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Published in:
Tetrahedron Letters

DOI:
[10.1016/S0040-4039\(00\)79733-4](https://doi.org/10.1016/S0040-4039(00)79733-4)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
1991

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Citation for published version (APA):

Jansen, J. F. G. A., & Feringa, B. (1991). Asymmetric 1,4-Additions to γ -Menthylxybutenolides. (part III) Enantioselective Synthesis of (-) Eudesmin. *Tetrahedron Letters*, 32(27). [https://doi.org/10.1016/S0040-4039\(00\)79733-4](https://doi.org/10.1016/S0040-4039(00)79733-4)

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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 activity⁴, an increasing interest in the stereocontrolled synthesis of these compounds is observed⁵. In particular the conjugate additions to non-chiral and chiral γ -alkoxy-enones have been reported to provide useful routes to several lignans⁶. 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 auxiliary⁷. 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-dimethoxybenzaldehyde⁸, 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-benzaldehyde⁹ 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 (¹H-NMR, ¹³C-NMR, COSY and NOESY) unambiguously 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 coworkers¹⁰ 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 diastereoisomers¹¹ 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-dioxabicyclo[3.3.0]octane structure of eudesmin, a conversion which 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 applicable¹². (-)-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, lit¹³ 107-109°C) following the reaction sequence presented here is 16%. The ^1H - and ^{13}C -NMR spectral data¹⁴ were in excellent agreement with those reported for racemic eudesmin as synthesized by Pelter, Ward and coworkers¹⁵ whereas an identical rotation ($[\alpha]_D^{20}$ -64.2° (c=1, CHCl_3) and mass spectrum¹⁶ 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 configuration¹⁷ of the Michael adduct **2** and X-ray analysis¹⁸.

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.

The investigations were supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for Scientific Research (NWO).

References and notes:

1. for part II, see: Jansen, J.F.G.A.; Jansen, C.; Feringa, B.L. *Tetrahedron Asym.* **1991**, 2 in press; for part I, see: Jansen, J.F.G.A.; Feringa B.L. *Tetrahedron Lett.* **1989**, 30 5481.
2. In 1990 isolated from 4 plant species: a) *Virola elongata*; Kato, M.J.; Yoshida, M.; Gottlieb, O.R. *Phytochemistry* **1990**, 29, 1799. b) *Zanthoxylum* species; Marcos, M.; Jimenez, C.; Villaverde, M.C.; Riguera, R.; Castedo, C.; Sternitz, F. *Planta Med.* **1990**, 56, 89. c) *Bupleurum salicifolium*; Gonzalez, A.G.; Estevez-Reyes, R.; Mato, C. *J. Nat. Prod.* **1990**, 52, 1139. d) *Magnolia officinalis*; Chen, C.C.; Huang, Y.L.; Chen, C.F. *Chung-hua Yao Hsueh Tsa Chih* **1990**, 42, 91 C.A. **1990**, 113, 46155j; over the period 1967-1990 isolated from about 50 plants.
3. First isolation by Maiden, J.H. *Am. J. Pharm.* **1896**, 68, 679.
4. MacRea, W.D.; Towers, G.H.N. *Phytochemistry* **1989**, 23, 1207.

5. Ward, R.S. *Chem. Soc. Rev.* **1982**, *11*, 75.
6. For examples, see: a) Damon, R.E.; Schlessinger, R.H.; Blount, J.F. *J. Org. Chem.* **1976**, *41*, 3773. b) Pelter, A.; Satyanarayana, P.; Ward, R.S. *Tetrahedron Lett.* **1981**, *22*, 1549. c) Tomioka, K.; Ishiguro, T.; Iitaka, Y.; Koga, K. *Tetrahedron* **1984**, *40*, 1303. d) Rehnberg, N.; Magnussen, G. *J. Org. Chem.* **1990**, *55*, 4340.
7. a) de Lange, B.; Feringa, B.L. *Tetrahedron Lett.* **1988**, *29*, 1303. b) Feringa, B.L.; J.C. de Jong, *J. Org. Chem.* **1988**, *53*, 1125. c) Feringa, B.L.; de Lange, B.; de Jong, J.C. *J. Org. Chem.* **1989**, *54*, 2471. d) Jansen, J.F.G.A.; Feringa, B.L. *Tetrahedron Asym.* **1990**, *1*, 719. e) de Jong, J.C.; Jansen, J.F.G.A.; Feringa, B.L. *Tetrahedron Lett.* **1990**, *31*, 3047.
8. Prepared according to Ong, B.S. *Tetrahedron Lett.* **1990**, *26*, 4225.
9. A related strategy to prepare optically active lignan precursors was recently reported by Pelter, Ward and coworkers: Pelter, A.; Ward, R.S.; Jones, D.M.; Maddocks, P. *Tetrahedron Asym.* **1990**, *1*, 857; see also ref. 1.
10. See part II; see Pelter et al, ref 9; Fujimoto, H.; Nakatsubo, F.; Higuchi, T. *Mokuzai Gakkaishi* **1982**, *28*, 555. C.A. **1982**, *98*, 71774q.
11. ¹³C-NMR data revealed 3 diastereoisomers however 4 diastereoisomers might be present.
12. See Fujimoto et al., ref 10; for the use of acids, see for instance: a) Ziegler, F.E.; Schwartz, J.A. *J. Org. Chem.* **1978**, *43*, 985. b) Pelter, A.; Ward, R.S.; Satyanarayana, P.; Collins, P. *J. Chem. Soc., Perkin Trans. I* **1983**, 643. c) Pelter, A.; Ward, R.S.; Pritchard, M.C.; Kay, I.T. *J. Chem. Soc., Perkin Trans. I* **1988**, 1603, 1615.
13. Kaku, T.; Ri, H. *J. Pharm. Soc. Japan* **1937**, *57*, 1015, 1020 (1937). C.A. **1938**, *32*, 3365.
14. All compounds showed spectral (¹H-NMR, ¹³C-NMR, IR, HRMS, COSY and NOESY) and analytical data in accord with the proposed structures.
15. Pelter, A.; Ward, R.S.; Watson, D.J.; Collins, P.; Kay, I.T. *J. Chem. Soc., Perkin Trans. I* **1982**, 175.
16. Pelter, A. *J. Chem. Soc. C* **1967**, 1376.
17. For the assignment of the absolute configuration of (+)-(5S)-menthyloxy-2[5H]-furanone, see: Feringa, B.L.; de Lange, B. *Tetrahedron* **1988**, *44*, 7213.
18. An X-Ray of (+) eudesmin ((+)-pinoresinol dimethylether) is known, see: Vasquez, M.; Fronczek, F.R.; Fisher, N.H. *Acta Cryst.* **1990**, *C46*, 342.

(Received in UK 5 April 1991)