

Total Synthesis of Natural (-)-Combretastatin D-1.

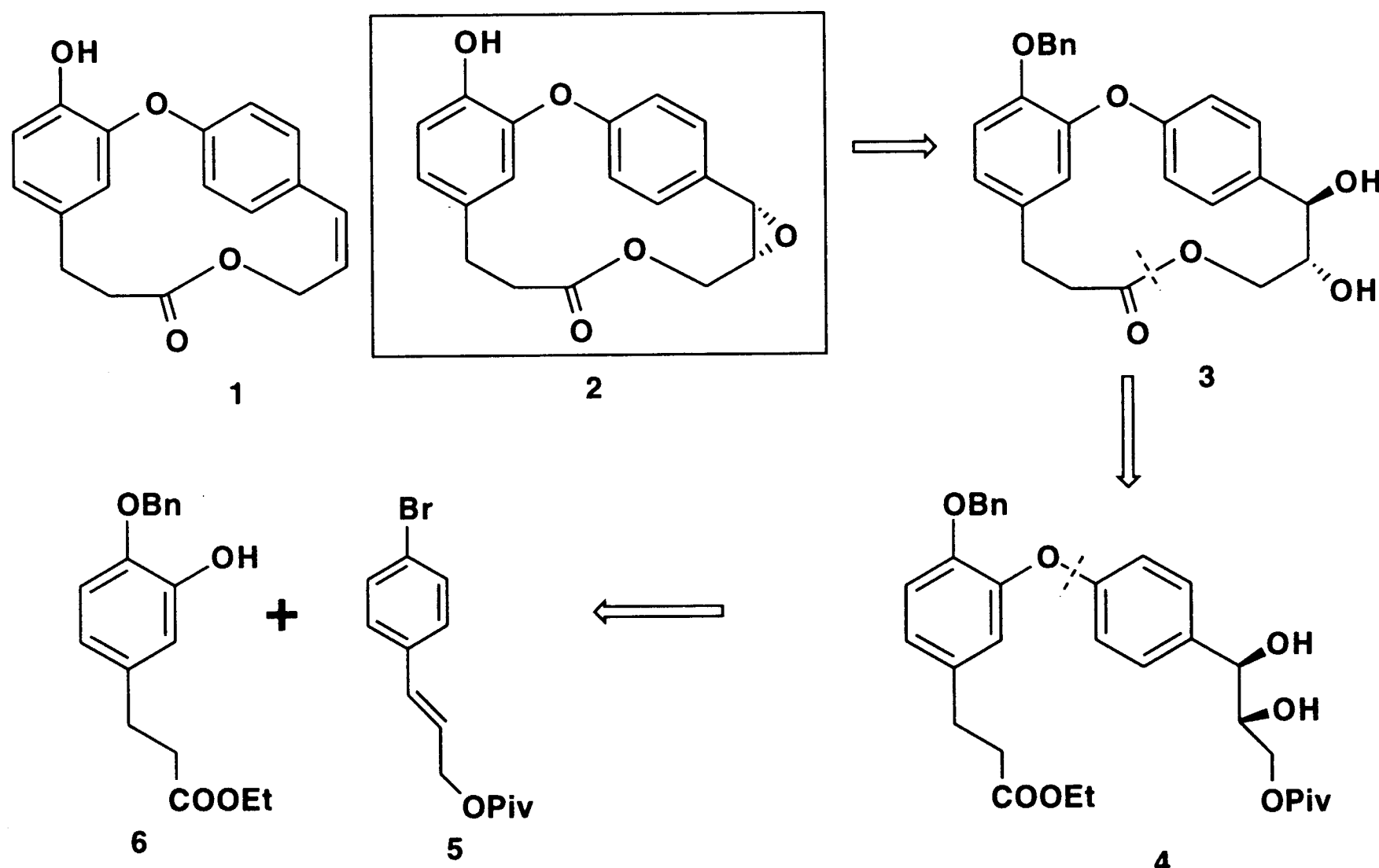
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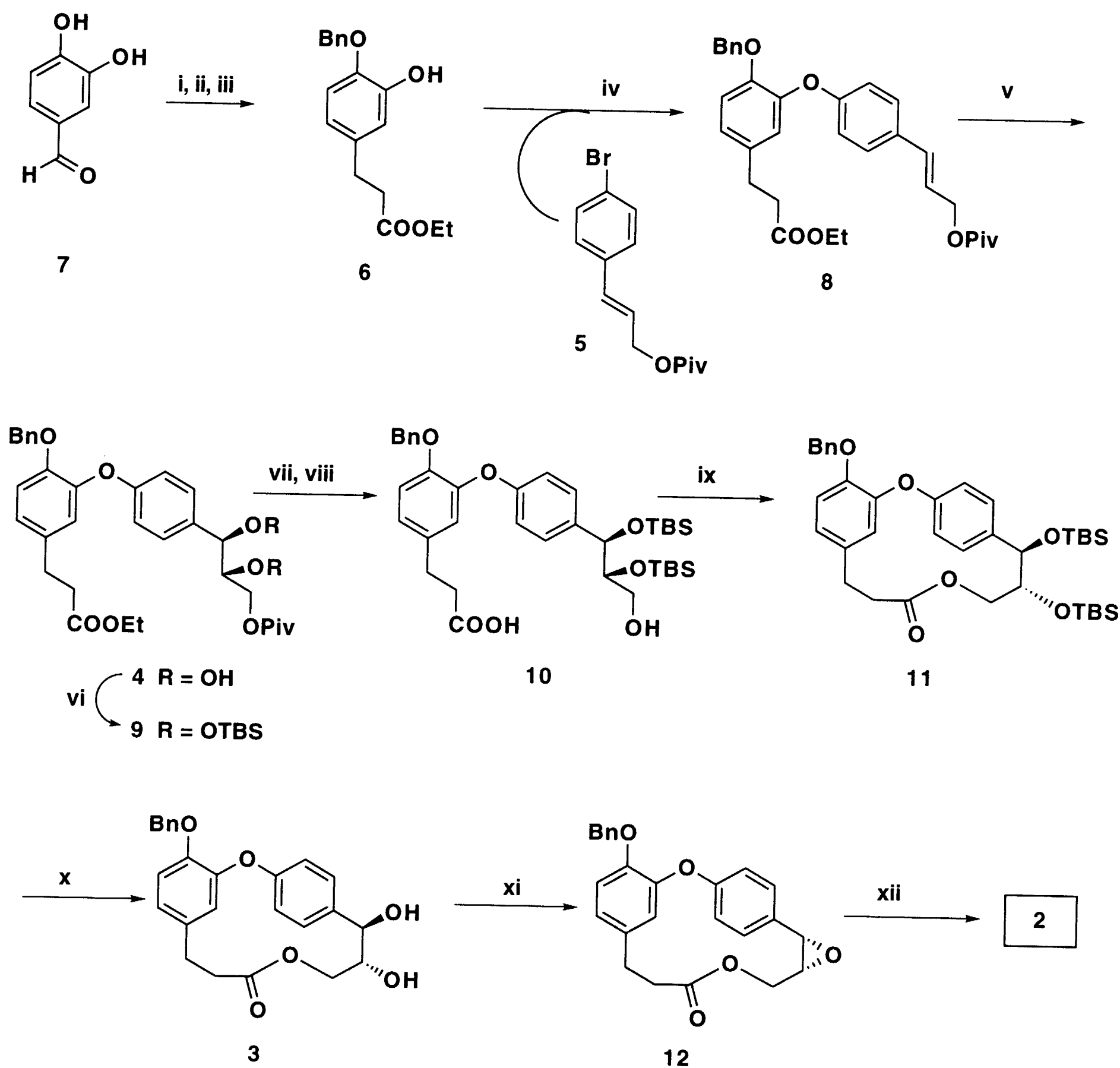
Abstract: Combretastatin D-1, (**2**), was synthesized *via* a 12 step sequence. Sharpless asymmetric dihydroxylation was used in order to introduce the appropriate asymmetry. Regiospecific cyclodehydration of the diol **3** gave the title compound in 96% ee.

Combretastatins^{1,2} are components of *Combretum caffrum*, a folk medical plant of South Africa. Combretastatins D-2, (**1**) and D-1 (**2**), are chemically classified as caffrane macrolactones and show PS cell line activity (P-388) corresponding to ED₅₀ 5.2 and 3.3 $\mu\text{g/mL}$ respectively². Although a number of papers concerning the synthesis of D-2 have been reported recently³, hitherto the total asymmetric synthesis of (-)-Combretastatin D-1 has remained elusive. Recently, Rychnovsky and Hwang⁴ have tried to synthesize **2** directly from **1**, using Jacobsen's epoxidizing reagent, however both chemical yield and optical purity were very low.

In conjunction with our interest in the total synthesis and the comparative evaluation of medium sized macrolactones, we present herein the first total synthesis of naturally occurring (-)-Combretastatin D-1, **2**. According to the following retrosynthetic scheme, benzyl group was chosen as the most suitable protective



Scheme 1



Reagents and conditions : (i) DMF, K_2CO_3 (ex.), $60^\circ C$, 4 h then 1.1 eq BnBr , RT, 12 h, 76 % ;
(ii) $Ph_3P=CHCOOEt$, benzene, RT, 93%; (iii) H_2 , Pd/C 5%, benzene, RT, 5h, 97%; (iv) 2 eq. $CuBr \cdot Me_2S$, 0.7 eq 5, K_2CO_3 (6eq), pyridine, 6h, $140^\circ C$, 78 %; v) 3 eq. $K_3Fe(CN)_6$, 3 eq. K_2CO_3 , 0.01 eq. $K_2OsO_2(OH)_4$, (DHQD) $_2$ PHAL (0.25 eq.), $tBuOH/H_2O$ 1:1, $0^\circ C$, 12h, 87%; vi) 2.2 eq. TBSCl, 2.4 eq. imidazole, DMF, RT, 3 h, 97 %; vii) LiOH 3N : THF : MeOH 1 : 1 : 1, $0^\circ \rightarrow RT$, 2 h, 94% ; viii) 1.1 eq. DIBAL, CH_2Cl_2 , $-78^\circ C$, 10 min, 96%; ix) 9 eq. DEAD , 8.8 eq. Ph_3P , toluene 0.0025 M final concentration, $45^\circ C$, 6 h addition, 81%; x) 2.5 eq. TBAF, THF, RT, 3 h, 94 %; xi) 4 eq. DEAD, 4 eq. Ph_3P , DMF, $145^\circ C$, 40min, 87%; xii) H_2 , Pd/C 10%, AcOEt, RT, 3h, 95%;

TBS = t Butyldimethylsilyl, Bn = Benzyl, Piv = Pivaloyl

group for the phenolic moiety (compound **6**), which will stand throughout the synthesis and will be easily removed at the final step in the presence of the epoxy group. On the other hand, Sharpless asymmetric dihydroxylation of the readily prepared *trans*-alkene **5**, will provide the proper intermediate for the construction of the correct epoxide in high enantioselective purity.

Thus, commercially available 3,4-dihydroxy-benzaldehyde **7** (Scheme 1), was benzylated selectively via an adopted known procedure.⁵ Subsequent Wittig elongation and selective catalytic hydrogenation furnished phenol **6** in high yield. Efficient coupling of phenol **6** with aryl bromide **5**⁶ was accomplished using a modified Ullmann protocol^{3a}. Introduction of asymmetry into the biaryl ether **8** was performed using the well known Sharpless catalyst (DHQD)₂PHAL for asymmetric dihydroxylation. The depicted 3R, 4R configuration of diol **4** should be expected, according to the literature⁷. Subsequent protecting group manipulations on chiral diol **4**, afforded seco-acid **10**. Cyclization of **10** into macrolactone **11** was efficiently carried out with a modified Mitsunobu⁸ reaction, already applied in previous syntheses of caffrane rings^{3c}, affording after desilylation the chiral macrolactonic diol **3** in high total yield.

Cyclodehydration of diols to cyclic ethers promoted by phosphoranes and oxyphosphonium salts is a well known procedure.^{9,10} The exact mechanism of this transformation is not always clear, however, it is believed that in the case of the preparation of styrene oxide, the cyclodehydration proceeds through the formation of the carbocation at the benzylic position.¹⁰ Since substrate **3** has no rotation between C3 and C4, the epoxide should be formed in high enantiomeric purity. Indeed, after heating diol **3** with excess DEAD, Ph₃P at 145° C for 40 min and subsequent hydrogenolysis of the benzyl group, the title compound **2** was synthesized in high overall chemical yield (83% on crystallized material¹¹). The reported optical rotation of the naturally occurring (-)-Combretastatin D-1, **2**, is -100°. The optical rotation of synthetic **2** was measured to be $[\alpha]_D = -96^\circ$ (c=0.015 in CHCl₃), leading to an optical purity of 96%. The observed high optical purity of **2** confirms the above postulated mechanism. According to the presented synthetic sequence, the absolute configuration of **2** is 3R, 4S, which is consistent with the originally reported¹ assignment.¹²

In conclusion, we have developed an effective design for the synthesis of the title compound and a concise synthetic plan which can be utilized to rapidly prepare a variety of related analogs.

Acknowledgement : We would like to thank Dr. N. Damianos of VIOCHROME S.A. for using their NMR facilities as well as, Prof. G. Kokotos of University of Athens for using their polarimeter. ICS would like to thank the National Institute of Scholarships for a graduate fellowship. We are grateful to Prof. E. Theodorakis for helpful discussions. Finally we thank Prof. G. R. Pettit and his Associate Director Dr. C. L. Herald of Cancer Research Institute for running the comparison experiments of synthetic and natural (-)-Combretastatin D-1.

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6. Compound **5** was prepared from p-bromobenzaldehyde by the following sequence : (i) 1.2 eq $\text{Ph}_3\text{P}=\text{CHCOOEt}$, benzene, 1 h, RT, 93%; (ii) 2.1 eq DIBAL, CH_2Cl_2 , -78°C , 20 min, 97%; (iii) PivCl , pyridine, DMF, $0^\circ \rightarrow \text{RT}$, 6 h, 87%.
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11. All new compounds gave satisfactory analytical and spectroscopic data. Synthetic **2** was compared with an authentic sample of natural **2** and they were found identical.
12. The revision of the configuration of natural (-)-Combretastatin reported in ref. 4, seems to be erroneous because : a) the necessary conditions required for the application of the advanced Mosher's method to calculate the absolute configuration are not fully fulfilled (according to Kakisawa¹³ who introduced this method) and b) the Jacobsen's epoxidation method which was applied leads to products with marginal optical excess (35%).
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(Received in UK 19 July 1995; revised 16 October 1995; accepted 19 October 1995)