Short and Stereoselective Total Synthesis of (±)-Dihydrosesamin and (±)-Acuminatin Methyl Ether by Radical Cyclisation of Epoxides Using a Transition-Metal Radical Source

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Abstract: Short, efficient and stereoselective synthesis of a furano lignans, (±)- Dihydrosesamin and (±)-Acuminatin Methyl Ether has been achieved in good overall yield through the radical cyclisation of epoxides using a Ti(III) reagent as the radical initiator.

Key words: stereoselective, radical cyclisation, epoxide, transition-metal

Lignans have attracted considerable interest over the years due to their widespread occurrence in nature[1] and broad range of biological activities[2]. A major subgroup of lignans is comprised of tri- and tetrasubstituted tetrahydrofurans, the synthesis of which poses interesting and often unsolved problems of stereocontrol. Dihydrosesamin is one of the representative biologically active furano lignans with two identical aromatic moieties, which was isolated from *Daphne tangutica Maxim.* and has been used in the treatment of rheumatism and toothache.[3a] Acuminatin methyl ether[1c] (also named as 3',4'-dimethoxy-3,4-methylenedioxy-7,9'-epoxylignan-9-ol)[3b] with two different aromatic groups was isolated from kernels of germinated seeds of *Virolamichelii.*[3b] Although only a few interesting syntheses providing these natural products have been reported,[4] intramolecular radical cyclisation of epoxides has

not yet been explored. We report here, short and stereoselective synthesis of (±)-dihydrosesamin (**4a**) and (±)-acuminatin methyl ether (**4b**) in good overall yield by intramolecular radical cyclisation of epoxides using a Ti(III) species as the radical source. The radical initiator Cp$_2$TiCl was generated[5] in situ from commercially available titanocene dichloride and zinc dust in tetrahydrofuran.

Thus, the known[6e] 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 78-80% 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, ½ H) and 3.19 (m, ½ H) in **3a** and at δ 3.13 (m, ½ H) and 3.20 (m, ½ H) in **3b**. Two isomers could not be separated by the usual chromatographic methods. The crude epoxide **3** was treated with Cp$_2$TiCl in THF (prepared in situ from Cp$_2$TiCl$_2$ and Zn-dust in THF) at room temperature for 1 h followed by acidic workup to furnish the cyclised product **4** together with a minor isomer in a ratio of 5:1 in 89–90% yield. Although, theoretically four isomers were possible, only two isomers were formed where the protons on C-2 and C-3 were
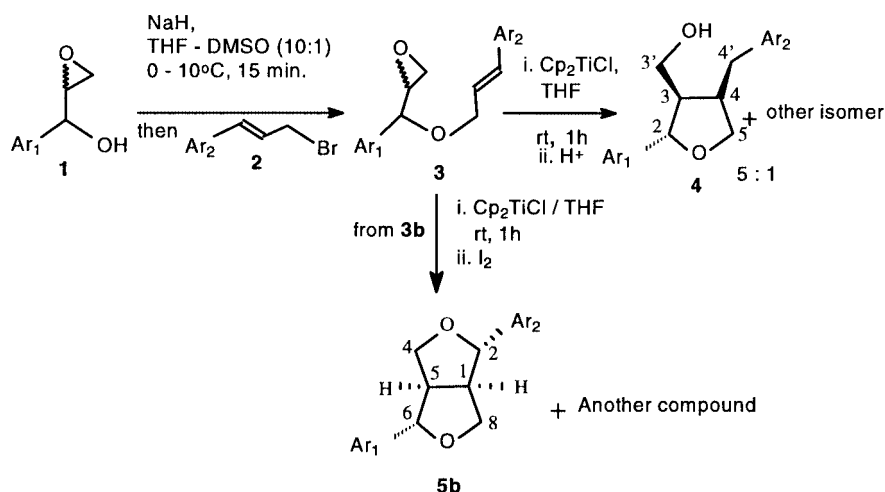
a, Ar$_1$ = Ar$_2$ = 3,4-Methylenedioxy phenyl
b, Ar$_1$ = 3,4-methylenedioxy phenyl
    Ar$_2$ = 3,4-dimethoxy phenyl

Scheme 1

trans. This can be rationalised from our earlier results[6] and by invoking well-known conformational effects in the intermediates[8] although the NOE experiment (no enhancement) on C_2-H and C_3-H remained inconclusive. The ratio of the two isomers was determined from the ^{1}H NMR spectrum of the crude cyclised product. The C-2 benzylic proton appeared as doublet at δ 4.79 ($J = 6.4$ Hz) for the major isomer and at δ 4.58 ($J = 8.0$ Hz) for the minor isomer in the crude product from **3a** and doublet at δ 4.79 ($J = 6.5$ Hz) for the major isomer and at δ 4.60 ($J = 7.9$ Hz) for the minor isomer in the crude product from **3b**. The major isomers **4a** and **4b** were separated by preparative TLC (20% ethyl acetate in petroleum ether) in 64% and 63% yields respectively. The spectral data[9] of the major isomer **4a** was identical with those of dihydrosesamin[3a,8] and the spectra data[9] of **4b** was identical with those of acuminatin methyl ether.[3b] The observed stereochemistries of the major products were further supported by performing the NOESY experiment on **4a** in CDCl$_3$. Since neither the minor isomer nor a derivative formed by reaction of its hydroxy group could be separated chromatographically in pure form, its stereochemistry remains uncertain. To our knowledge, this is the first report of the synthesis of acuminatin methyl ether (**4b**). The stereochemistry of the major product was finally confirmed by synthesising the bicyclic compound **5b** from **3b**. Thus, when **3b** was treated with Cp$_2$TiCl in THF followed by addition of iodine, a major compound **5b** along with a trace of another compound were furnished. The major compound **5b** was separated by preparative TLC in 88% yield and its spectral data[10] were identical with a natural compound, kobusin,[11] which is also named as methyl piperitol[12] or spinescin.[13]

In conclusion, we have successfully achieved short and stereoselective total synthesis of furano lignans containing both similar or different aromatic substituents, dihydrosesamin and acuminatin methyl ether in good overall yield by radical cyclisation of epoxides using a transition-metal radical source.

Acknowledgement

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(9) Spectral data of **4a**: ^{1}H NMR (300 MHz) δ 1.61 (br s, O*H*), 2.32-2.37 (m, 1H, C$_3$-*H*), 2.53 (dd, $J = 13.2$ and 10.3 Hz, 1H, C$_4'$-*H*), 2.63-2.76 (m, 1H, C$_4$-*H*), 2.87 (dd, $J = 13.2$ and 5.1 Hz, 1H, C$_4'$-*H*), 3.69-3.78 (m, 2H, C$_3'$-*H*), 3.89 (dd, $J = 10.6$ and 6.9 Hz, 1H, C$_5$-*H*), 4.04 (dd, $J = 8.4$ and 6.4 Hz, 1H, C$_5$-*H*), 4.79 (d, $J = 6.4$ Hz, 1H, C$_2$-*H*), 5.93 (s, 2H, OC*H*$_2$O), 5.94 (s, 2H, OC*H*$_2$O), 6.62-6.83 (m, 6H, Ar-*H*); ^{13}C NMR (75 MHz) δ 33.3, 42.3, 52.6, 60.9, 72.9, 82.9, 100.8, 100.9, 106.3, 108.1, 108.3, 108.9, 119.0, 121.4, 134.2, 137.1, 145.9, 146.9, 147.8, 147.8. Spectral data of **4b**: ^{1}H NMR (300 MHz) δ 1.56 (br s, O*H*), 2.33-2.42 (m, 1H, C$_3$-*H*), 2.56 (dd, $J = 13.2$ and 10.6 Hz, 1H, C$_4'$-*H*), 2.68-2.78 (m, 1H, C$_4$-*H*), 2.92 (dd, $J = 13.2$ and 5.0 Hz, 1H, C$_4'$-*H*), 3.72-3.95 (m, 3H, 2C$_3'$-*H* and C$_5$-*H*), 3.86 (s, 3H, OC*H*$_3$), 3.87 (s, 3H, OC*H*$_3$), 4.05 (dd, $J = 8.5$ and 6.5 Hz, 1H, C$_5$-*H*), 4.79 (d, $J = 6.5$ Hz, 1H, C$_2$-*H*), 5.94 (s, 2H, OC*H*$_2$O), 6.68-6.88 (m, 6H, Ar*H*); ^{13}C NMR (75 MHz) δ 33.1, 42.3, 52.7, 55.9, 60.9, 72.9, 82.8, 100.9, 106.3, 108.0, 111.3, 111.9, 119.1, 120.4, 132.9, 137.0, 146.9, 147.5, 147.8, 149.0.

(10) Spectral data of **5b**: ^{1}H NMR (300 MHz) δ 3.05-3.11 (m, 2H, C$_1$-*H* and C$_5$-*H*), 3.87-3.89 (m, 2H, C$_4$-*H* and C$_8$-*H*), 3.87 (s, 3H, OC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$), 4.21-4.27 (m, 2H, C$_4$-*H* and C$_8$-*H*), 4.73 (d, $J = 3.7$ Hz, 1H, benzylic proton), 4.74 (d, $J = 4.0$ Hz, 1H, benzylic proton), 5.94 (s, 2H, OC*H*$_2$O), 6.76-6.90 (m, 6H, Ar*H*); ^{13}C NMR (75 MHz) δ 54.5, 54.7, 56.3, 56.4, 72.1, 72.2, 86.1, 86.2, 101.4, 106.9, 108.5, 109.7, 111.6, 118.6, 119.7, 134.0, 135.5, 147.5, 148.3, 149.1, 149.6.

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