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Reaction of Diazomethane with Clerocidin. Preparation of New Clerodane Diterpenoid Derivatives

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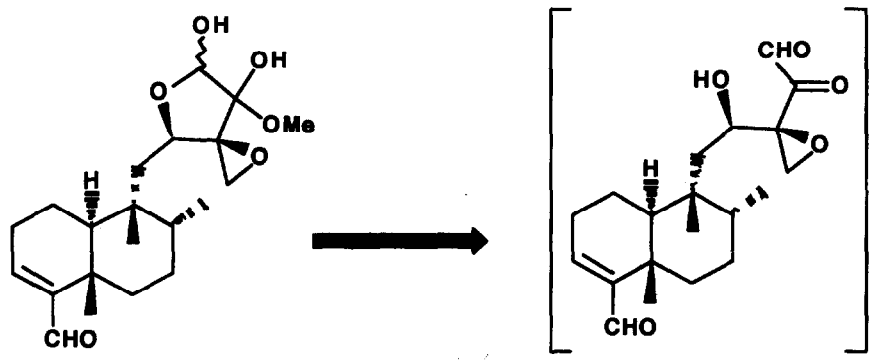
Abstract: Reaction of **1** with diazomethane in MeOH gave the ketone **2** as well as the diepoxide **4**. The alcohol **3**, obtained by hydrolysis of **2** was acetylated and oxidized to give **6**.

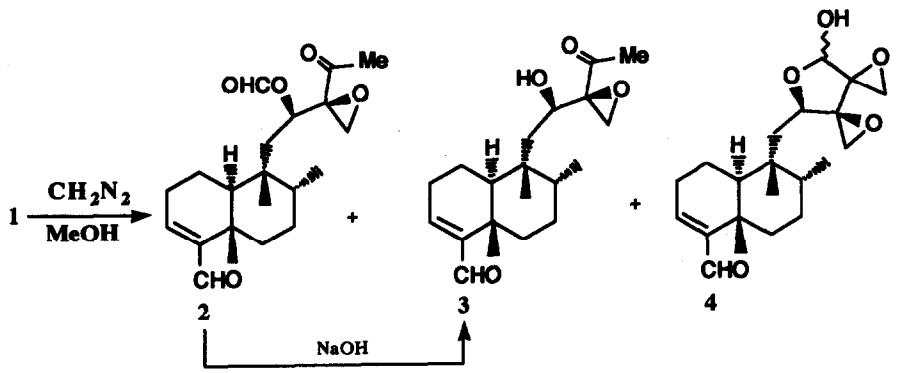
Clerocidin, a natural clerodane diterpenoid was isolated from *Oidiodendron truncatum* as a methanol adduct **1**[1,2]. This molecule, which showed antibacterial activity[3], was found to be a potent DNA topoisomerase II inhibitor[4,5]. In order to design new DNA gyrase inhibitors, we were interested in an "open form" of the oxygenated part of clerocidin.



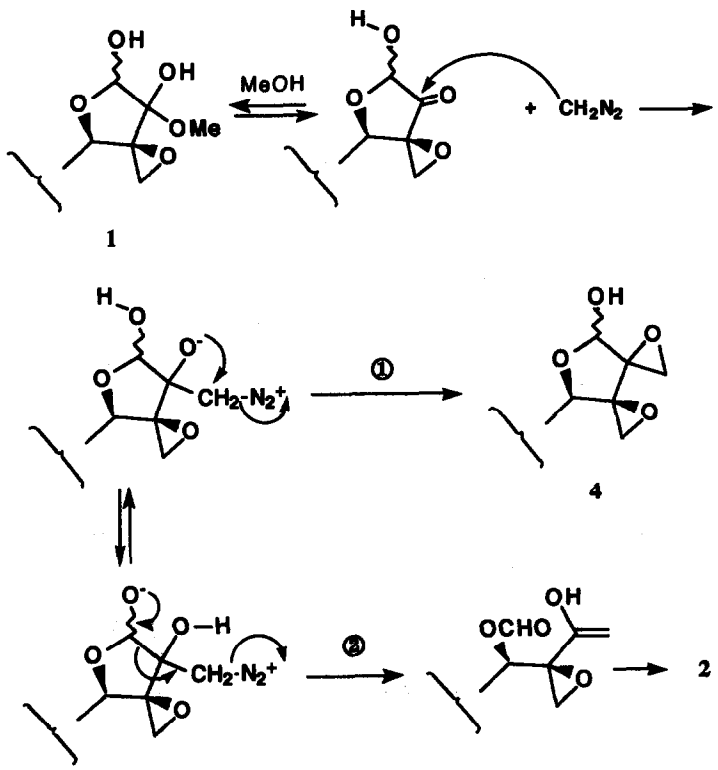
1

" open form " of clerocidin

In this paper we describe the reaction of **1** with diazomethane and the acetylation and oxidation of the acetylated intermediate **3**.



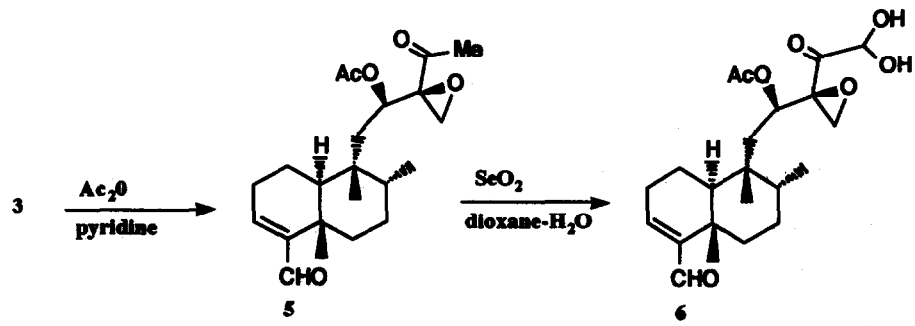
Reaction of diazomethane with **1** in MeOH at - 5 °C gave a mixture of **2**[6] (43%), **3**[7] (< 5 %) and **4**[8] (15 %), which were easily separated by chromatography. These reactions involved two mechanisms for the loss of dinitrogen following the attack of diazomethane on the ketone



Scheme 2

function of the oxygenated ring (Scheme 2). The first mechanism (①) provided the diepoxide **4** by a classical reaction[9]. The second (②) was "non-classical", beginning with a shift of the anomeric hydrogen, followed by the opening of the sugar-like moiety, furnishing the ketone **2**.

Treatment of **2** with one equivalent of *0.1N* NaOH in EtOH gave the alcohol **3** in quantitative yield. Acetylation of **3** with Ac_2O/pyridine at 0 °C provided the pure crystalline derivative **5**[10] in 85 % yield.



Oxidation (SeO_2, aq. dioxane, reflux 48 h)[11] of the acetyl derivative **5** furnished in 60 % yield after chromatography, the corresponding aldehyde **6**[12], isolated as hydrate.

None of these semi-synthetic clerodane derivatives showed better biological activity than clerocidin . Nevertheless derivative **4** displayed weak antibacterial properties.

Acknowledgements:

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References and Notes

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6. Compound **2**: white crystals, mp. 98 °C, ^{1}H NMR ($CDCl_3$) δ: 0.93 (d, *J* = 7.0 Hz, 3H, **Me**-11); 1.00 (s, 3H, **Me**-12); 1.17 (s, 3H, **Me**-10); 1.20 -1.93 (m, 9H, **CH_2**-4, **CH**-6, **CH_2**-7, **CH**-8, **CH**-8a, **CH_2**-13); 2.01 (s, 3H, CO**CH_3**-20); 2.27-2.40 (m, 3H, **CH_2**-3, **CH**-8); 2.97 (d, J_{AB}= 5.0 Hz, 1H, **CH_2** epoxide); 3.00 (d, J_{AB}= 5.0 Hz, 1H, **CH_2** epoxide);5.33 (m, 1H, **H**-14); 6.48 (m, 1H, **H-2**); 7.96 (s, 1H, O**CHO**-17); 9.24 (s, 1H, **CHO**-9). ^{13}C NMR, EA, IR and MS spectral data were in accord with the structure. $[\alpha]_D^{25}$ + 49 ° (c 0.25, $CHCl_3$).
7. Compound **3**: white crystals, mp. 110 °C. ^{1}H , ^{13}C NMR, EA, and IR spectral data were in accord with the structure. $[\alpha]_D^{25}$ + 93 ° (c 0.1, $CHCl_3$).
8. Compound **4**: white crystals, mp 135-140 °C. ^{1}H NMR ($CDCl_3$): mixture of 2 anomers. EA, IR and ^{13}C spectral data were in accord with the structure. $[\alpha]_D^{25}$ + 97 ° (c 0.125, $CHCl_3$).
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10. Compound **5**: purified by flash chromatography, ^{1}H NMR ($CDCl_3$) δ: 0.99 (d, *J* = 7.0 Hz, 3H, **Me**-11); 1.06 (s, 3H, **Me**-12); 1.23 (s, 3H, **Me**-10); 1.26 -1.95 (m, 9H, **CH_2**-4, **CH**-6, **CH_2**-7, **CH**-8, **CH**-8a, **CH_2**-13); 2.04 (s, 3H, CO**CH_3**-20); 2.06 (s, 3H, OCO**CH_3**-17); 2.36-2.43 (m, 3H, **CH_2**-3, **CH**-8); 2.98 (d, J_{AB}= 5.0 Hz, 1H, **CH_2** epoxide);3.01 (d, J_{AB}= 5.0 Hz, 1H, **CH_2** epoxide) 5.29 (m, 1H, **H**-14); 6.54 (m, 1H, **H-2**); 9.29 (s, 1H, **CHO**-9).
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12. Compound **6**: purified by chromatography, amorphous powder (mixture of isomers).^{1}H, ^{13}C NMR, EA and IR spectral data were consistent with the proposed structure.

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