Tetrahedron Letters, Vol. 33, No. 29, pp. 4213-4216, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Synthesis of Combretastatin D-2+

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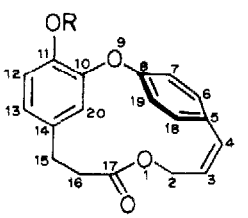
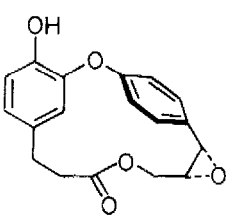
Abstract: *The synthesis of combretastatin D-2 methyl ether (2) by macrolactonization of hydroxy acid 11 under modified Mitsunobu conditions is described. In accord with the literature, attempts to cyclize 11 via various conventional macrolactonization methods failed.*

Combretastatin D-2 (**1**)[1], a trace constituent of *Combretum caffrum* (Combretaceae) and a PS cell line inhibitory macrocyclic lactone, has been shown to possess a new oxygen heterocyclic ring. The 15-membered meta and paracyclophane subunit is now characteristic of a range of antitumor antibiotics including combretastatin D-1 (**3**)[2]. Attempts to close the 15-membered ring through use of conventional macrolactonization techniques were unsuccessful and Boger *et al*[3]. overcame this obstacle by an intramolecular Ullmann coupling. We now report the synthesis of combretastatin D-2 methyl ether (**2**) by macrolactonization of the hydroxy acid **11** using modified Mitsunobu conditions[4] under high dilution (Scheme).



1 R = H
2 R = CH_3

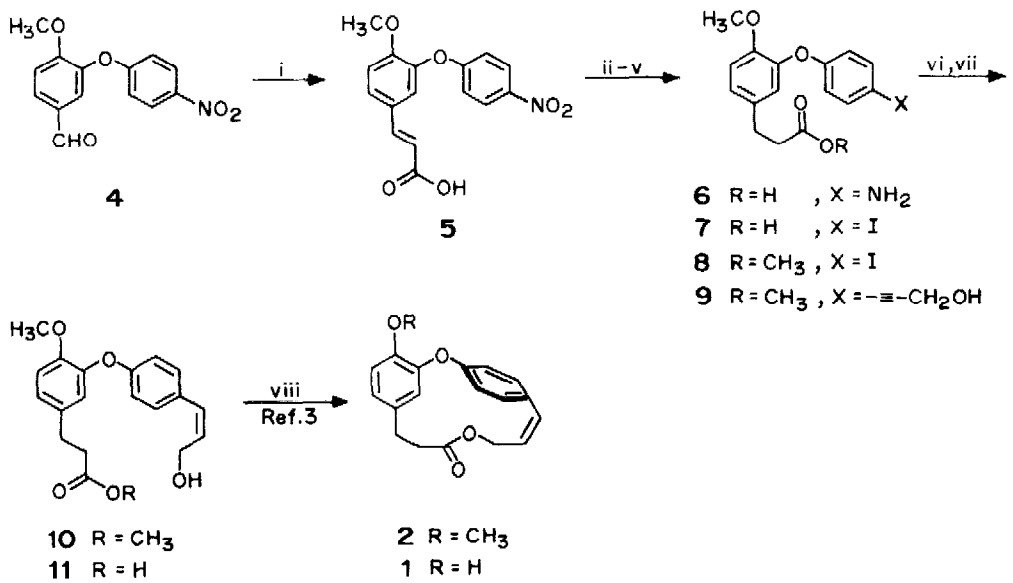


3

Ullmann coupling[5] of isovanillin with 4-chloronitrobenzene yielded the biaryl ether **4** which was transformed into the α,ß-unsaturated acid **5** by Knoevenagel condensation with malonic acid in pyridine using catalytic amount of piperidine. One step reduction of the double bond and the nitro group of **5** (H_2-10% Pd/C) gave the amino compound **6** which on diazotization followed by treatment with potassium iodide afforded the iodo acid **7**. Esterification (DMS, K_2CO_3, acetone) of the acid to **8** followed by its reaction with propargyl alcohol using bis(triphenylphosphine)palladium dichloride and cuprous iodide in triethylamine[6] gave the acetylenic

compound **9**. Partial reduction of the triple bond using poisoned Lindlar's catalyst afforded the *cis* hydroxy ester **10** which was hydrolyzed to obtain the hydroxy acid **11**. Efforts to close the 15-membered ring through use of a range of macrolactonization procedures failed to provide combretastatin D-2 methyl ether[7] (**2**). Only the cyclic diolide could be isolated from the macrolactonization attempts conducted with use of high dilution[8], including the Mitsunobu conditions as reported by Justus and Steglich[4]. However, further modified Mitsunobu conditions using still higher dilution afforded the required lactone[9] **2** in 20% yield by dropwise addition of **11** to a solution of diethyl azodicarboxylate (DEAD, 7.7 equiv) and triphenylphosphine (7.5 equiv.) in toluene. Since the demethylation[3] of **2** is known, this constitutes the formal total synthesis of combretastatin D-2 (**1**).

Scheme



Reagents: (i) $CH_2(COOH)_2$, pyridine, piperidine, 80%, (ii) H_2, 10% Pd/C, 85%; (iii) H_2SO_4, $NaNO_2$, 5°C and then KI, 67%; (iv) DMS, K_2CO_3, acetone 96%; (v) H-C≡C-CH_2OH, $(PPh_3)_2$ $PdCl_2$, CuI, Et_3N, 56%; (vi) H_2, Pd-$CaCO_3$, 95% (vii) 10% aq. methanolic KOH, 98%; (viii) DEAD, PPh_3, toluene, 8 h, 20%.

Acknowledgement: One of the authors (NJG) thanks the University Grants Commission, New Delhi for financial support.

REFERENCES AND NOTES

+ NCL Communication No.5382

1. Singh, S. B.; Pettit, G. R. *J. Org. Chem.* **1990**, *55*, 2797-2800.

2. (a) Pettit, G. R.; Singh, S. B.; Niven, M. L. *J. Am. Chem. Soc.* **1988**, *110*, 8539-8540.
(b) Itokawa, H.; Takeya, K.; Mori, N.; Sonobe, T.; Mihashi, S.; Hamanaka, T. *Chem. Pharm. Bull.* **1986**, *34*, 3762-3768 and references cited therein.
(c) Sano, S.; Ikai, K.; Katayama, K.; Takesako, K.; Nakamura, T.; Obayashi, A.; Ezure, Y.; Enomoto, H. *J. Antibiot.* **1986**, *39*, 1685-1696 and references cited therein.

3. Boger, D. L.; Sakya, S. M.; Yohannes, D. *J. Org. Chem.* **1991**, *56*, 4204-4207.

4. Justus, K.; Steglich, W. *Tetrahedron Lett.*, **1991**, *32*, 5781-5784.

5. Tomita, M.; Fujitani, K.; Aoyagi, Y. *Chem. Pharm. Bull.* **1965**, *13*, 1341-1345.

6. Sonogashira, K.; Tohda, Y. ; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467-4470.

7. (a) Holmberg, K.; Hansen, B. *Acta. Chem. Scan.* **1979**, *33B*, 410-412.
(b) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn* **1979**, *52*, 1989-1993.
(c) Hanaoka, M.; Ogawa, N.; Arata, Y. *Tetrahedron Lett.* **1973**, 2355-2358.

8. (a) Deshmukh, A.R.A.S.; Joshi, G. D.; Gore, K. G.; Kulkarni, G. H.; *Syn. Commun.*, **1990**, *20*, 2259-2265.
(b) Neises, B.; Steglich, W. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 522-524.

9. All new compounds reported here gave satisfactory spectral and analytical data.

Preparation of lactone-**2**: To a solution of triphenylphosphine (0.401 g, 1.53 mmol, 5.0 equiv.) in dry deaerated toluene (380 ml) under argon was added DEAD (0.279 g, 1.6 mmol, 5.1 equiv.) and the mixture was stirred for 2 min. A solution of **11** (0.099 g, 0.302 mmol, 1.0 equiv.), pre-dissolved in 2 ml dry THF and diluted with toluene (80 ml) was added dropwise using a syringe pump to the vigorously stirred reaction mixture at 25°C. When half of the solution of **11** had been added (4 h), the mixture was treated again with PPh_3 (0.2 g, 0.763 mmol, 2.5 equiv.) and DEAD (0.138 g, 0.793 mmol, 2.6 equiv) before the addition of **11** was continued. When the addition of **11** was complete, (4 h), the reaction mixture was concentrated in vacuo (< 35°C) to afford a red oil. Column chromatography (silica gel, pet-ether/acetone) yielded **2** (17 mg, 20%) as a white crystalline solid. m.p. 129-130° (lit.[3] 130-132°C);

^{1}H-NMR ($CDCl_3$, 200 MHz), δ: 7.31 (d, 2H, J = 8.3 Hz, C_{18} & C_6-H), 7.09 (d, 2H, J = 8.3 Hz, C_{19} and C_7-H), 7.10 (d, 1H, 10.6 Hz, C_4-H), 6.81 (d, 1H, 8.2 Hz, C_{12}-H), 6.66 (dd, 1H, 8.2 1.8 Hz, C_{13}-H), 6.04 (dt, 1H, 10.6, 6.8 Hz, C_3-H), 5.10 (d, 1H, 1.8 Hz, C_{20}-H), 4.64 (d, 2H, 6.8 Hz, C_2-H_2), 3.93 (s, 3H, OCH_3), 2.87 (t, 2H, C_{15}-H_2), 2.29 (t, 2H, C_{16}-H_2).

IR ($CHCl_3$): 1733 (C=O), 1590, 1525, 1509, 1425, 1380, 1350, 1270, 1220, 1160, 1135, 1100, 1040, 990, 920, 880, 850 cm^{-1}.

EIMS m/e (relative intensity): 310 (M^+,100), 251(13), 149(29), 135(13), 132(6), 131(21), 121(38), 120(47), 115(40), 107(18), 103(28), 77(24).

(Received in UK 25 March 1992)