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SHORT COMMUNICATIONS

Chemically Rational Approach to the Synthesis of Precursors of the "Prenyl" Fragment in Epothilones

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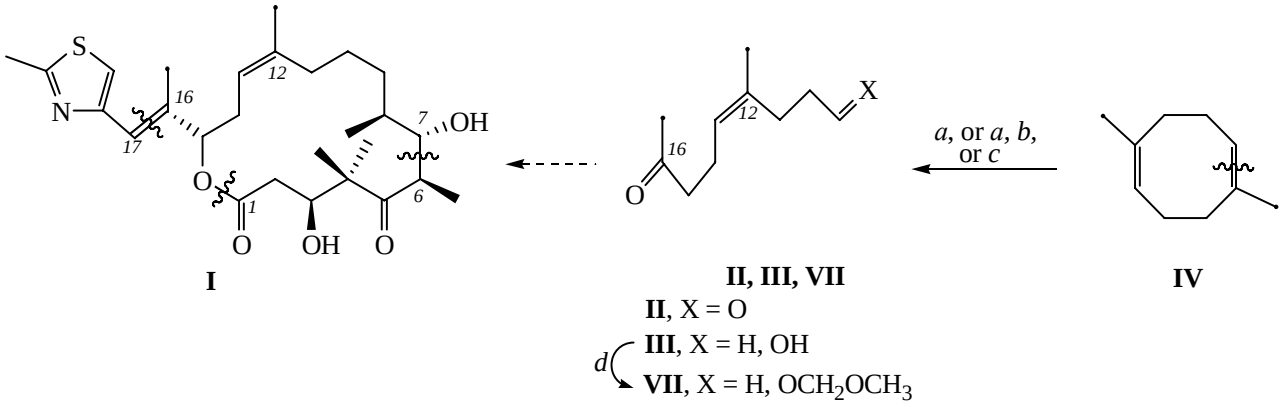
An important stage in the synthesis of the antineoplastic agent epothilone D (**I**) possessing taxol-like activity is a stereoselective building of block-synthons with 12,13-*Z*-trisubstituted double bond [1–3]. In our approach to compound **I** [4] this problem was solved by the use of α,ω-bifunctional *Z*-olefins **II** and **III** with a desired stereochemistry readily available by ozonolysis cleavage of *cis*-1,5-dimethylcyclooctadiene (**IV**) [5–7].

First by chemo- and stereoselective olefination of ketoaldehyde **II** with phosphorane **V** [8] we obtained ester **VI** [with *Z*-isomer content not exceeding 3–4% (^{1}H NMR data)]. Therewith occurred a terminal extension of the chain, and the skeleton of the C^7–C^{16} fragment of epothilones was formed. Further introduction of C^{15}-hydroxy function of epothilones in the synthons was demonstrated by an example of compound **VII**. To carry out a regioselective oxidation of methyl ketone **VII** at the CH_2 group adjacent to the carbonyl we first by treating with N,N-(bistrimethylsilyl)acetamide obtained a mixture of enol ethers (**VIII**, 85%) (similar procedure see. [9]) that further without purification was subjected to oxidation with *m*-$ClC_6H_4CO_3H$ [10, 11]. The purification of reaction products on SiO_2 afforded individual hydroxyketone **IX** in a 40% yield with respect to the starting compound **VII**. Note that the use of Me_3SiI for enolsylilation of ketone **VII** [12, 13] gave less pure mixture of ethers **VIII** (Scheme 1).

Thus in this study we demonstrated the fundamentl possibility of an efficient construction of synthetic equivalents for the upper hemisphere of epothilones from 1,5-dimethylcyclooctadiene.

Methyl 2,6-dimethyl-10-oxoundeca-(2*E*,6*Z*)-dienoate (VI). Colorless oily fluid. IR spectrum, ν, cm^{-1}: 748, 850, 1090, 1360, 1648, 1714. ^{1}H NMR spectrum, δ,

Scheme 1.



(*a*) O_3, cyclohexane–MeOH, then Me_2S; (*b*) $NaBH(OAc)_3$; (*c*) see [7]; (*d*) CH_3OCH_2Cl, *i*-$PrEt_2N$, $(CH_2)_2Cl_2$, 55°C, 5 h, 95%.

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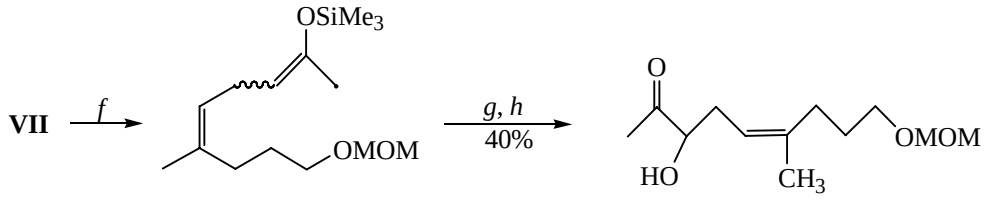

VIII **IX**

(*e*) 1.1 equiv of compound **V**, CH_2Cl_2, 20°C;(*f*) 1.1 equiv of $CH_3C(O)N(SiMe_3)_2$, C_6H_{14}, 20°C, 2 h; (*g*) 1.1 equiv of *m*-$ClC_6H_4CO_3H$, $CHCl_3$, –78°C; (*h*). SiO_2.

ppm: 1.60 d (3H, C^6H_3, *J* 1.0 Hz), 1.80 d (3H, C^2H_3, *J* 1.3 Hz), 2.08 s (3H, $C^{11}H_3$), 2.05–2.30 m (6H, CH_2), 2.40–2.50 m (2H, C^9H_2), 3.70 s (3H, OCH_3), 5.10 t (1H, =C^7H, *J* 6.3 Hz), 6.70 t (H, =C^3H, *J* 8.2 Hz). ^{13}C NMR spectrum, δ, ppm: 12.20 (C^6H_3), 22.04 (C^8), 23.02 (C^2H_3), 26.85 (C^4), 29.76 (C^{11}), 30.28 (C^5), 43.55 (C^9), 51.50 (OCH_3), 124.29 (C^7), 127.57 (C^2), 134.94 (C^6), 141.80 (C^3), 168.40 (CO_2Me), 208.30 (C=O).

6-Methyl-9-methoxymethyloxy-5*Z*-nonen-2-one (VII). Oily fluid. ^{1}H NMR spectrum, δ, ppm: 1.50–1.70 m (2H, C^8H_2), 1.60 s (3H, CH_3), 1.95–2.10 m (2H, C^4H_2), 2.08 s (3H, C^1H_3), 2.20 m (2H, C^7H_2), 2.40 t (2H, C^3H_2, *J* 7.3 Hz), 3.50 s (3H, OCH_3), 3.45 m (2H, CH_2O), 4.55 s (2H, OCH_2O), 5.05 m (1H, =CH). ^{13}C NMR spectrum, δ, ppm: 22.04 (C^4), 23.16 (CH_3), 27.90 (C^8), 28.13 (C^7), 43.73 (C^3), 55.02 (OCH_3), 67.13 (C^9), 96.30 (OCH_2O), 123.60 (C^5), 135.79 (C^6), 208.52 (C=O).

3-Hydroxy-6-methyl-9-methoxymethyloxy-5*Z*-nonen-2-one (IX). Oily fluid. ^{1}H NMR spectrum, δ, ppm: 1.60–1.80 m (2H, C^8H_2), 1.90 d (3H, CH_3, *J* 1.0 Hz), 2.12 m (2H, C^4H_2), 2.22 s (3H, C^1H_3), 2.40 m (1H), 2.45 (1H, C^7H_2), 3.35 s (3H, OCH_3), 3.50 t (2H, CH_2O, *J* 6.0 Hz), 4.23 m (1H, OC<u>H</u>), 4.62 s (2H, OCH_2O), 5.15 t (1H, =CH, *J* 7.1 Hz). ^{13}C NMR spectrum, δ, ppm: 23.41 (CH_3), 29.00 (C^1), 27.85 (C^8), 28.48 (C^7), 29.69 (C^4), 55.19 (OCH_3), 67.32 (C^9), 76.71 (C^3), 96.41 (OCH_2O), 118.79 (C^5), 138.81 (C^6), 209.66 (C=O).

IR spectra were recorded on spectrophotometers UR-20 and Specord M-80 (from thin films and mulls in mineral oil). NMR spectra were registered on a spectrometer Bruker AM-300 at operating frequencies 300.13 (^{1}H) and 75.47 MHz (^{13}C) from solutions in $CDCl_3$, internal reference TMS. Compounds **II** and **III** were obtained as described in [5–7].

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