hz, 2H, C-16).

Combretastatin D-2 benzyl ether (**42**): A solution of diol **40** (4 mg, 0.0095 mmol), PPh_3 (10.0 mg, 0.0461 mmol), imidazole (1.30 mg, 0.019 mmol), and triiodoimidazole (6.76 mg, 0.015 mmol) in tetrachloroethylene (0.48 mL) was stirred at 140 °C for 0.5 h. After the reaction mixture had cooled down, EtOAc was added and the organic layer was washed with saturated $Na_2S_2O_3$, H_2O, and saturated NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% ethyl acetate/hexanes) yielded 3.4 mg (0.0087 mmol, 92%) of olefin **42** as a colorless oil. $R_f = 0.40$ (silica gel, 10% EtOAc in hexane); IR (neat): $\tilde{\nu} = 1728$, 1510, 1500, 1110 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.44$ (d, $J = 7.5$ Hz, 2H, Ar), 7.33–7.19 (band, 6H, Ar, C-4), 7.04 (m, 2H, Ar), 6.76 (d, $J = 8.0$ Hz, 1H, C-12), 6.54 (dd, $J = 6.0$, 2.3 Hz, 1H, C-13), 5.98 (dt, $J = 11.5$, 6.5 Hz, 1H, C-3), 5.17 (s, 2H, O*CH*$_2$Ph), 5.05 (d, $J = 2.4$ Hz, 1H, C-20), 4.59 (d, $J =$

7.0 Hz, 2H, C-2), 2.80 (t, $J = 5.5$ Hz, 2H, C-15), 2.22 (t, $J = 5.5$ Hz, 2H, C-16); FAB HRMS (NBA): calcd for $C_{25}H_{22}O_4$ $(M)^+$ 386.1518; found $m/e =$ 386.1530.

Combretastatin D-2 (from **42**): A solution of the above olefin (3 mg, 0.0077 mmol) and $AlCl_3$ (1.6 mg, 0.012 mmol) in CH_2Cl_2 (0.4 mL) was stirred at 25 °C for 30 min. Ethyl acetate was added to the reaction mixture and the organic layer was washed with H_2O, and saturated NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% ethyl acetate/hexanes) yielded 1.48 mg (0.0050 mmol, 65%) of combretastatin D-2 and 0.6 mg (0.0015 mmol, 20%) of recovered **42**.

Combretastatin D-1 benzyl ether (**46**): A solution of the diol **40** (50 mg, 0.12 mmol) in DMF (2 mL) was treated with PPh_3 (13 mg, 0.049 mmol) and DEAD (0.08 mL, 0.48 mmol) at 145–150 °C for 40 min. EtOAc was added to the reaction mixture and the organic layer was washed with 1N HCl, H_2O and saturated NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 25–35% ethyl acetate/hexanes) yielded 41 mg (0.10 mmol, 87%) of compound **46** as a white amorphous solid. $R_f = 0.68$ (silica gel, 30% EtOAc in hexane); IR (KBr): $\tilde{\nu} = 1730, 1550, 1205, 1114$ cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.52$ (dd, $J = 8.0$, 2.0 Hz, 1H, C-6), 7.48 (d, $J = 7.5$ Hz, 1H, Ar), 7.38–7.24 (band, 5H, OCH_2Ph and C-18), 7.10 (dd, $J = 8.5$, 2.5 Hz, 1H, C-7), 7.07 (dd, $J = 8.5$, 2.5 Hz, 1H, C-19), 6.81 (d, $J = 8.0$ Hz, 1H, C-12), 6.57 (dd, $J = 8.1$, 2.1 Hz, 1H, C-13), 5.21 (s, 2H, OCH_2Ph), 4.98 (d, $J = 1.9$ Hz, 1H, C-20), 4.33 (d, $J = 5.0$ Hz, 1H, C-4), 4.23 (dd, $J = 12.5$, 5.0 Hz, 1H, C-2), 3.91 (dd, $J = 12.0$, 9.0 Hz, 1H, C-2), 3.47 (m, 1H, C-3), 3.10 (dd, $J = 16.6$, 12.0 Hz, 1H, C-15), 2.56 (dd, $J = 16.6$, 6.3 Hz, 1H, C-15), 2.37 (ddd, $J = 17.6$, 6.8, 1.8 Hz, 1H, C-16), 2.13 (ddd, $J = 17.6$, 12.6, 1.8 Hz, 1H, C-16); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 172.5$, 156.4, 150.6, 146.0, 137.6, 133.0, 131.8, 128.7, 128.6, 127.9, 126.1, 124.1, 123.3, 121.3, 115.3, 113.2, 71.7, 62.6, 55.8, 52.9, 31.0, 26.8; FAB HRMS (NBA): calcd for $C_{25}H_{22}O_5$ $[M]^+$ 402.1467; found $m/e =$ 402.1556.

Combretastatin D-1 (**7**): A solution of combretastatin D-1 benzyl ether (35 mg, 0.087 mmol) and Pd/C (10%, 5 mg) in EtOAc (8 mL) was stirred at 25 °C under hydrogen for 3 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure to give 25 mg (0.082 mmol, 95%) **7** as white crystals. $R_f = 0.47$ (silica gel, 30% EtOAc in hexane), $[\alpha]_D = -96$ ($c = 0.015$ in $CHCl_3$); see ref. [27].

Combretastatin D-1-(*S*)-[*O*-acetyl] mandelate (**47**)**:** A solution of **7** (14 mg, 0.045 mmol) and (*S*)-(+)-*O*-acetylmandelic acid (12 mg, 0.063 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was treated with DCC (13 mg, 0.064 mmol) and DMAP (1.6 mg, 0.013 mmol) at 25 °C for 3 h. EtOAc was added to the reaction mixture and the organic layer was washed with 1N HCl, H_2O, and saturated NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 30–35% ethyl acetate/hexanes) yielded 20 mg (0.040 mmol, 90%) of a white solid. $R_f = 0.51$ (silica gel, 30% EtOAc in hexane); $[\alpha]_D = +5.3$ ($c = 0.010$ in $CHCl_3$); IR (thin film): $\tilde{\nu} = 3022, 2921, 1740, 1596, 1506, 1431, 1367, 1203, 1153, 1047, 987, 869, 829, 754$ cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.65 (m, 2H, Ar), 7.48 (dd, $J = 8.5$, 2.0 Hz, 1H, C-6), 7.41 (m, 3H, Ar), 7.32 (dd, $J = 8.5$, 2.0 Hz, 1H, C-18), 7.03 (dd, $J = 8.5$, 2.5 Hz, 1H, C-7), 7.00 (dd, $J = 8.5$, 2.5 Hz, 1H, C-19), 6.87 (d, $J = 8.0$ Hz, 1H, C-12), 6.66 (dd, $J = 8.5$, 1.8 Hz, 1H, C-13), 6.30 (s, 1H, C*-H, 5.05 (s, 1H, C-20), 4.33 (d, $J = 4.0$ Hz, 1H, C-4), 4.25 (dd, $J = 12.0$, 5.0 Hz, 1H, C-2), 3.89 (dd, $J = 12.0$, 9.0 Hz, 1H, C-2), 3.47 (m, 1H, C-3), 3.15 (dd, $J = 16.5$, 12.5 Hz, 1H, C-15), 2.61 (dd, $J =$ 17.5, 6.0 Hz, 1H, C-15), 2.40 (ddd, $J = 17.5$, 6.5, 1.7 Hz, 1H, C-16), 2.24 (s, 3H, OAc), 2.13 (ddd, $J = 17.2$, 12.3, 1.3 Hz, 1H, C-16); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 172.1$, 170.3, 166.9, 155.8, 152.8, 138.7, 136.0, 133.1, 131.9, 74.3, 62.5, 55.7, 52.8, 30.8, 27.1, 20.7; FAB HRMS (NBA): calcd for $C_{28}H_{24}O_8$ $[M+Na]^+$ 511.1369; found $m/e = 511.1360$.

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