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A New, Effective Route to Methyl Substituted 3,3a,4,6a-Tetrahydro-2*H*-cyclopenta[*b*]furan-2-ones.

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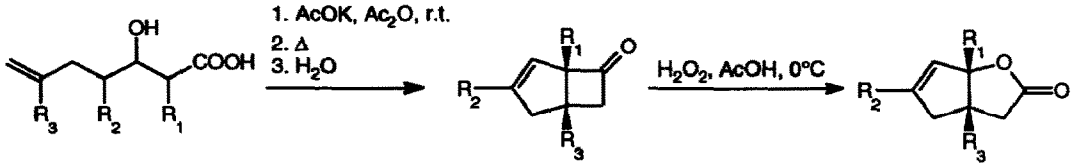
Abstract: 3,3a,4,6a-Tetrahydro-2*H*-cyclopenta[*b*]furan-2-ones **1**, important starting materials in the synthesis of linear condensed triquinane sesquiterpenes, have been prepared in an efficient manner by an effective bicyclization of 3-hydroxy-6-heptenoic acids, followed by a Baeyer-Villiger oxidation of the bicyclo[3.2.0]hept-3-en-6-one intermediates.

In 1986, Curran et al.[1] reported a very efficient reaction for the opening of 3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-ones with organocopper reagents ("RCu"/$MgBr_2$) and provided an operationally simple method to effect the S_N2'-anti opening of vinyl lactones **1a-c** with good to excellent regioselectivity.

This reaction was essential in the construction of trans-3,5-disubstituted-cyclopentenes, versatile precursors for a tandem radical cyclization to produce linear condensed triquinane sesquiterpenes such as hirsutene,[2,3] Δ-capnellene,[4] hypnophilin, and coriolin.[5] The Curran procedure is very elegant and efficient and therefore serves as the key step in several other syntheses.[6,7,8]

It should be noted however that the preparation of the starting vinyl lactones is a long and time consuming sequence.[9] This paper deals with an improved approach to 3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-ones **1** (Scheme 1). It consists of an efficient bicyclization of 3-hydroxy-6-heptenoic acids **2** into the corresponding bicyclo[3.2.0]hept-3-en-6-ones **3**, followed by regioselective Baeyer-Villiger oxidation of them to generate the vinyl lactones.



2a $R_1, R_2, R_3 = H$	**3a** (62%)	**1a** (95%)
2b $R_1 = CH_3$; $R_2, R_3 = H$	**3b** (63%)	**1b** (82%)
2c $R_2 = CH_3$; $R_1, R_3 = H$	**3c** (63%)	**1c** (92%)
2d $R_3 = CH_3$; $R_1, R_2 = H$	**3d** (78%)	**1d** (95%)

Scheme 1

The bicyclization was performed through an intramolecular [2+2] cycloaddition of *in situ* generated unsaturated ketenes, obtained by treatment of 3-hydroxy-6-heptenoic acids **2** with potassium acetate and acetic anhydride firstly at room temperature (2 h) and then at reflux conditions (4 h).[10,11]

The conversion of bicyclo[3.2.0]hept-3-en-6-ones **3** into the title compounds[12] was carried out with 30% hydrogen peroxide in 90% acetic acid at 0°C for 12 h. The esters of 3-hydroxy-6-heptenoic acids were prepared in good yields by a Reformatsky reaction using the procedure of Rathke and Lindert[13] or by alkylation of the dianion of ethyl acetoacetate[14] followed by chemioselective reduction with sodium borohydride in methanol. The hydrolysis of the esters was performed with a 10% methanolic solution of potassium hydroxide at room temperature.

The results obtained so far indicate this to be a general procedure, superior to the more traditional methods to prepare 3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one (**1a**) and its 3a-, 5- and 6a-methyl derivatives (**1b-d**). Further prospects for the utilization of bicyclo[3.2.0]hept-3-en-6-ones in organic synthesis are currently under consideration.

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9. Although the vinyl lactone **1a** is readily available (Meinwald, J.; Seidel, M. C.; Cadoff, B. C. *J. Am. Chem. Soc.* **1958**, *80*, 6303), the preparation of vinyl lactones **1b**[2,3] and **1c**[4] stems on a six step synthetic sequence. The vinyl lactone **1d** has been prepared[4] by opening compound **1a** with MeMgBr/CuBr·Me_2S, followed by a standard iodolactonization and a base promoted elimination with DBU.
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11. **3d**: obtained as a clear oil either after kugelrohr distillation (100°C/25 mbar, 68% yield) or after flash chromatography (petroleum ether : diethyl ether = 8 : 2, R_f 0.5, 78% yield): IR (film): ν 1779 cm^{-1}; ^1H NMR($CDCl_3$): δ 5.86 (m, 1H), 5.56 (m, 1H), 3.78 (m, 1H), 3.03 (dd, 1H, J = 17.8, 3.0 Hz), 2.83 (dd, 1H, J = 17.8, 4.4 Hz), 2.61 (m ,2H), 1.38 (s, 3H) ppm; ^{13}C NMR($CDCl_3$): δ 208.4; 134.3, 126.3, 78.2, 59.3, 47.8, 35.2, 24.4 ppm.
12. **1d**: obtained as an oil after flash chromatography (petroleum ether : diethyl ether = 1 : 1, R_f 0.2, 95% yield). IR (film) ν 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.05 (m, 1H), 5.85 (m, 1H), 5.05 (m, 1H), 2.30-2.65 (m, 4H), 1.35 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 177.2 (C), 137.3 (CH), 129.1 (CH), 95.51 (CH), 46.49 (CH_2), 44.34 (C), 43.27 (CH_2), 25.17 (CH_3) ppm.
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