An Efficient Stereoselective Synthesis of Cytotoxic 8-Epipuupehedione

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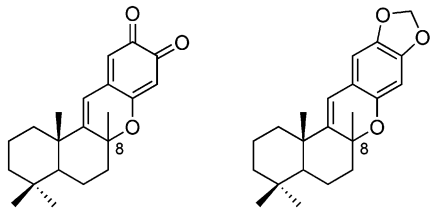
An efficient and highly stereoselective synthesis of cytotoxic 8-epipuupehedione (**1b**) was achieved starting from natural (−)-drimenol (**6**). The key step to obtain stereoselectivity was the simultaneous demethylation and oxidation of the dihydrobenzopyran methoxy derivatives **10a** and **10b**.

Marine sponges are recognized as a rich source of structurally unique and biologically active terpenoids.[1] Puupehedione (**1a**) was isolated from a sponge of the order *Verongida* and was characterized as a metabolite featuring a sesquiterpene unit joined to a shikimate-derived moiety.[2] The cytotoxic activity of **1a** and its synthetic, non-natural, 8-epimer **1b** was assayed against the cell lines P-338, A-549, HT-29, and MEL-28,[3] and the most active compound was found to be 8-epipuupehedione (**1b**).

The syntheses previously reported for **1a** and **1b**[3,4] were based on electrophilic cyclization of suitable intermediates to the respective dihydrobenzopyrans as methylenedioxy derivatives (**2a** and **2b**), followed by oxidative cleavage of the methylenedioxy moiety. As we have previously established,[3] the oxidative process involves ring opening and subsequent cyclization to obtain **1a** and **1b** in the same 1:4 relative proportion, independent of the C-8 epimeric ratio for the starting methylenedioxy derivatives.



1a (C_8-Meα) **2a** (C_8-Meα)
1b (C_8-Meβ) **2b** (C_8-Meβ)

Our strategy here involves nucleophilic addition of the organolithium derived from **5** to drim-7-en-11-al (**7**),[5] easily available from natural (−)-drimenol (**6**)[6,7] (Figure 1). The aromatic synthon **5** was prepared in high yield from 3,4-dimethoxybenzaldehyde (Figure 2). Addition of aldehyde **7** to the aryllithium derived from **5**, and subsequent deprotection of the silyl ether, afforded **8**/**9** in a ratio of 3:1 (^{1}H and ^{13}C NMR). Acid-mediated cyclization of the mixture gave **10a** and **10b** in a ratio of 1:3. Simultaneous demethylation and oxidation of the epimeric dihydrobenzopyrans **10a**(C_8-Me$_\alpha$) and **10b**(C_8-Me$_\beta$) with AgO−HNO_3[8] led to *o*-quinones **1a** and **1b** (1:3). A further straightforward route was studied. Direct treatment of the condensation product with acid, without previous deprotection of the *tert*-butyldimethylsilyl ether, afforded **10a** and **10b** in a ratio 1:8.

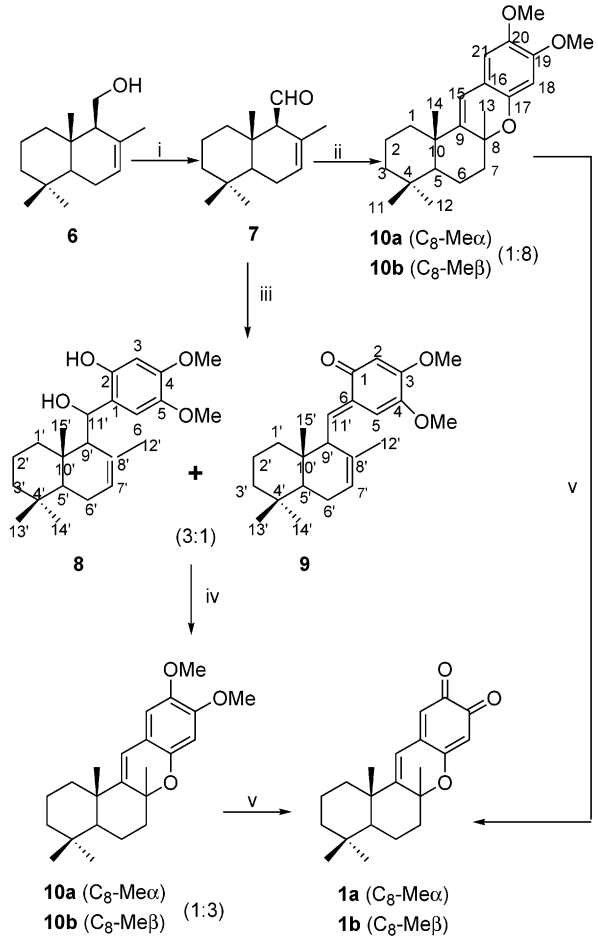


Figure 1. Summary of synthetic transformations to produce 8-epipuupehedione (**1b**). Reagents: (i) PCC, CH_2Cl_2; (ii) BuLi, **5**, Et_2O, **7**, TsOH, C_6H_6; (iii) BuLi, **5**, Et_2O, **7**, TBAF, THF; (iv) TsOH, C_6H_6; (v) AgO−HNO_3, THF.

Simultaneous demethylation−oxidation of the mixture gave the epimeric **1a** and **1b** (1:8). The relative proportion was the same as that obtained for the dihydrobenzopyran methoxy derivatives, since the well-known reaction with AgO in acid medium[8] avoids ring opening, due to very fast oxidation. These results suggest that, under acidic conditions, the main product arises from attack on the less hindered α side, and the epimeric ratio seems to depend on the effective free nucleophilic group.

The present work represents the shortest and most efficient synthesis for the highly bioactive 8-epipuupehedione (**1b**).

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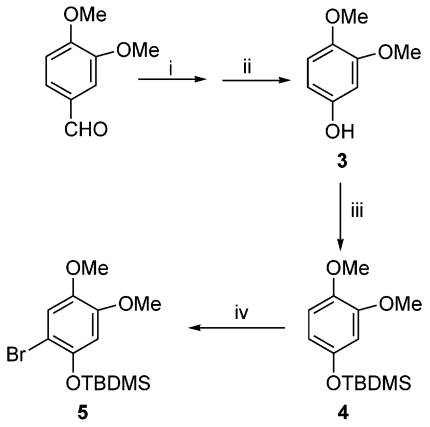

Figure 2. Synthesis of 2-bromo-1-*tert*-butyldimethylsilyloxy-4,5-dimethoxybenzene (**5**). Reagents: (i) m-CPBA, CH_2Cl_2; (ii) NaOH−MeOH; (iii) TBDMSCl, imidazole, DMF; (iv) Br_2, $CHCl_3$.

Experimental Section

General Experimental Procedures. NMR spectra were recorded on a Bruker AM-200 and a Bruker Avance DRX-300 spectrometer. Carbon multiplicity was established by a DEPT pulse sequence. HRMS were obtained on a trisector WG AutoSpecQ spectrometer. Chromatographic separations were carried out on Merck silica gel 60 (230−400 mesh), using hexane−EtOAc gradients of increasing polarity. All organic extracts were dried over magnesium sulfate and evaporated under reduced pressure, below 65 °C.

Synthesis of 5 (2-Bromo-1-*tert*-butyldimethylsilyloxy-4,5-dimethoxybenzene). TBDMSCl (18.0 mmol) and imidazole (15.0 mmol) were added to a solution of phenol **3** (15.0 mmol) in anhydrous DMF and stirred for 15 h. Usual workup[3] and column chromatography gave **4** (92%) as a colorless oil: HRMS (FAB+) found 291.1394 (calcd for $C_{14}H_{24}O_3NaSi$, $[M + Na]^+$ 291.1392). Compound **4** (5.9 mmol) was treated, at 0 °C, with bromine (6.0 mmol) in chloroform. After stirring for 1 h, a solution of sodium thiosulfate was added, and the mixture was further stirred 1 h. Usual workup[3] and column chromatography gave **5** (95%) as a colorless oil: HRMS (FAB+) found 369.0495 (calcd for $C_{14}H_{23}O_3NaSiBr$, $[M + Na]^+$ 369.0498).

Synthesis of 10a (9-Dehydro-19,20-di-*O*-methylpuupehenol) and 10b (9-Dehydro-8-epi-19,20-di-*O*-methylpuupehenol). Aryllithium Addition. A 1.6 M solution of butyllithium in hexane (3.0 mL) was added, at −78 °C, to a solution of **5** (4.5 mmol) in anhydrous Et_2O, under N_2. After stirring for 45 min, **7** (1.96 mmol) was added, and the stirring continued for 1 h, at −78 °C. Water was added and the mixture was extracted with Et_2O.

Cyclization. The crude obtained above, by aryllithium addition, was dissolved in benzene, *p*-toluenesulfonic acid (2.0 mmol) was added, and the mixture was stirred at rt for 16 h. Usual workup[3] and column chromatography gave **10a/10b** (ratio 1:8) (90% from **7**) as a colorless oil: ^{1}HNMR ($CDCl_3$, 300 MHz) **10a** δ 6.58 (1H, s, H-21), 6.45 (1H, s, H-18), 6.09 (1H, s, H-15), 1.36 (3H, s, Me-13), 1.21 (3H, s, Me-14), 0.95 (3H, s, Me-11), 0.87 (3H, s, Me-12); **10b** δ 6.54 (1H, s, H-21), 6.42 (1H, s, H-18), 6.06 (1H, s, H-15), 1.40 (3H, s, Me-13), 1.15 (3H, s, Me-14), 0.92(3H, s, Me-11), 0.87 (3H, s, Me-12); ^{13}CNMR ($CDCl_3$, 75 MHz), signals asignable to **10b**, δ 149.5 (C-9), 148.7 (C-19), 145.6 (C-17), 143.1 (C-20), 114.9 (C-16), 113.9 (C-15), 109.3 (C-21), 100.5 (C-18), 77.9 (C-8), 52.1 (C-5), 41.5 (C-3), 41.4 (C-7), 38.9 (C-10), 37.9 (C-1), 33.7 (C-4), 33.5 (C-11), 26.0 (C-13), 23.5 (C-14), 21.6 (C-12), 19.2 (C-6), 18.8 (C-2); HRMS (FAB+) found 379.2251 (calcd for $C_{23}H_{32}O_3Na$, $[M + Na]^+$ 379.2249).

Silyl Ether Deprotection. The crude (0.8 g) previously obtained, by aryllithium addition, was dissolved in THF, and tetrabutylammonium fluoride (1.1 mmol) was added. After stirring for 15 min at rt, water was added and the mixture was extracted with Et_2O. Workup[3] gave **8/9** (ratio 3:1) as a colorless oil: ^{1}HNMR ($CDCl_3$, 200 MHz) asignable to **8** (11-(2-hydroxy-4,5-dimethoxyphenyl)drim-7-en-11-ol, δ 6.43 (1H, s, H-3), 6.37 (1H, s, H-6), 5.69 (1H, bs, H-7′), 5.42 (1H, bs, H-11′), 2.51 (1H, bs, H-9′), 1.62 (3H, s, Me-12′), 1.07 (3H, s, Me-14′), 0.94 (3H, s, Me-13′), 0.91 (3H, s, Me-15′). Fractions of pure **9** (6-(7-drimen-11-yliden)-3,4-dimethoxy-2,4-cyclohexadienone) could be obtained: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.11 (1H, d, J = 12.7 Hz, H-11′), 6.15 (1H, s, H-5), 5.79 (1H, s, H-2), 5.59 (1H, bs, H-7′), 3.00 (1H, bd, J = 12.7 Hz, H-9′), 1.53 (3H, s, Me-12′), 0.99 (3H, s, Me-14′), 0.92 (3H, s, Me-13′), 0.89 (3H, s, Me-15′); ^{13}CNMR ($CDCl_3$, 50 MHz) δ 184.1 (C-1), 164.7 (C-3), 148.6 (C-11′), 147.8 (C-4), 133.7 (C-8′), 131.8 (C-6), 123.1 (C-7′), 104.2 (C-2), 100.1 (C-5), 54.4 (C-9′), 49.8 (C-5′), 42.3 (C-3′), 41.0 (C-1′), 38.6 (C-10′), 33.3 (C-13′), 33.2 (C-4′), 23.7 (C-6′), 22.5 (C-14′), 22.0 (C-12′), 18.6 (C-2′), 15.0 (C-15′); HRMS (FAB+) found 379.2249 (calcd for $C_{23}H_{32}O_3Na$, $[M + Na]^+$ 379.2249).

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