Pergamon

Tetrahedron Letters 41 (2000) 9337–9338

TETRAHEDRON LETTERS

A short and stereoselective total synthesis of (±)-sesamin by radical cyclisation of an epoxide using a transition-metal radical source

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Received 30 June 2000; revised 19 September 2000; accepted 27 September 2000

Abstract

A short, efficient and stereoselective synthesis of a furofuran lignan, (±)-sesamin, has been achieved in good overall yield through the radical cyclisation of an epoxide using a Ti(III) reagent as the radical initiator.

Keywords: stereoselective; radical cyclisation; epoxide; transition-metal.

Due to the widespread occurrence in nature[1] and the broad range of biological activities,[2] lignans have attracted considerable interest over the years. A major subgroup of lignans is comprised of substituted 3,7-dioxabicyclo-octanes, the synthesis of which poses interesting and often unsolved problems of stereocontrol. Sesamin is one of the representative biologically active furofuran lignans which was isolated from hydrocotyle plants.[3] Although a few interesting syntheses providing this natural product have been reported,[4] an intramolecular radical cyclisation route has not yet been explored. We report here, a short and stereoselective synthesis of (±)-sesamin (**4**) in good overall yield by intramolecular radical cyclisation of an epoxide using a Ti(III) species as the radical source. The radical initiator Cp_2TiCl was generated[5] in situ from commercially available titanocene dichloride and zinc dust in tetrahydrofuran.

Thus, the known[6] isomeric mixture of epoxides **1** on treatment with the bromide **2** in the presence of NaH in THF–DMSO afforded the epoxides **3** (Scheme 1) as an isomeric mixture in a ratio of 1:1 in 78% yield.[7] The ratio was determined from the distinguishable signals of the secondary proton attached to the epoxide carbon in ^{1}H NMR at δ 3.14 (m, 1/2 H) and at δ 3.19 (m, 1/2 H). The two isomers could not be separated by the usual chromatographic methods.

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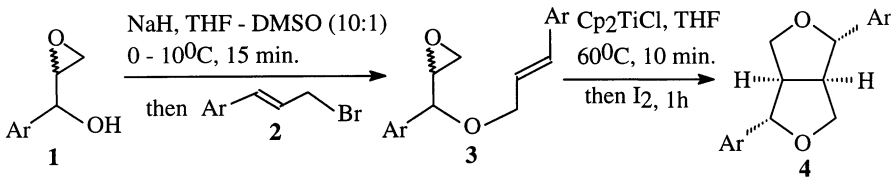
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01698-1



Scheme 1. Ar = 3,4-methylenedioxy phenyl

The crude epoxide **3** was treated with Cp_2TiCl in THF (prepared in situ from Cp_2TiCl_2 and Zn-dust in THF) at 60°C and the resulting solution was stirred with an excess of I_2 at that temperature for 1 h to furnish (±)-sesamin (**4**)[8] as the only product[9] in 93% yield; mp 123–124°C [lit. mp for (–)-sesamin[8] 123–124.5°C, for (±)-sesamin[4d] 129–130°C].

In conclusion, we have successfully achieved a short and stereoselective total synthesis of a furofuran lignan, sesamin, in good overall yield by radical cyclisation of an epoxide using a transition-metal radical source.

Acknowledgements

We gratefully acknowledge the financial support from the Department of Science and Technology, New Delhi. C.G. thanks CSIR, New Delhi for the award of a Junior Research Fellowship.

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