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SYNTHESIS OF COMBRETASTATIN D-2.

AN EFFICIENT ROUTE TO CAFFRANE MACROLACTONES

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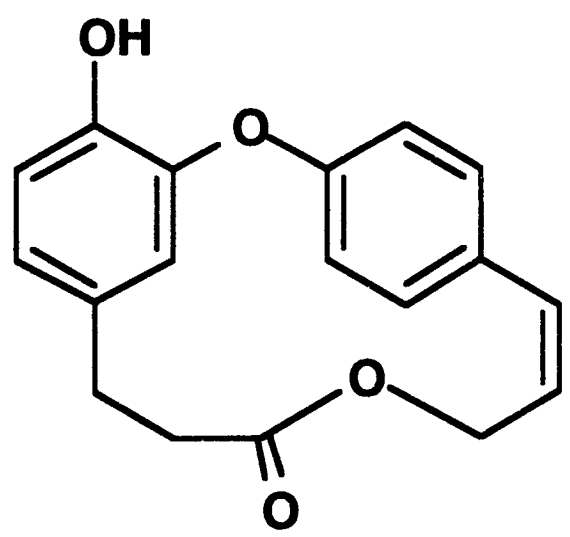
Abstract: Combretastatin D-2, (**1**), was synthesized *via* a 10 step sequence. Macrolactonization was performed on saturated substrate **12** in high yield and the double bond was established *via* dehalogenation of intermediate **15**.

Over the course of the last 10 years, a great number of 14- and 15- membered naturally occurring macrolactones and macrolactams bearing a *cis*-styrene ether subunit, have been discovered. Among them, caffranes[1,2,3] like combretastatin D-2, (**1**) and *ansa*-peptides of the general formulae **2** and **3** (e.g. nummularines[4] daechuines[5] and sanjoinines[6]), are the most interesting due to their unusual chemical structure and significant biological properties. Combretastatin D-2, (**1**), shows a PS cell line activity corresponding to ED_{50} 5.2 μg/mL[2]. In conjunction with our interest in the total synthesis and the comparative evaluation of medium sized macrolactones possessing a *cis*-styrene ether subunit, we present herein an efficient route for the construction of the caffrane ring.



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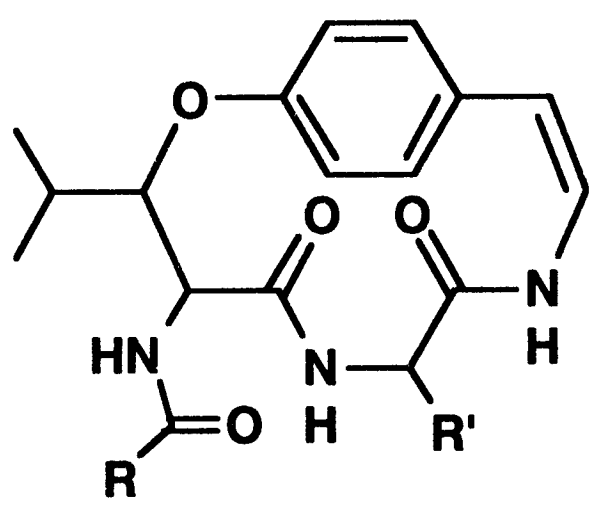

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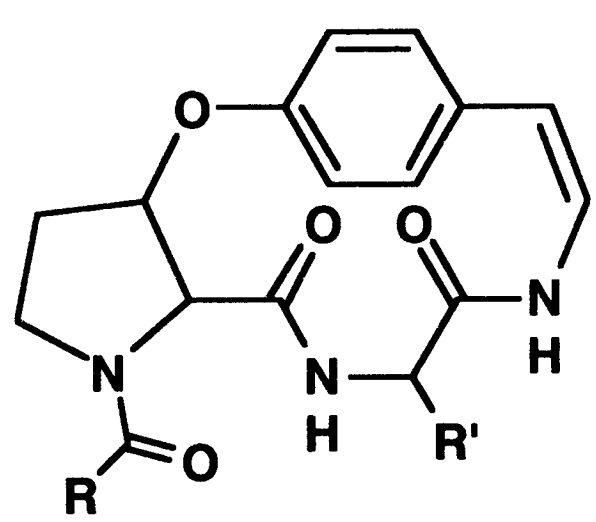
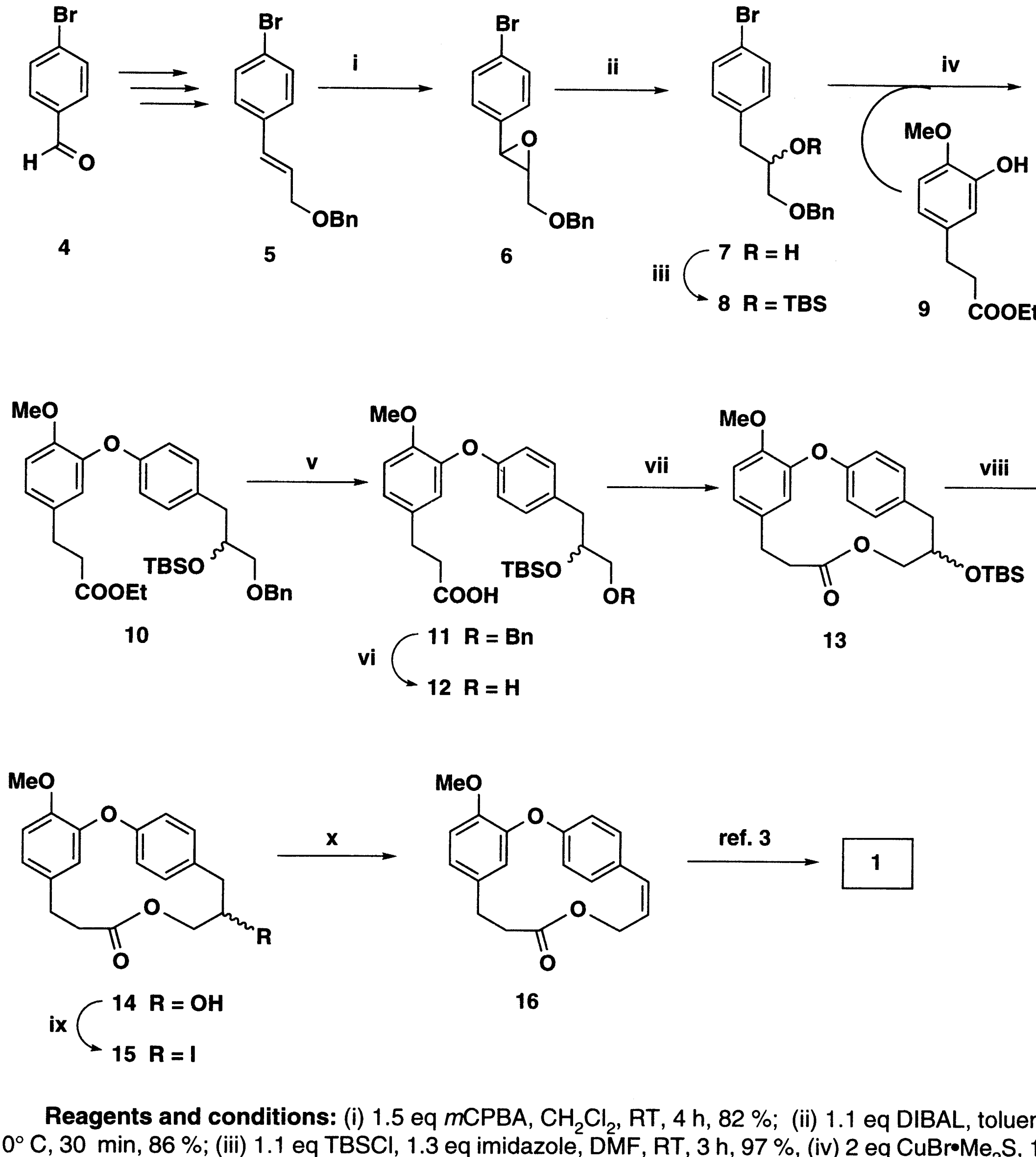


3

Methods reported to date concerning the synthesis of this kind of medium sized rings suffer from the low to moderate yields during the macrolactonization step[7]. Deshpande *et al.*[8] achieved the synthesis of **1** *via* a modified[9] Mitsunobu macrolactonization in only 20% yield. In order to avoid this problem Boger *et al.*[3,7] performed the synthesis of several medium sized meta- and paracyclophane macrolactones and macrolactames *via*

Scheme



Reagents and conditions: (i) 1.5 eq *m*CPBA, CH_2Cl_2, RT, 4 h, 82 %; (ii) 1.1 eq DIBAL, toluene, 0° C, 30 min, 86 %; (iii) 1.1 eq TBSCl, 1.3 eq imidazole, DMF, RT, 3 h, 97 %, (iv) 2 eq CuBr•Me_2S, 1.5 eq **9**, 6 eq K_2CO_3, pyridine, 6 h, 140° C, 92 %, (v) LiOH 3N : THF : MeOH 1 : 1 : 1, 0° → RT, 2 h, 94%; (vi) cat. 10% Pd/C, H_2, AcOEt, RT, 4 h, 100 %; (vii) 9 eq DEAD , 8.8 eq Ph_3P, toluene 0.0025 M final concentration, 45° C, 5 h addition, 84%; (viii) 1.2 eq TBAF, THF, RT, 30 min, 94 %; (ix) 2 eq I_2, 2 eq Ph_3P, 3 eq imidazole, toluene, 80° C, 30 min, 95 %; (x) 10 eq KF, DMSO 0.15M, 115° C, 4 h, 87 %.

TBS = tButyldimethylsilyl, Bn = Benzyl

an intramolecular Ullman cyclization in good to moderate yields (37% in the case of **1**[3]). On the other hand, Schmidt *et al.*[10] had observed during their synthesis of the 13- membered macrolactame, zizyphine A, that the hydroxylated precursor gives better yields during cyclization than the olefinic analog. This unexpected result may be explained in strain energy terms. Indeed, performing MM3 calculations[11] for the strain energy of **16** and its hydroxylated analog **14**, we measured a *ca.* 28 kJ/mole strain energy difference[12] in favor of **14**.

Having the above in mind, we decided to perform our synthesis using a protected hydroxyl intermediate as precursor for the cyclization. The well known DIBAL procedure[13] for the stereoselective opening of allylic epoxides was used, in order to establish the necessary hydroxyl moiety in our substrate. Accordingly, allylic ester **5**, which was easily prepared from *p*-bromo-benzaldehyde **4**[14] was treated with *m*CPBA and the resultant epoxide **6** was regiospecifically opened with DIBAL (regioselectivity > 9 : 1). The derived alcohol **7** was then protected in the form of a TBS ether and subsequently subjected to an intermolecular Ullmann coupling with 1.5 eq. of phenol **9**[15] providing, after optimization of the reaction conditions, the diaryl ether **10** in 92% yield. Subsequent deprotection of the terminal functionalities afforded the desired macrolactonization precursor **12** in 94% total yield.

The Mitsunobu protocol[16], modified according to Justus and Steglich[8], was chosen for the cyclization. We have observed that in order to avoid the formation of the dimer it is crucial to perform the addition of the *seco* acid into the reaction mixture at elevated temperatures (40 - 50° C). In this way, the reaction proceeded faster so that the addition period could be reduced to 5h and the final dilution to 0.0025 M (instead of 0.0005 M[4]). Thus, after cleavage of the silyl ether, hydroxyl-macrolactone **14** was synthesized in 81 % overall yield from **12**. Significantly, under these conditions, dimer formation was not observed at all.

Efforts to induce elimination of water from alcohol **14** with several methods (CSA, TsOH, $CuSO_4$-silica gel, H_2SO_4 etc) or elimination of the respective methylsulfonate ester after treatment with NaI - HMPA, ^tBuOK or DBU, failed to provide **16** in satisfactory yields. Elimination was taking place in a very slow rate and, concequently, several byproducts due to the hydrolysis of the lactone were usually detected in the reaction mixtures. Finally, a two-step sequence involving the transformation of **14** to the corresponding iodide **15**[17] and subsequent dehydrohalogenation, under neutral conditions (KF, DMSO), provided the unsaturated macrolactone **16** in good yield (86% total yield for two steps). Deprotection of the aryl methyl ether of **16** according to Boger *et al.*[3] afforded **1** identical in all compared respects with that reported for the natural product[18].

In conclusion, a new and efficient way for the preparation of unsaturated caffranes is presented. The general aspect is to perform the macrolactonization on a saturated substrate and then to restore the unsaturation *via* dehydrohalogenation at a latter step.

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12. After Monte Carlo minimization the calculated tortion energies for compounds **16** and **14** were 45.17 and 17.37 kJ/mole respectivelly.
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14. Compound **5** was prepared from **4** by the following sequence : (i) 1.2 eq Ph_3P=CHCOOEt, benzene, 30 min, RT, 93%; (ii) 2.1 eq DIBAL, CH_2Cl_2, -78° C, 20 min, 97%; (iii) 1.1 eq NaH, THF, 0° C, RT, 30 min then 1.2 eq BnBr, cat. Bu_4NI, 3h, RT, 94%.
15. For the preparation of **9** see ref. 3.
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18. Data for comp. **1** : mp 152-4° C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (d, 2 H, J = 8.4 Hz, C18-H and C6-H), 7.11 (d, 1 H, J = 10.5 Hz, C4-H), 7.10 (d, 2 H, J = 8.4 Hz, C19-H and C7-H), 6.86 (d, 1 H, J = 8.2 Hz, C12-H), 6.64 (ddd, 1H, J = 8.2, 1.9, 0.9, C13-H), 6.07 (dt, 1 H, J = 10.5, 6.8 Hz, C3-H), 5.45 (s, 1 H, OH), 5.06 (d, 1 H, J = 1.9Hz, C20-H), 4.65 (d, 2 H, J = 6.8 Hz, C2-H_2), 2.87 (t, 2 H, J = 5.2 Hz, C15-H_2), 2.30 (t, 2 H, J = 5.2 Hz, C16-H_2); ^{13}C NMR ($CDCl_3$, 125 MHz), δ 173.3 (C17), 155.5 (C8), 149.2 (C10 or C11), 142.4 (C10 or C11), 137.7 (C3), 135.4 (C4), 132.0 (C5), 129.0 (C6), 125.6 (C18), 123.9 (C19), 121.8 (C13), 115.3 (C12), 112.5 (C20), 59.0 (C2), 31.3 (C16), 26.8 (C15); IR (thin film) ν_{max} 3426, 2958, 2923, 2853, 1730 (C=O), 1517, 1501, 1282, 1216, 1154.

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