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ScienceDirect
Tetrahedron 63 (2007) 11838–11843
Tetrahedron

Synthesis of (+)-lagerstronolide from (+)-sclareol

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Received 24 July 2007; revised 10 September 2007; accepted 17 September 2007
Available online 22 September 2007

Abstract—The γ-acetoxybutenolide (+)-lagerstronolide was synthesized from (+)-sclareol, with an overall yield of 10%. The absolute stereochemistry for the natural compound (−)-lagerstronolide has been correctly established.

1. Introduction

Lagerstroemia is an important member of Lythraceae consisting of 31 genera. This genus contains more than 56 species of trees or shrubs with colourful flowers distributed from south-eastern Asia to Australia.[1] (+)-Lagerstronolide is a metabolite isolated from *Lagerstreomia lancasteri*, which contains a unit of γ-hydroxybutenolide.[2] The γ-hydroxybutenolide group is present in several compounds with important biological activities, such as luffolide (which has anti-inflammatory activity),[3] dysidiolide (which is an inhibitor of the cdc25A protein phosphatase)[4] and its analogue (which has antitumoural properties),[5] this biological activities prompted us to the synthesis of (+)-lagerstronolide (Fig. 1).

In the last years our group has been involved in the use of readily available (+)-sclareol, as the substrate for the preparation of scarce natural products with important biological activities.[6]

2. Results and discussion

The synthesis of (+)-lagerstronolide from (+)-sclareol needed to dehydrate the tertiary hydroxyl group of the bicyclic system into a terminal double bond and change the functionality of the side chain to the required γ-hydroxybutenolide. The synthesis was planned according to Scheme 1. (+)-Lagerstronolide can be obtained from a γ-butenolide as **9**, which could be synthesized from the ketone **5a**. This last compound could be obtained from (+)-sclareol by dehydration of the hydroxyl group on the decalin and degradation of the side chain of two carbon atoms. So the synthesis will be achieved as follows:

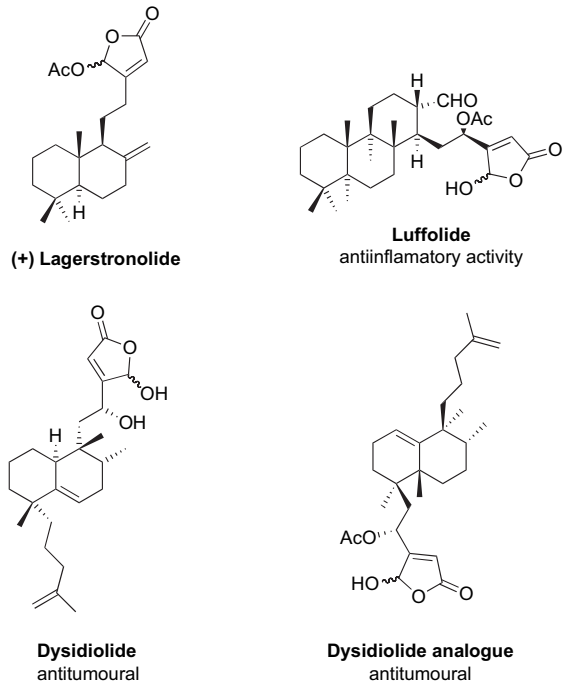

Figure 1.

1. Synthesis of intermediate **5a** from (+)-sclareol.
2. Synthesis of the butenolide ring in the side chain.
3. Synthesis of the γ-acetoxybutenolide.

2.1. Synthesis of intermediate 5a from (+)-sclareol

Oxidation of sclareol[7] with $KMnO_4$ and ensuing reduction[8] with LAH gave diols **1a/1b**. The elimination of the hydroxyl group to the tetrasubstituted double bond has been achieved by our group.[9] In this case we planned to use the pyrolysis of

Keywords: Diterpenes; (+)-Lagerstronolide; (+)-Sclareol; γ-Hydroxybutenolide.
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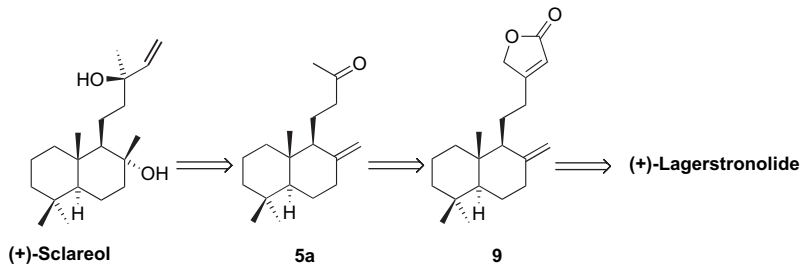
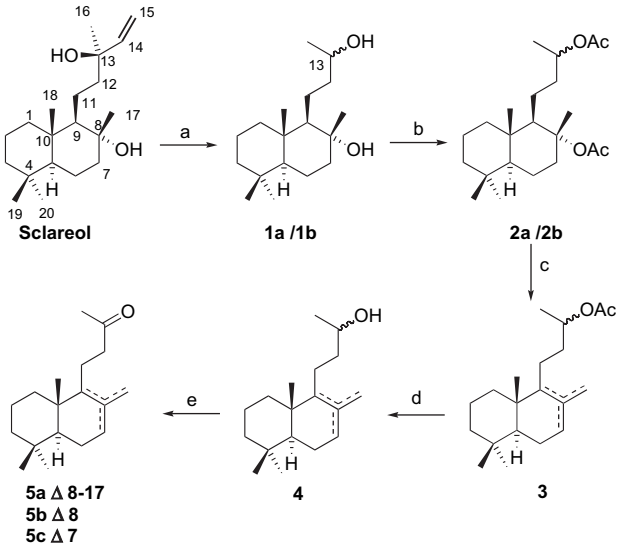
doi:10.1016/j.tet.2007.09.036



Scheme 1. Retrosynthesis of (+)-lagerstronolide from (+)-sclareol.

an acetate. Acetylation of diols **1a/1b** gave the mixture of epimeric acetates at C-13, **2a/2b**. The elimination of the acetoxyl group in the bicyclic system by pyrolysis on silica gel[10] gave a mixture of olefins **3**. As this mixture is very difficult to separate we decided to go on with the synthesis. Hydrolysis of the secondary acetoxyl group with K_2CO_3 in MeOH (3%) gave the mixture of inseparable alcohols **4**. TPAP oxidation[11] of **4** gave the mixture of methylketones **5a**–**5c**, the desired **5a** being the major compound (70% by ^{1}H NMR of the mixture) (Scheme 2). In order to separate **5a** from the other two isomers it was decided to epoxidize the mixture to obtain epoxides **6a**–**6c** and recovering the unreacted **5a**, due to the less reactivity of the terminal double bond. This compound is now very easy to separate by chromatography in a 61% yield. In this manner we got intermediate **5a** in large quantity, which allows us to continue with the synthesis. The analogue of compound **5a** with a hydroxyl group at C-3 has been synthetized via other routes.[12]



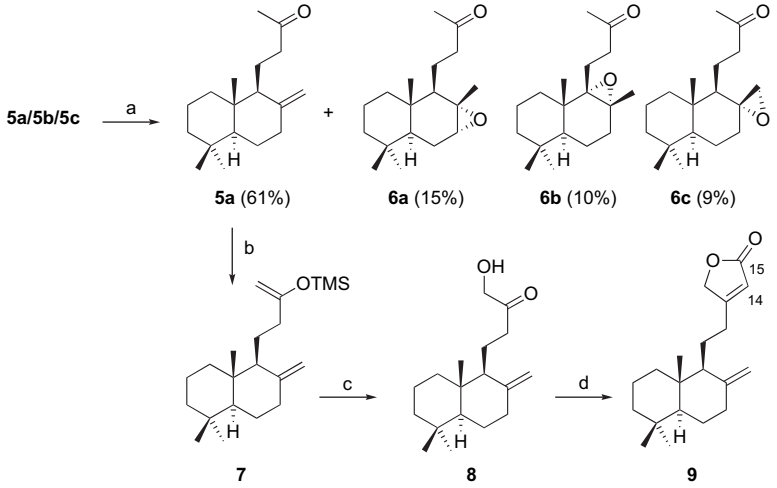
Scheme 2. (a) $KMnO_4$, acetone, $MgSO_4$, rt 6 h (80%), see Refs. 7 and 8; (b) AcCl, *N*,*N*-dimethylaniline, DCM (93%); (c) SiO_2, 100 °C (90%); (d) K_2CO_3/MeOH 3% (90%); (e) TPAP, NMO, DCM, molecular sieves 3 Å (100%).

2.2. Synthesis of the butenolide ring in the side chain

The hydroxylation of **5a** was achieved by treatment with LDA in the presence of TMSCl[13] followed by oxidation[14] of the intermediate silyl enol ether with *m*-CPBA, affording the hydroxyketone **8**. The synthesis of the required γ-butenolide **9** was carried out in high yield, by treatment of **8** with Bestmann ketene.[15] This compound is being tested for biological activity as compounds with this group, such as ajugarin A, have antifeedant activity[16] Scheme 3.

2.3. Synthesis of the γ-acetoxybutenolide

The synthesis of the γ-butenolide ring of (+)-lagerstronolide was achieved following Faulkner methodology[17] for the synthesis of γ-hydroxybutenolides that we have previously used.[18] It is necessary to obtain first the furan derivative, which was achieved by DIBAL[19] reduction of **9** and chromatography to give the required furan ring in high yield



Scheme 3. (a) *m*-CPBA, DCM; (b) LDA, TMSCl, THF, −78 °C (100%); (c) *m*-CPBA, DCM (90%); (d) $Ph_3P{=}C{=}C{=}O$, benzene, 90 °C (60%).