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ASYMMETRIC 1,4-ADDITIONS TO γ-MENTHYLOXYBUTENOLIDES. (part III)[1] ENANTIOSELECTIVE SYNTHESIS OF (-) EUDESMIN.

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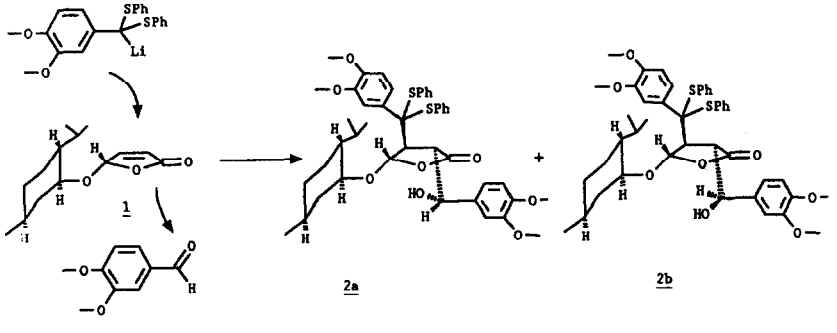
Key Words: Eudesmin, enantioselective, diastereoselective, Michael-addition, aldol condensation

Abstract : Based on an enantioselective Michael Addition of the aryldithiane of 3,4-dimethoxybenzaldehyde, to (5S)-menthyloxy-2[5H]-furanone optically pure (-) Eudesmin was synthesized in 16% overall yield.

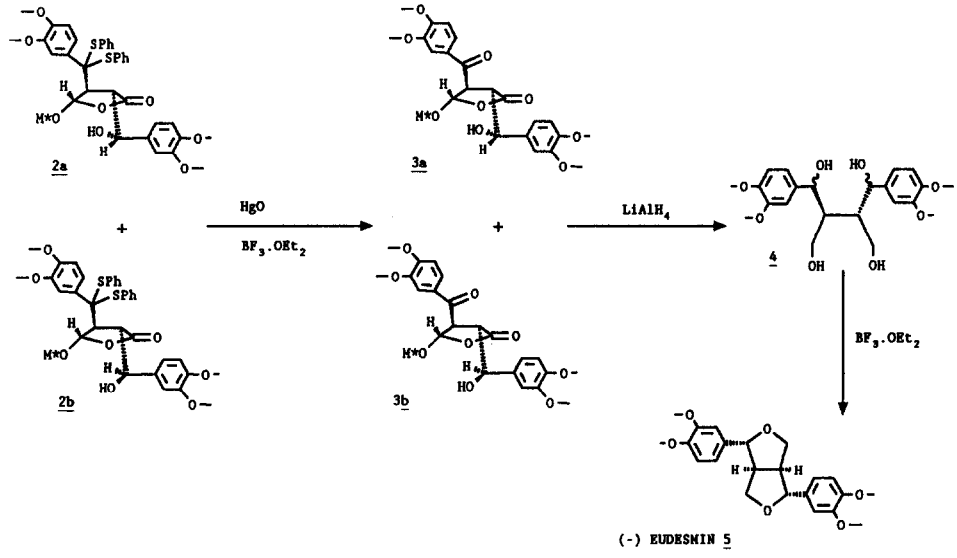
Lignans like eudesmin **(5)** [2] [3] are biological active constituents in many plants. Due to the interesting biological activity, for instance **5** displays cAMP phosphodiesterase inhibitory activity[4], an increasing interest in the stereocontrolled synthesis of these compounds is observed[5]. In particular the conjugate additions to non-chiral and chiral γ-alkoxy-enones have been reported to provide useful routes to several lignans[6]. We have extensively explored enantiomerically pure γ-menthyloxyfuranone **1** as a chiral synthon due to the excellent stereocontrol exerted by the γ-menthyloxy substituent, the easy way of preparation from furfural and the use of cheap d- or l-menthol as chiral auxiliary[7]. In this paper we wish to present our results on the first asymmetric synthesis of (-) eudesmin using (+) (5S)-menthyloxy-2[5H]-furanone.



scheme 1

The synthesis is based on the tandem Michael addition-aldol condensation of **1** with a benzyllithium derivative and an arylaldehyde. Thus the addition of the alkyl-lithium compound, prepared from the diphenyldithiane derivative of 3,4-dimethoxybenzaldehyde[8], using n-butyllithium in THF, with **1** at -90°C in THF followed by quenching of the resulting lactone enolate anion with 3,4-dimethoxy-benzaldehyde[9] at -90°C and subsequent warming of the solution to -20°C provided lactone **2** in 62% yield. (scheme 1)

Much to our surprise two diastereoisomeric products **2a** and **2b** were obtained in a 60/40 ratio. Extensive NMR studies (^{1}H-NMR, ^{13}C-NMR, COSY and NOESY) unambiquously showed that the lithiated dithiane compound added trans with respect to the menthyloxy substituent in **1** and that the addition of 3,4-dimethoxybenzaldehyde to the resulting enolate occurred exclusively trans with respect to the dithiane. It also revealed that the diastereoisomers **2a** and **2b** are epimeric at the secondary carbinol stereogenic center indicating low selectivity in the enolate addition to the aldehyde. The stereochemical assignment of **2a** and **2b** is based on NOESY NMR data and molecular models and depicted in scheme 1; the NOE effects of the proton at the carbinol stereogenic center are very distinctive in this respect. The stereochemical outcome of the aldol reaction is in contrast with our previous findings as well as the recent work of Pelter and Ward on stereoselective tandem 1,4-additions-aldol condensations with **1** and various arylaldehydes. A similar observation on low diastereoselectivity in the quenching of lactone enolates with arylaldehydes has however been made by Fujimoto and coworkers[10] in a related synthesis of racemic pinoresinol. The reason for this large difference in selectivity due to an apparently small substituent effect in the aromatic aldehyde remains obscure at present and needs further study. This lack of selectivity at the exocyclic stereogenic center has no effect on the synthesis of (-)-**5** since both isomers can be converted into (-)-eudesmin.



scheme 2

Next the thioketal was deprotected using mercury(II)oxide in combination with BF_3 etherate in aqueous THF (10% H_2O) to yield the corresponding ketones **3a** and **3b** in 89% yield. (scheme 2) Reduction of the ketolactones with lithiumaluminiumhydride in THF afforded, after quenching with wet THF (5% H_2O) and continuous extraction with THF during 16 hr followed by removal of the d-menthol by distillation, the corresponding pure tetrol **4**. This product is obtained in 67% yield as a mixture of at least three diastereoisomers[11] which differ only in the configurations at the benzylic positions. (vide infra)

One of the most important steps in this synthesis is the final ring closure of the tetrol **4** to the 2,6-diaryl-3,7-dioxabicylo[3.3.0]octane structure of eudesmin, a conversion with has been studied extensively for racemic **4**. We have chosen for the ring closure as described by Fujimoto and coworkers using BF_3 etherate, however ring closure with the aid of acids might also be applicable[12]. (-)-Eudesmin **5** was obtained from this treatment, after chromatography (SiO_2/dichloromethane, followed by ether) of the crude product, in 44% yield. The overall yield of (-) eudesmin (mp 107-109°C, lit[13] 107-109°C) following the reaction sequence presented here is 16%. The ^1H- and ^{13}C-NMR spectral data[14] were in excellent agreement with those reported for racemic eudesmin as synthesized by Pelter, Ward and coworkers[15] whereas an identical rotation ($[\alpha]_D^{20}$ -64.2° (c=1, $CHCl_3$) and mass spectrum[16] was obtained for the synthetic optically pure (-)-eudesmin and the natural product (-)-**5**. The absolute configuration (1S,2R,5S,6R) of the synthetic eudesmin is based on the configuration[17] of the Michael adduct **2** and X-ray analysis[18].

In conclusion we describe here the first complete asymmetric synthesis of (-) eudesmin starting from furfural and 3,4-dimethoxybenzaldehyde using d-menthol as chiral auxiliary.

Acknowledgement.
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