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Volkan Kumbaraci, Hande Gunduz, Meric Karadeniz

PII: S0040-4039(13)01625-0
DOI: http://dx.doi.org/10.1016/j.tetlet.2013.09.071
Reference: TETL 43571

To appear in: *Tetrahedron Letters*

Received Date: 23 January 2013
Revised Date: 6 August 2013
Accepted Date: 12 September 2013

Please cite this article as: Kumbaraci, V., Gunduz, H., Karadeniz, M., Facile syntheses of (-)-montagnetol and (-)-erythrin, *Tetrahedron Letters* (2013), doi: http://dx.doi.org/10.1016/j.tetlet.2013.09.071

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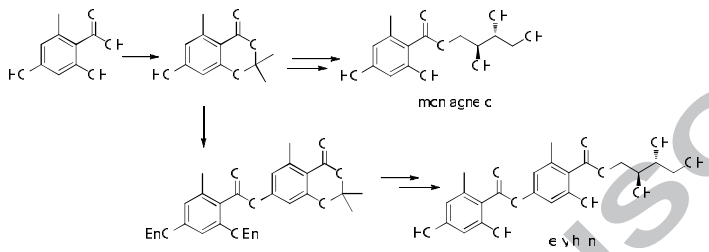

Tetrahedron Letters
journal homepage: www.elsevier.com

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Volkan Kumbaraci*, Hande Gunduz, Meric Karadeniz

Istanbul Technical University, Department of Chemistry, Maslak, 34469 Istanbul, Turkey

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
1,3-Benzodioxin-4-one
Orsellinic acid
Montagnetol
Erythrin
Thermolysis

ABSTRACT

A novel synthetic method is introduced to prepare the biologically important montagnetol and erythrin compounds starting from a 1,3-benzodioxin-4-one, synthesized from commercially available orsellinic acid and erythritol.

Several biologically active natural products contain *ortho*-functionalized salicyclic and orsellinic acid units, e.g., montegnatol and erythrin. Montegnatol and erythrin have a number of biological activities including antioxidant properties.[1] They were isolated as natural products from the lichen *Roccella montagnei* and their structures were confirmed by their synthesis, but without confirming their configuration.[2,3]

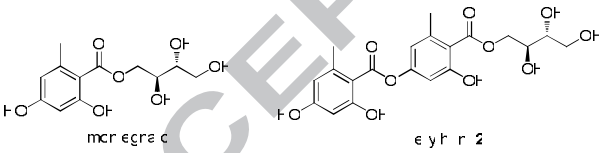
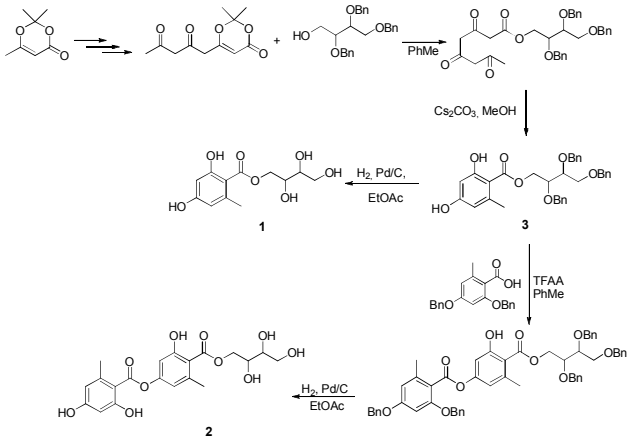


Figure 1. (-)-Montegnatol and (-)-erythrin

The absolute configuration of montegnatol and erythrin was studied by Barrett and coworkers. They reported an efficient biomimetic synthesis of (+)- and (-)-montagnetol and erythrin starting from 1,3-dioxin-4-one. As shown in Scheme 1, they formed an orsellinic acid derivative by dehydrative cyclization of a triketoester. The triketoester was synthesized in three steps: thermolysis, ketene trapping and crossed-Claisen condensation. These steps were followed by esterification with a protected erythritol, cyclization and hydrogenolysis, which gave montegnatol.[4]

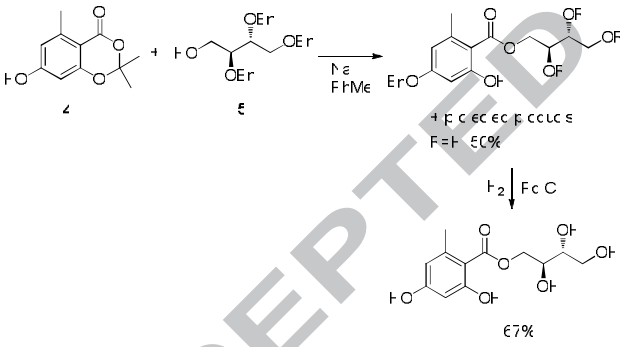


Scheme 1. Reported synthetic routes toward (+)- and (-)-montegnatol and erythrin[4]

*Corresponding author. Tel.: +90-212-285-6829; fax: +90-212-285-6386; e-mail: kumbaracii@itu.edu.tr

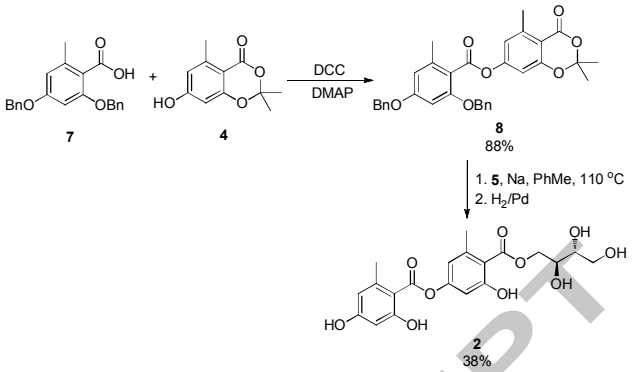
Benzodioxinone compounds are thermally and photolytically active towards nucleophiles. It is known that 1,3-benzodioxin-4-one undergoes photolytic reactions with alcohols to form salicylate derivatives efficiently.[5] In addition, 1,3-benzodioxin-4-one derivatives have been used in synthetic polymer chemistry. Our group has studied the synthesis of oligoesters and cross-linked polymers by photolytic reactions of 1,3-benzodioxin-4-ones with hydroxyl groups.[6-8] Also, thermal decomposition reactions of 1,3-benzodioxin-4-ones have been studied. However, the yields were very low and the reactions needed a catalyst.[9-11]

In this study, a new and shorter method is offered to obtain montegnatol and erythrin starting from orsellinic acid using benzodioxinone chemistry. The reaction steps can be summarized as follows: synthesis of a dioxinone derivative of orsellinic acid, esterification and hydrogenolysis. To increase the yield in the thermal reactions, we used an excess of sodium in order to enhance the nucleophilicity of the D-erythritol. Thus, 1,3-benzodioxin-4-one **(4)** was reacted with benzyl-protected D-erythritol **(5)** to give compound **(3)** as in Barrett's pathway. The reaction was monitored by TLC and mainly two products were observed. To our surprise, however, GC-MS analysis showed that there was none of the desired compound **(3)** in the reaction mixture. The esterification reaction had proceeded well, but a mixture of two different deprotected esters was obtained. One of these products (**11**) formed unexpectedly, possessing a benzyl group on the phenol (at 5.37 ppm). Thus, excess sodium metal caused deprotection of some of the benzyl groups on the aliphatic side chain, but also at the same time, mediated benzylation of the sterically suitable aromatic hydroxyl group. The NMR yield of compound **11** was approximately 70%. Finally, hydrogenolysis removed the benzyl protecting group to give (-)-montagnetol **(1)** (Scheme 2). Thus, (-)-montegnatol was prepared from simple starting materials in two steps.



Scheme 2. Synthesis of (-)-montagnetol **(1)**

In the second part of this study (Scheme 3), being different from Barrett's strategy, we aimed to synthesize erythrin starting from two orsellinic acid derivatives: benzyl protected **7** and the 1,3-benzodioxin-4-one derivative **4** from orsellinic acid. These two compounds were reacted in the presence of DCC to afford new compound **8**. Next, 1,3-benzodioxin-4-one **8** possessing an aromatic ester was treated with benzyl-protected D-erythritol **(5)** in the presence of sodium metal, which underwent the ketene trapping reaction. This was followed by hydrogenolysis of the crude product without any purification to afford (-)-erythrin. This strategy has less synthetic steps than those routes reported previously.



Scheme 3. Synthesis of (-)-erythrin **(2)**

The ^{1}H-NMR, ^{13}C-NMR and physical data of the prepared compounds were found to be in good agreement with those reported.[4]

In conclusion, we have developed a facile synthetic pathway to synthesize biologically important (-)-montagnetol and (-)-erythrin. Only two starting materials are required for the syntheses of both compounds. Both of the starting materials are benzodioxinone derivatives of orsellinic acid. Moreover, as purification is not necessary before the hydrogenolysis reaction, this method requires fewer synthetic steps to achieve the target molecules.

Acknowledgments

We thank Istanbul Technical University, Research Funds for financial support.

Supplementary Material

Supplementary material for this article is available online at http:\\pubs.acs.org.

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