AN ADVENTITIOUS SYNTHESIS OF PEDERINOLACTONE

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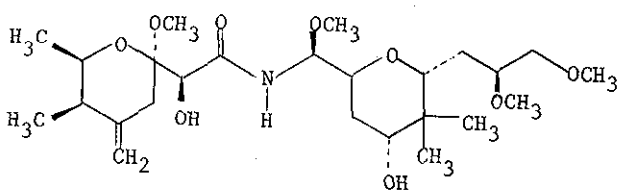
The synthesis of pederinolactone (2) is reported.

Many species of staphylinid beetle of the genus Paederus contain the biochemically intriguing vesicant pederin (1) in their haemolymph (1). While the structure and stereochemistry of pederin ultimately rests on two independent X-ray crystallographic studies (2,3), there has also been considerable chemical investigation of the pederin molecule. One particularly novel transformation which has been encountered is the acidic methanolysis of pederin in an oxygen-containing atmosphere, which results in the formation of pederinolactone, a compound first isolated and postulated to have structure 2 by Cardani et al. (4). That formula 2 correctly portrays pederinolactone was established by an X-ray structure determination (5).



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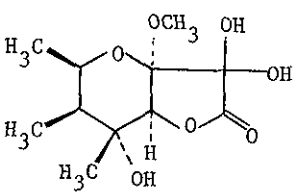
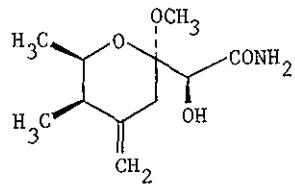


2

In the course of our studies directed toward the synthesis of pederamide (3), an intermediate in our projected synthesis of pederin (6), we have observed formation of pederinolactone upon attempted hydrolytic removal of the acetonide functionality from the spiro-acetonide 4.



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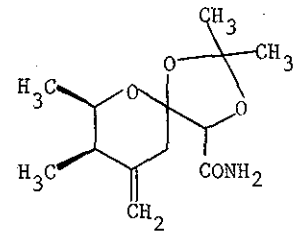

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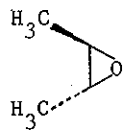
Compound 4 was prepared in the following manner. The epoxide ring of trans-2-butene epoxide, 5, was opened with the ethylenediamine complex of lithium acetylide in dimethylsulfoxide (room temperature, 7 days). The resulting acetylenic alcohol was treated with two equivalents of n-butyllithium in tetrahydrofuran (THF) (-40°C, 1 h) followed by addition of gaseous carbon dioxide. Upon acidification, acetylenic acid 6



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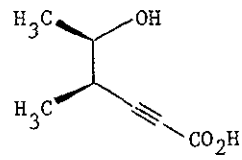

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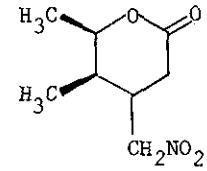

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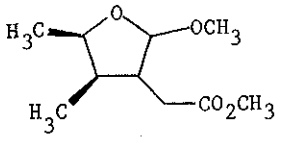
was obtained in 30% overall yield (7,8). Acid 6 was partially hydrogenated (5% palladium on barium sulfate, quinoline, methanol) to give the cis olefin, which lactonized spontaneously upon distillation. The resulting α,β-unsaturated lactone was treated with nitromethane (Triton-B, room temperature, 10 h), giving the desired Michael reaction adduct, 7, in 72% yield from 6 (7,8).

Generation of the aci-nitro anion of 7 with sodium methoxide (1 eq, methanol solution, room temperature) followed by quenching in acidic methanol (sulfuric acid, methanol, -35°C) gave the rearranged Nef reaction product, cyclic acetal methyl ester 8 in 98% yield (7,8,9). Transketalization (ethanedithiol, chloroform, hydrogen chloride, room temperature, 10 h) (10) of 8 gave a 96% yield of dithiolane lactone 9 (7,8).



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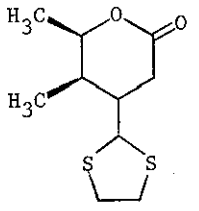

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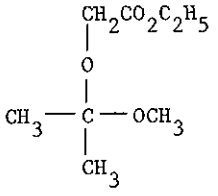
The enolate anion of protected ethyl glycolate 10 (generated with lithium diisopropylamide, THF, -78°C, 1 h) was condensed with 9 (2 h, -78°C), and the product was deprotected with hydrochloric



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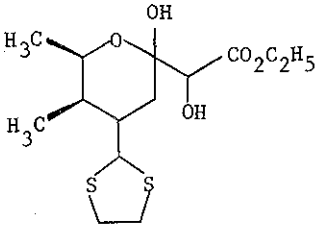
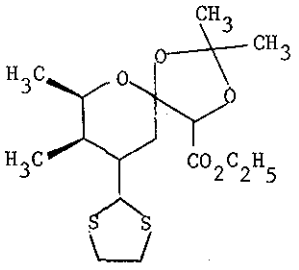


11

acid in THF (1 h, room temperature) to give hemiketal 11 in 83% yield (7,11). Compound 11, when treated with phosphorus pentoxide in acetone (room temperature, 15 h), afforded, in 81% yield, acetonide ester 12 (7,8).



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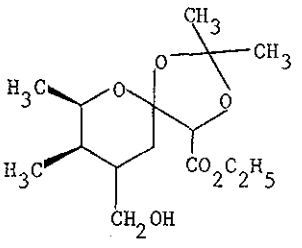
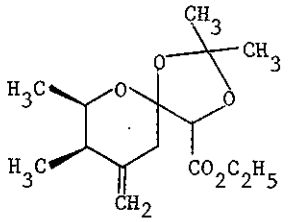


13

Mercuric ion catalyzed hydrolysis of the sulfur-containing protecting group (mercuric chloride, mercuric oxide, 4:1 acetonitrile-water, 62°C, 8 h) led to the expected aldehyde, which was then reduced (sodium borohydride, ethanol, 0°C, 15 min) to alcohol 13 in 92% overall yield (7). Acetonide olefin 14 was generated by dehydration (12, 13) of 13 (1. o-nitrophenylselenocyanate, tri-n-butyl phosphine, THF, room temperature, 6 h; 2. silica gel column chromatographic purification of the intermediate aryl selenide; 3. 30% hydrogen peroxide, THF, room temperature, 10 h) in 83% yield, after purification by alumina column chromatography (7,8). Treatment of 14 with ammonium hydroxide (ethanol, room temperature, 6 days) formed amide 4 in 78% yield (7,11).



14

When amide 4 was dissolved in acidic methanol (3% hydrochloric acid in anhydrous methanol, room temperature, 31 h), in an attempt to generate 3, we found, to our great surprise, that pederinolactone was formed in 27% yield, after recrystallization (mp 130-135°C, resolidifies, remelts at 170°C; lit (4) mp 125°C, resolidifies, remelts at 170°C). Initial identification of this product was made on the basis of a comparison of our IR, NMR and low and high resolution mass spectral data with those reported in the literature (4). Further confirmation was provided by direct comparison of our IR and NMR spectra with those of authentic pederinolactone (14).

In a related experiment, we found that pederinolactone was formed in 65% yield by allowing 4 to stand in boron trifluoride-methanol solution for 19 hours at room temperature.

Notable features in the formation of 2 from either 1 or 4 are: 1. the regiospecificity of the allylic oxidation reaction which appears to have taken place, 2. the formation of a tertiary alcohol rather than a methyl ether at the site of the former methylene substituent, and 3. the unexpected ease of this rather complex transformation. It would be interesting to know what role the pederamide side-chain plays in the oxidative process, and whether this process is in any way related to the

remarkable biological activity of pederin itself.

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14. These spectra were kindly provided by Professor Cardani.

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