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Total Synthesis of Ethisolide from " Naked Sugars "

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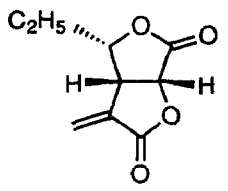
Key Words : Ethisolide, 7-oxabicyclo[2 2.1]hept-5-en-2-one, radical cyclization.

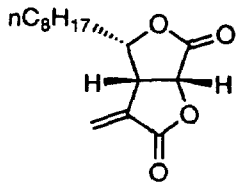
Abstract : A total synthesis of (±)-ethisolide was realized from (±)-7-oxabicyclo[2.2.1]hept-5-en-2-one by using a radical cyclization as a key step

Ethisolide [1], isoavenaciolide [1, 2] and avenaciolide [3] are three bislactone secondary mold metabolites isolated from fermentation broths of *Aspergilus* and *Penicillium* species, and have been reported to possess antifungal and antibacterial activities [1,3 a, e]

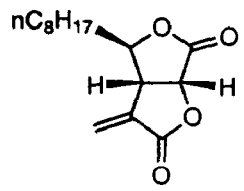
Scheme I



(-)-ETHISOLIDE



(-)-ISOAVENACIOLIDE

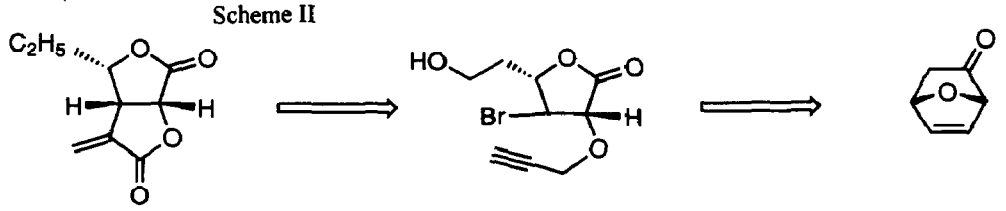


(-)-AVENACIOLIDE

Ethisolide has been synthetized in a racemic form by using a glycolate Claisen rearrangement as the key step of the synthesis [4] Furthermore, optically active ethisolide has been obtained from D-ribose [5] and from L-quebrachitol [6].

Here, we would like to describe a very short synthesis of (±)-ethisolide from (±)-7-oxabicyclo[2.2 1]hept-5-en-2-one (oxanorbornenone) by using a radical cyclization reaction as shown in the retrosynthetic plan given below (Scheme II)

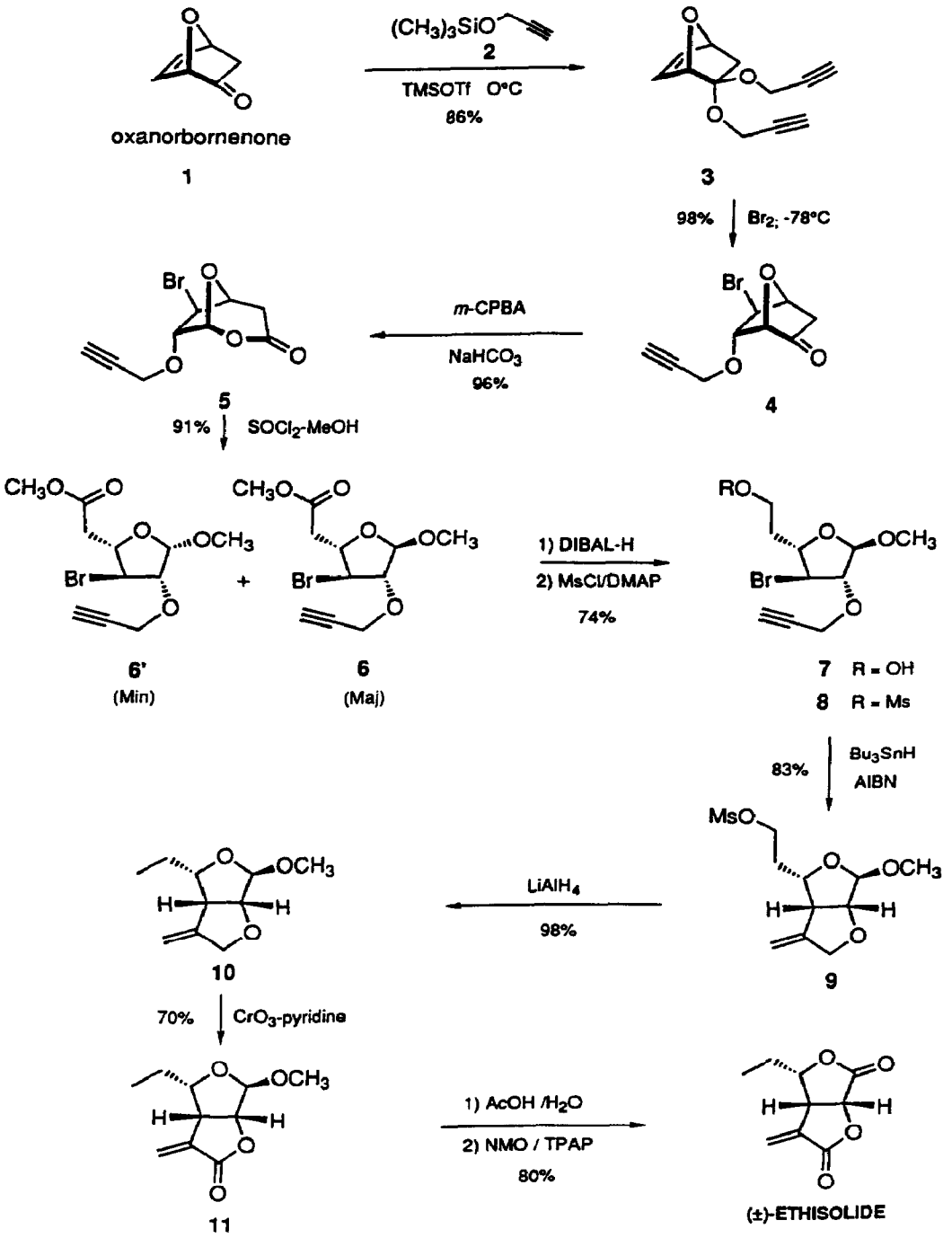
Scheme II



(-)-ETHISOLIDE **7** **1**

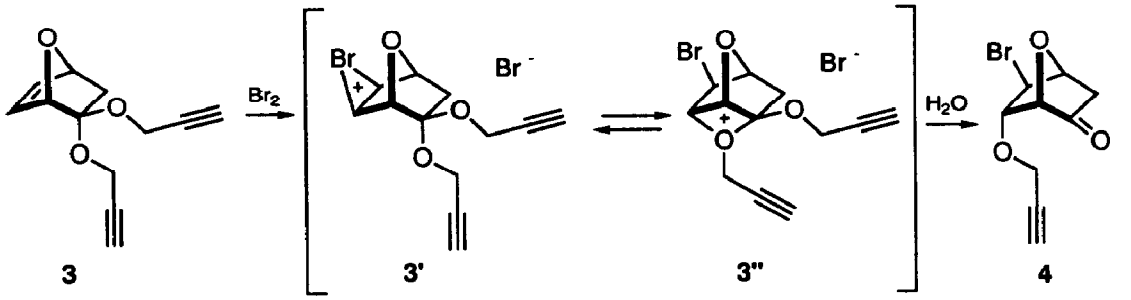
(±)-7-Oxanorbornenone **1**, prepared according to the Vogel's procedure [7] was transformed into ketal **3** by treatment of **1** with propargylic silylether **2** in the presence of trimethylsilyltriflate at 0°C in CH_2Cl_2. When the propargylic silylether **2** was rigourously anhydrous the ketal **3** was obtained with a yield of 86%

Scheme III : Synthesis of (±)-Ethisolide



The chemoselective bromination of the propargylic ketal **3** by bromine in CH_2Cl_2 at -78°C produced compound **4** which was isolated in a 98% yield. This result can be interpreted in terms of formation of intermediates **3'** ⇄ **3"** that lead to the regioselective and stereoselective migration of one of the propargylic group to produce, after hydrolysis, compound **4** [8].

Scheme IV



Oxidation of **4** with *meta*-chloroperbenzoic acid (*m*-CPBA) in a buffered solution of CH_2Cl_2 at room temperature furnished lactone **5** (96%). Treatment of **5** with $SOCl_2$ [9] in methanol gave a mixture of two anomeric furanosides **6** and **6'** (91%) in a ratio 8 / 1. Reduction of the mixture **6** + **6'** with diisobutylaluminium-hydride (DIBAL-H) in tetrahydofuran at -50°C led to the formation of the alcohol **7** (82%) which was then treated with methanesulfonyl chloride in the presence of 4-N,N-dimethylaminopyridine (DMAP) at room temperature in CH_2Cl_2 to afford the corresponding mesylate **8** (90%). The bicyclic structure of ethisolide was built up by treatment of **8** with tri-*n*-butyltin hydride in the presence of a catalytic amount of azobisisobutyronitile (AIBN) in refluxing benzene for twelve hours [10] Under these conditions a 5-exo-dig radical cyclization took place to afford **9** [11] in 83% yield. The reduction of the mesylate group with lithium aluminium hydride (LAH) led nearly quantitatively to the formation of the ethyl side chain of (±)-ethisolide. The oxidation of the resulting compound **10** by chromium oxide-pyridine in CH_2Cl_2 afforded **11** [12] (70%) which was then hydrolyzed (by 50% aqueous acetic acid, 80°C, 4 hours) to form lactol **12** quantitatively. The transformation of **12** into (±)-ethisolide [13] was realized in good yield (80%) using a catalytic amount of tetra-*n*-propylammoniumperruthenate (TPAP) in the presence of N-methylmorpholine N-oxide (NMO) [14].

(±)Ethisolide was obtained in 11 steps from oxanorbornenone with an overall yield of 24%.

Since both (-)- and (+)-7-oxanorbornenone can be obtained in optically pure forms [7b, 15] natural (-)-ethisolide and its enantiomer should be obtained with the same ease as (±)-ethisolide.

Acknowledgements

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   b) Spectral data of **4:**

   IR: 3280; 2110; 1755cm^{-1}. ^{1}**H NMR** ($CDCl_3$) δ (ppm): 2.26 (d, *J* = 18.0 Hz, 1H); 2 57 (t, *J* = 2.5 Hz, 1H); 2.60 (dd, *J* = 18.0 Hz, *J* = 6.5 Hz, 1H); 4.08 (d, *J* = 1.5 Hz, 1H); 4.24 (AB, *J* = 16.0 Hz, *J* = 2.5 Hz, 2H); 4.51 (d, *J* = 5.5 Hz, 1H), 4.63 (m, 1H); 4.89 (d, *J* = 6.5 Hz, 1H). ^{13}**C NMR** ($CDCl_3$) δ (ppm): 42.0 (t); 50.5 (d); 58.2 (t); 76.3 (s); 77.8 (d); 83.6 (d), 83.7 (d); 85.3 (d); 205.0 (s). **MS:** 187-189 (M^+-56, 4); 173-175 (1); 165 (34); 145-148 (3); 119 (52); 81 (100).

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11. Spectral data of **9**:

    IR: 1660; 1350; 1170 cm^{-1}. ^{1}**H NMR** ($CDCl_3$) δ (ppm): 1.80-2.05 (m, 2H); 3.00 (s, 3H); 3.30 (s, 3H); 4.15-4.30 (m, 3H); 4.40 (m, 3H); 4.51 (d, *J* = 6.3 Hz, 1H); 4 90 (s, 1H); 5.00 (br.s, 1H); 5.15 (br.s, 1H). ^{13}**C NMR** ($CDCl_3$) δ (ppm): 31 4 (t); 37.2 (q); 49 8 (d); 54 3 (q); 67.7 (t); 72.5 (t); 74.8 (d); 88.3 (d); 107 6 (d); 108 6 (t); 146.4 (s). **MS:** 247 (M^+-31, 3); 126 (100)
12. Spectral data of **11:**

    IR: 1770, 1650 cm^{-1}. ^{1}**H NMR** ($CDCl_3$) δ (ppm): 1.05 (t, *J* = 7 4 Hz, 3H); 1.45-1 60 (m, 2H); 3.38 (s, 3H); 3.57 (m, 1H); 4.10 (m, 1H), 4.35 (d, *J* = 6.9 Hz, 1H); 5.02 (s, 1H); 5.68 (m, 1H); 6.41 (m, 1H). ^{13}**C NMR** ($CDCl_3$) δ (ppm): 11.0 (q); 23.6 (t); 44.4 (d); 54 2 (q); 80.3 (d); 84.3 (d); 105.2 (d); 125.7 (t); 133.1 (s); 169.5 (s). **MS:** 167 (M^+-31, 4); 140 (100)
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