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Short and Stereoselective Synthesis of (±)-Dihydrosesamin by A Radical Cyclisation Reaction

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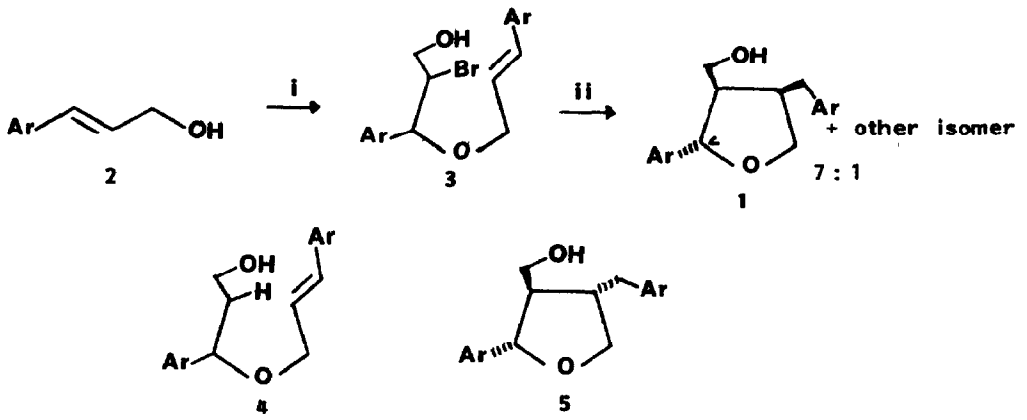
Abstract : A short and stereoselective synthesis of (±)-Dihydrosesamin 1 has been achieved from 2 by intramolecular radical cyclisation reaction in good overall yield.

Due to the widespread occurrence in nature and broad range of biological activities[1], lignans have attracted a considerable attention of organic chemists over the years. A major sub-group of lignans is comparised of tri- and tetrasubstituted tetrahydrofurans, and the synthesis[2] of this type of compound poses interesting and often unsolved problems of stereocontrol. Following our recent work on radical cyclisation reactions[3] towards the synthesis of 3,7-dioxabicyclo lignans[4], we turned our attention to furanolignans. In this paper, we report an exceptionally short and highly stereoselective total synthesis of (±)-Dihydrosesamin 1[5] involving a radical cyclisation reaction as the key step in good overall yield. Dihydrosesamin was isolated from Daphne tangutica Maxim. and also by the hydrogenation of natural sesamin[6] and has been used in the treatment of rheumatism, toothache etc.

Treatment of trans-cinnamyl alcohol 2 with N-bromosuccinimide (0.4 eq.) in CH_2Cl_2 afforded the bromohydrin 3[7] (Scheme-1) in 80% yield (based on recovered starting alcohol) as a viscous oil. Radical cyclisation of 3 with n-Bu_3SnH and AIBN (cat.) in refluxing benzene (0.02M) for 10h. furnished the 5-exo-trig cyclised product (80%) and the reduced product (4, 10%). The cyclised product was found to be a mixture of two isomers in a ratio of 7:1. The ratio was determined from two doublets for C-2 methine proton in ^1H NMR of the crude mixture at δ 4.79 (J=6.2 Hz) for the major isomer and at δ 4.58 (J=8 Hz) for the minor isomer. The major isomer was separated by exhaustive preparative TLC (20% ethylacetate in petroleum ether) in 60% yield as a resinous mass. The spectral data[8] of the major isomer were identical with those of (±)-Dihydrosesamin.[2a] The major isomer could not be obtained in pure form, always contaminated with the major isomer. By comparing the spectral data of the minor isomer-entriched isomeric mixture with those of the other possible isomers already reported,[2a] it could be predicted that the minor isomer might be 5.

In conclusion, a two step stereoselective synthesis of (±)-Dihydrosesamin has been accomplished by a radical cyclisation reaction, in best overall yield reported so far.



Ar = 3,4-methylenedioxyphenyl

Scheme-1. Reagents and conditions : I, NBS (0.4 eq), CH_2Cl_2, -15°C to room temp., 20h; ii, n-Bu_3SnH, AIBN (Cat.), benzene, reflux, 10h.

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7. Selected spectral data for 3 : IR(neat) : 3400(br), 2900, 1610, 1500, 1485, 1440, 1370, 1250, 1190 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 2.57 (brs, 1H), 3.81-4.18 (m, 5H), 4.52 (d, J=8 Hz, 1H), 5.93 (s, 2H), 5.97 (s, 2H), 5.98-6.11 (m, 1H), 6.38 (d, J=16 Hz, 1H), 6.63-6.90 (m, 6H).
8. Selected spectral data for 1 : IR(neat) : 3420(br), 2900, 1610, 1500, 1490, 1440, 1250, 1190, 1100 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.72 (brs, 1H), 2.28-2.42 (m, 1H), 2.52 (dd, J=13 and 10 Hz, 1H), 2.66-2.84 (m, 1H), 2.88 (dd, J=13 and 5 Hz, 1H), 3.70-4.0 (m, 3H), 4.13 (dd, J=8.5 and 7 Hz, 1H), 4.79 (d, J=6.2 Hz, 1H), 5.93 (s, 2H), 5.94 (s, 2H), 6.61-6.92 (m, 6H); ^{13}C NMR 33.0, 42.2, 52.4, 60.4, 72.7, 82.7, 100.7, 100.8, 106.1, 107.9, 108.1, 108.9, 119.0, 121.3, 134.1, 137.0, 146.0, 146.7, 147.6, 147.6.

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