

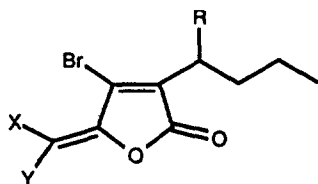
SYNTHESIS OF 5-ALKYL-4-BROMO-5-HYDROXY-2(5H)-FURANONES AND  
5-ALKYLIDENE-4-BROMO-2(5H)-FURANONES

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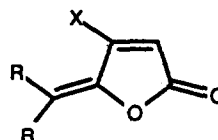
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**Abstract.**- Treatment of monoalkylsubstituted allenic esters **4** with NBS and water in the darkness yields  $\beta$ -bromo- $\alpha,\beta$ -butenolides **5**, that are easily transformed into 5-alkyl-4-bromo-5-hydroxy-2(5H)-furanones **8** and 5-alkylidene-4-bromo-2(5H)-furanones **2**.

In our studies directed to the synthesis of fimbrolides **1**, marine metabolites isolated from *Delisea fimbriata*,<sup>1</sup> an easy and smooth access to  $\gamma$ -alkylidene- $\beta$ -bromo- $\alpha,\beta$ -butenolides, **2**, compatible with the functional groups present in these natural products, was required. Although the preparation of the analogous  $\beta$ -oxygene compounds **3** is well documented,<sup>2</sup> there are only two poor and inconvenient methods described for the synthesis of the bromobutenolides **2**: one is based on the treatment of levulinic acid derivatives with concentrated sulphuric acid under reflux conditions,<sup>3</sup> and the other on the formation of 5-alkyl-4-bromo-5-hydroxy-2(5H)-furanones using the dianion of (E)-3-bromopropenoic acid.<sup>4</sup> Both methods have already been applied to the synthesis of fimbrolides.

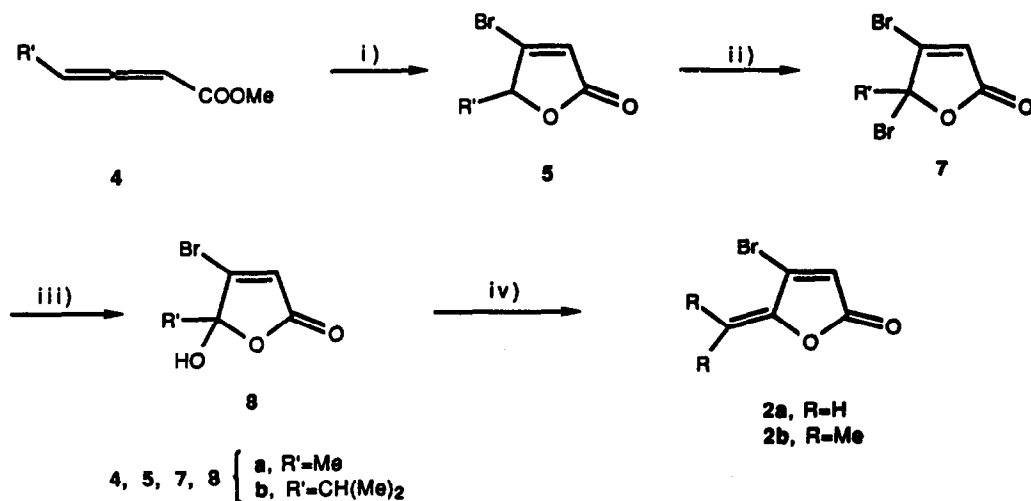


**1** R=H, OH, OAc  
X,Y=H, Cl, Br, I



**2**, X=Br  
**3**, X=OH, OMe

We have found now that the bromolactonization of  $\gamma$ -monoalkyl substituted allenic esters 4,<sup>5</sup> easily available in multi-gram scale, provides a useful and general preparative entry to the desired lactones 2 (Scheme 1). In a recent publication<sup>6</sup> we reported the difficulties found in the preparation of 4-bromo-5-methyl-2(5H)-furanone, 5a, a possible precursor of 2, by bromination of methyl 2,3-pentadienoate, 4a, a reaction that gives good yields with other substituents in the allenic ester. However, when *N*-bromosuccinimide (NBS) in water and in the darkness is used as brominating agent<sup>7</sup> we have found that bromolactones 5 are formed easily and directly.



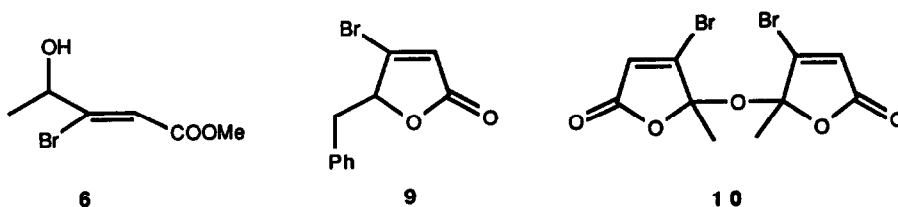
- i) 4a: NBS, H<sub>2</sub>O, rt; 4b: NBS, H<sub>2</sub>O, rt followed by CHCl<sub>3</sub>, reflux, cat. *p*-TsOH;  
 ii) NBS, CCl<sub>4</sub>, hv, 55°C; iii) THF, H<sub>2</sub>O, rt; iv) P<sub>2</sub>O<sub>5</sub>, C<sub>6</sub>H<sub>6</sub>, reflux

Scheme 1

Thus, treatment of 4a with NBS gave 5a in 66% yield and from the reaction a 4% yield of the new bromohydrin methyl (*Z*)-3-bromo-4-hydroxy-2-pentenoate,<sup>8</sup> 6, was also isolated; the configuration of the double bond was deduced by the presence of a quartet at  $\delta$  4.43 in its pmr spectrum.

Allylic bromination of butenolide 5a (NBS, irradiation with an incandescent lamp) afforded crude dibromolactone 7a,<sup>6</sup> a moisture sensitive substance as other  $\gamma$ -bromo- $\alpha,\beta$ -butenolides,<sup>9</sup> in 78% yield. Treatment of 7a with tetrahydrofuran/water allowed the isolation of the new 4-bromo-5-hydroxy-5-methyl-2(5H)-furanone, 8a (63% yield from 5a). Finally, dehydration of 8a with P<sub>2</sub>O<sub>5</sub> in benzene under reflux conditions<sup>4</sup> gave crude 4-bromo-5-methylene-2(5H)-furanone, 2a, in 62% yield (gc), that was purified by flash chromatography with hexane-ether 10:1 as eluent (41% yield). This compound, that is unstable as its simplest analogue  $\gamma$ -methylene- $\alpha,\beta$ -butenolide or

protoanemonin,<sup>10</sup> was obtained as a white solid (m.p. 60-61°C dec.) after recrystallization with ether-hexane. Two minor compounds, 5-benzyl-4-bromo-2(5H)-furanone (9, 4% yield) and bis(4-bromo-5-methyl-2-oxo-5H-furan-5-yl)ether (10, 4% yield), were also isolated in the reaction with phosphorous pentoxide. Conventional basic dehydrobromination methods failed with compound 7a, but transformation into 2a with fair yields (56%) was also accomplished using LiBr in refluxing DMF, a method already applied by Dana and co-workers<sup>11</sup> to other bromolactones, although some lactone 8a (16% yield) was also obtained as a by-product.



The same reaction sequence was utilized to obtain 2b. Improving significantly the previous described synthesis<sup>12</sup> we prepared allene 4b by the Wittig methodology.<sup>5</sup> Treatment of 4b with NBS in water at room temperature and heating the crude bromohydrin in chloroform with a trace of *p*-toluenesulphonic acid gave pure 5b (58% yield), that was submitted to allylic bromination affording the new dibromolactone 7b in 88% yield. Hydrolysis of this compound resulted in the quantitative isolation of  $\beta$ -bromo- $\gamma$ -hydroxy- $\alpha,\beta$ -butenolide 8b, that by dehydration with P<sub>2</sub>O<sub>5</sub> gave crude 4-bromo-5-isopropylidene-2(5H)-furanone, 2b (64% yield by gc), being further purified by flash column chromatography.

This methodology represents a new and elegant entry not only to  $\gamma$ -alkylidene- $\beta$ -bromo- $\alpha,\beta$ -butenolides 2, but also to 5-alkyl-4-bromo-5-hydroxy-2(5H)-furanones 8. Lactones 8 were till now only accessible by treatment of the difficultly available lithium (E)-3-bromo-3-lithiopropenoates with aliphatic aldehydes,<sup>4,13</sup> and by the method recently used by Jefford and co-workers<sup>14</sup> in the first synthesis of bromobekereleide, also a marine natural product, whose structure is closely related to that of fimbrolides.

The application of this strategy to the synthesis of fimbrolides and beckerelides is object of ongoing investigations in our laboratories.

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- 8.- All new compounds were characterized spectroscopically (pmr, cmr, ir, and ms) and by elemental analyses (C, H, Br) except the dibromo derivatives 7 and the minor compounds 9 and 10. Representative pmr (80 MHz, CDCl<sub>3</sub>, δ) data are: 2a: 5.21 (dd, J=3.1 Hz, J'=0.8 Hz, 1H), 5.32 (dd, J=3.1 Hz, J'=1.8 Hz, 1H), 6.45 (dd, J=1.8 Hz, J'=0.8 Hz, 1H); 2b: 2.07 (s, 3H), 2.28 (s, 3H), 6.32 (s, 1H); 8a: 1.71 (s, 3H), 3.85 (br. s, 1H), 6.24 (s, 1H); 8b: 0.86 (d, J=6.8 Hz, 3H), 1.19 (d, J=6.8 Hz, 3H), 2.31 (m, 1H), 3.76 (br. s, 1H), 6.31 (s, 1H). Representative cmr (20 MHz, CDCl<sub>3</sub>, δ) data are: 2a: 97.4, 121.9, 137.0, 153.9, 166.4; 2b: 18.6, 21.6, 121.6, 128.1, 133.3, 142.5, 166.8; 8a: 23.5, 107.2, 122.4, 152.1, 168.8; 8b: 15.2, 16.0, 33.1, 110.3, 123.1, 151.5, 169.1.
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