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# Stereoselective synthesis of trisubstituted tetrahydrofurans by radical cyclisation reaction using a hypophosphite salt. Application to the total synthesis of (±)-dihydrosesamin

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**Abstract**—The stereoselective synthesis of tetrahydrofurans has been achieved from bromoalkynes and bromoalkenes by intramolecular radical cyclisation using a hypophosphite salt. This radical cyclisation strategy has successfully been applied to the total synthesis of a naturally occurring bioactive furanolignan, dihydrosesamin. © 2002 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

The formation of carbon–carbon bonds by radical cyclisation has become an invaluable synthetic tool in organic chemistry especially in the total synthesis of complex natural products.[1] The majority of radical reactions are based on tributyltin hydride as the reducing agents, mainly tri-*n*-butyl tin hydride. However, organo-tin compounds are toxic and the separation of tin residues from the products can be laborious. Organo-silanes such as tris(trimethylsilyl)-silane[2] are good alternatives to tin hydrides. Although silanes are much less toxic, the development of a more ecofriendly and cost effective alternative to *n*-$Bu_3SnH$ would allow much more industrial applications of radical methodology. Hypophosphorus acid and its salts mainly, 1-ethylpiperidine hypophosphite (EPHP),[3] are effective radical reducing agents for organic halides. We report here a successful application of EPHP in the radical cyclisation of various haloalkenes and haloalkynes leading to the stereoselective synthesis of trisubstituted tetrahydrofurans, the important intermediates in the synthesis of natural products such as lignans.[4] This radical cyclisation methodology has also been applied to the total synthesis of a furanolignan, (±)-dihydrosesamin.

## 2. Results and discussion

The radical precursors **1a**–**6a**[4b] were prepared from the corresponding cinnamyl compounds by treatment with *N*-bromosuccinimide and propargyl alcohol at −15°C to room temperature under nitrogen atmosphere.[5] Compound **7a** was prepared from 3,4-dihydro-2*H*-pyran under identical reaction conditions. For the preparation of compound **8a**, allyl alcohol was used instead of propargyl alcohol. The bromo-ethers were found to be a mixture of *threo* and *erythro* isomers in a ratio of 1:1. The ratio was determined from the only distinguishable signals in $^1$H NMR spectra for the methylene protons adjacent to the triple bond as two double doublets at $\delta$ 3.87 ($J$=16 and 2.4 Hz) and at $\delta$ 4.12 ($J$=16 and 2.4 Hz) for **1a** and two double doublets at $\delta$ 9.93 ($J$=16.2 and 2.4 Hz) and at $\delta$ 4.15 ($J$=16.1 and 2.4 Hz) for **2a**. No such distinguishable signals were observed in $^1$H NMR spectra of **3a**–**8a**. Two isomers in **1a**–**8a** could not be separated by usual chromatographic methods and hence the crude mixture of isomers were used in the next step for the radical cyclisation. Treatment of the bromoalkyl propargyl ethers or bromoalkyl allyl ethers with EPHP in the presence of AIBN in refluxing benzene furnished the corresponding trisubstituted tetrahydrofuran derivatives (Scheme 1). Thus, a series of bromoalkyl allyl ethers and bromoalkyl prapargyl ethers **1a**–**8a** were subjected to radical cyclisation and the results are summarised in Table 1. The cyclisation of bromoalkyl propargyl ethers **1a**–**6a** was found to be highly stereoselective. The substituents at C-2 and C-3 in the products **1b**–**6b** are in *trans* orientation as expected from our earlier studies[4] and by invoking well-known conformational effects in the intermediates.[6] The cyclised compound **8b** was found to be a mixture of two compounds in a 5:1 ratio. The ratio of the two diastereomers was determined from the $^1$H NMR spectrum of the crude cyclised product. The only distinguishable signal of the benzylic methine proton appeared as a doublet at 5.19 (d, $J$=7.7 Hz) for the major isomer and at $\delta$ 5.05 ($J$=8.7 Hz) for the minor isomer. The

*Keywords*: stereoselective; radical cyclisation; hypophosphite salt; furanolignan.

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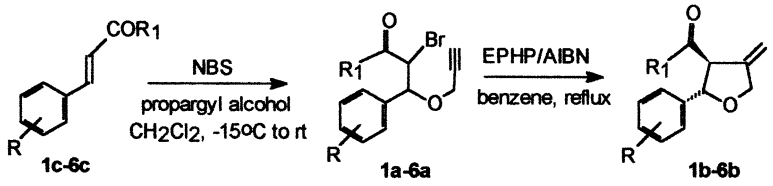
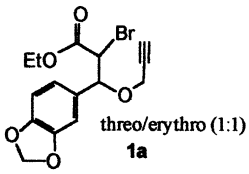
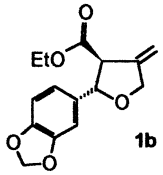
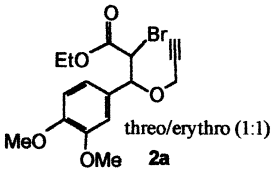
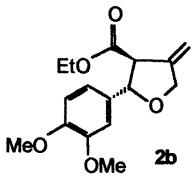
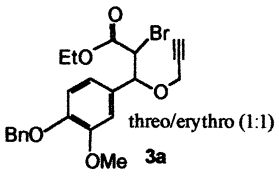
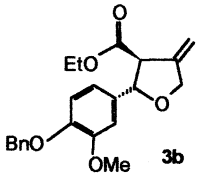
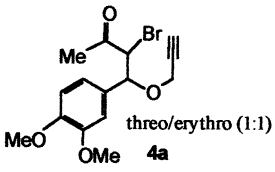
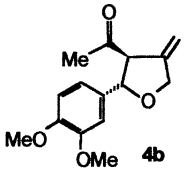
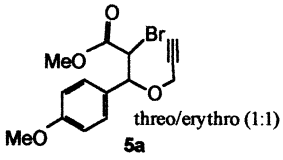
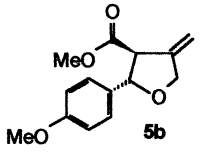
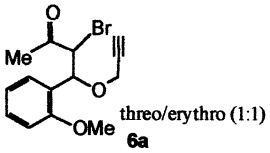
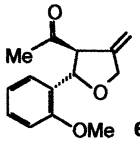
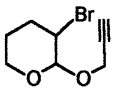
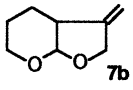
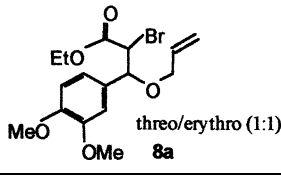
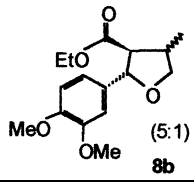
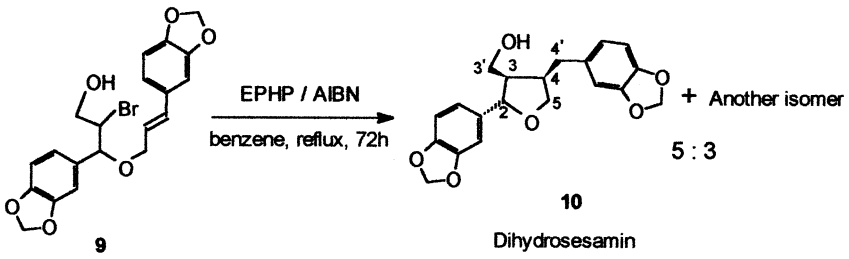



**Scheme 1.**

**Table 1.** Radical cyclisation of bromoalkynes and bromoalkenes with EPHP

| Entry | Substrate | Product | Reaction time (h) | Yield (%) |
|---|---|---|---|---|
| 1 |  threo/erythro (1:1) **1a** |  **1b** | 4 | 80 |
| 2 |  threo/erythro (1:1) **2a** |  **2b** | 5 | 78 |
| 3 |  threo/erythro (1:1) **3a** |  **3b** | 4 | 89 |
| 4 |  threo/erythro (1:1) **4a** |  **4b** | 3 | 75 |
| 5 |  threo/erythro (1:1) **5a** |  **5b** | 2.5 | 87 |
| 6 |  threo/erythro (1:1) **6a** |  **6b** | 3 | 81 |
| 7 |  **7a** |  **7b** | 3 | 63 |
| 8 |  threo/erythro (1:1) **8a** |  (5:1) **8b** | 3 | 84 |




**Scheme 2.**

two isomers could not be separated by usual chromatographic methods.

This radical cyclisation strategy was then applied to the stereoselective total synthesis of a naturally occurring bioactive furanolignan (±)-dihydrosesamin. Dihydrosesamin is one of the representative biologically active furanolignans with two identical aromatic moieties, which was isolated from *Daphne tangutica Maxim.* and has been used in the treatment of rheumatism and toothache.[7] Thus, the bromo-alcohol **9**[4d] on treatment with EPHP in the presence of AIBN in refluxing benzene for 72 h afforded a mixture of two diastereomers in a 5:3 ratio in 70% isolated yield (5.5% of starting material **9** recovered) (Scheme 2). The ratio of the two diastereomers was determined from the $^1$H NMR spectrum of the crude cyclised product. The C-2 benzylic proton appeared as doublet at $\delta$ 4.78 ($J$=6.5 Hz) for the major isomer and at $\delta$ 4.57 ($J$=8.0 Hz) for the minor isomer. The major diastereomer was separated by preparative TLC (20% ethyl acetate in petroleum ether) in 50% isolated yield and the spectral data of **10** was identical with those of dihydrosesamin.[4d,6] The minor isomer or derivatives formed by reaction of its hydroxy group, such as benzoate and acetate, could not be separated by preparative TLC in pure form, always contaminated with the major isomer. So the stereochemistry of the minor isomer remains uncertain.

Although the tin hydride-mediated cyclisations of **1a**, **2a**, **7a** and **9** have been previously reported[4a–d] to furnish the tetrahydrofuran derivatives **1b**, **2b**, **7b** and **10** respectively, the use of EPHP reagent offers certain advantages over tin hydride. The reagent is non-toxic in nature, no reduction products were isolated, the reaction time was reduced and above all the pure products were isolated in high yield without much effort. Although similar EPHP-mediated cyclisations have been reported recently,[3d,g,h] to our knowledge we have demonstrated here for the first time the EPHP-mediated cyclisation of bromoalkyl allyl esters to form tetrahydrofurans.

In conclusion, tetrahydrofuran derivatives have been prepared stereoselectively and in good yield by radical cyclisation using EPHP salt. This methodology was successfully applied to the synthesis of a natural furanolignan, dihydrosesamin.

## 3. Experimental

Melting points were determined in open capillary tubes and are uncorrected. $^1$H and $^{13}$C NMR were recorded in $CDCl_3$ on 300 and 75 MHz spectrometer (Bruker), respectively and IR were recorded using a Shimadzu FT IR-8300 instrument. Diethyl ether, tetrahydrofuran and benzene were dried over sodium and were freshly distilled from calcium hydride. Dichloromethane was freshly distilled from phosphorus pentoxide. Petroleum ether of boiling range 60–80°C and silica gel of 60–120 mesh was used for column chromatography.

### 3.1. Typical procedure for the preparation of the bromoalkyl propargyl/allyl ethers 1a–8a

**3.1.1. Preparation of ethyl-2-bromo-3-(3,4-methylenedioxyphenyl)-3-(prop-2-ynyloxy)propanoate 1a.** To a stirred solution of *N*-bromosuccinimide (3.0 g, 17 mmol) and propargyl alcohol (3.3 mL, 57 mmol) in dry $CH_2Cl_2$ (15 mL) at −15°C (ice–salt bath) was added dropwise a solution of cinnamic ester **1c** (2.5 g, 12 mmol) in dry $CH_2Cl_2$ (10 mL) under nitrogen for 30 min. The reaction mixture was stirred for 2 h at that temperature and left overnight at room temperature. It was then diluted with $CH_2Cl_2$ (30 mL), washed successively with 1N aqueous NaOH (20 mL) and brine (10 mL), then dried ($Na_2SO_4$). Solvent was removed under reduced pressure and the residue obtained was purified by column chromatography over silica gel (25% ethyl acetate/petroleum ether) to afford **1a**[4b] (3.2 g, 79%) as a viscous oil.

**3.1.2. Preparation of ethyl-2-bromo-3-(3,4-dimethoxyphenyl)-3-(prop-2-ynyloxy)propanoate 2a.** Compound **2a** (0.69 mg, 88%, colourless crystals, mp 81°C)[4b] was prepared from **2c** (0.5 g, 2.12 mmol) by following the same procedure as described for **1a**.

**3.1.3. Preparation of ethyl-2-bromo-3-(3-methoxy-4-benzyloxyphenyl)-3-(prop-2-ynyloxy)propanoate 3a.** Compound **3a** (0.57 g, 80%, viscous oil) was prepared from **3c** (0.5 g, 1.6 mmol) by following the same procedure as described for **1a**. [Found: C, 59.17; H, 5.18. $C_{22}H_{23}O_5Br$ requires C, 59.06; H, 5.19%]; $\nu_{max}$ (neat) 3286, 2981, 2937, 1739, 1595, 1514, 1463, 1454, 1421, 1371, 1261 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 1.24 (t, $J$=7.2 Hz, 3H), 2.34 (t, $J$=2.4 Hz, 1H), 3.76 (dd, $J$=15.6, 2.4 Hz, 1H), 4.01 (dd, $J$=15.6, 2.4 Hz, 1H), 3.79 (s, OC$H_3$), 4.17 (d, $J$=10.2 Hz, 1H), 4.17–4.25 (m, 2H), 4.78 (d, $J$=10.2 Hz, 1H), 5.05 (s, OC$H_2$Ph), 6.79–6.82 (m, 3H, Ar$H$), 7.20–7.36 (m, 5H, Ar$H$); $\delta_C$ (75 MHz, $CDCl_3$) 14.4, 48.0, 56.4, 56.7, 62.6, 71.2, 75.5, 79.1, 81.2, 111.0, 113.5, 121.9, 127.7, 128.3, 128.9, 137.3, 149.3, 150.1, 169.0.

**3.1.4. Preparation of 3-bromo-4-(3,4-dimethoxyphenyl)-4-(prop-2-ynyloxy)butan-2-one 4a.** Compound **4a** (0.41 g, 78%, viscous oil) was prepared from **4c** (0.30 g, 1.46 mmol) by following the same procedure as described for **1a**. [Found: C, 52.71; H, 5.05. $C_{15}H_{17}O_4Br$ requires C, 52.79; H, 5.02%]; $\nu_{max}$ (neat) 3286, 3003, 2937, 2906, 2837, 1720, 1595, 1517, 1464, 1421, 1359, 1313, 1232 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 2.43 (s, 3H), 2.48 (t, $J$=2.4 Hz, 1H), 3.83 (dd, $J$=16.2, 2.4 Hz, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 4.05 (dd, $J$=16.2, 2.4 Hz, 1H), 4.25 (d, $J$=10.1 Hz, 1H), 4.88 (d. $J$=10.1 Hz, 1H), 6.86–6.98 (m, 3H, Ar*H*); $\delta_C$ (25 MHz, $CDCl_3$) 25.9, 55.3, 56.3, 56.4, 75.8, 78.9, 80.7, 110.4, 111.1, 122.0, 128.5, 149.7, 150.1, 201.2.

**3.1.5. Preparation of methyl-2-bromo-3-(4-methoxyphenyl)-3-(prop-2-ynyloxy)propanoate 5a.** Compound **5a** (0.53 g, 79%, viscous oil) was prepared from **5c** (0.40 g, 2.08 mmol) by following the same procedure as described for **1a**. [Found: C, 51.06; H, 4.71. $C_{14}H_{15}O_4Br$ requires C, 51.38; H, 4.65%]; $\nu_{max}$ (neat) 3288, 3003, 2954, 2906, 2839, 1745, 1612, 1514, 1434, 1305, 1251, 1174 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 2.43 (t, $J$=2.4 Hz, 1H), 3.76 (s, 3H, OC*H*$_3$), 3.79 (s, 3H, OC*H*$_3$), 3.93 (q, $J$=5.6 Hz, 2H), 4.25 (d, $J$=9.9 Hz, 1H), 4.87 (d, $J$=9.9 Hz, 1H), 6.87 (d, $J$=8.1 Hz, 2H, Ar*H*), 7.27 (d, $J$=8.4 Hz, 2H Ar*H*). $\delta_C$ (75 MHz, $CDCl_3$) 47.7, 53.4, 55.6, 56.6, 75.6, 79.1, 80.8, 114.3, 128.2, 129.9, 160.6, 169.4.

**3.1.6. Preparation of 3-bromo-4-(2-methoxyphenyl)-4-(prop-2-ynyloxy)butan-2-one 6a.** Compound **6a** (0.43 g, 82%, viscous oil) was prepared from **6c** (0.30 g, 1.70 mmol) by following the same procedure as described for **1a**. [Found: C, 54.06; H, 4.99. $C_{14}H_{15}O_3Br$ requires C, 54.02; H, 4.86%]; $\nu_{max}$ (neat) 3290, 3078, 3004, 2941, 2839, 1720, 1600, 1492, 1463, 1438, 1357, 1286, 1247, 1211 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 2.41 (t, $J$=2.4 Hz, 1H), 2.42 (s, 3H), 3.86 (s, 3H, OC*H*$_3$), 3.93 (dd, $J$=15.7, 2.4 Hz, 1H), 4.08 (dd, $J$=15.7, 2.4 Hz, 1H), 4.53 (d, $J$=8.8 Hz, 1H), 5.41 (d, $J$=8.8 Hz, 1H), 6.90–7.05 (m, 2H, Ar*H*), 7.29–7.36 (m, 2H, Ar*H*). $\delta_C$ (75 MHz, $CDCl_3$) 26.3, 53.8, 55.5, 56.4, 74.9, 75.1, 78.9, 111.1, 120.8, 128.3, 130.1, 131.7, 158.2, 200.9.

**3.1.7. Preparation of 3-bromo-2-(prop-2-ynyloxy)tetrahydro-2*H*-pyran 7a.** Compound **7a** (1.04 g, 80%, viscous oil)[3d,e] was prepared from 3,4-dihydro-2*H*-pyran (0.5 g, 5.95 mmol) by following the same procedure as described for **1a**.

**3.1.8. Preparation of ethyl-3-(allyloxy)-2-bromopropanoate 8a.** Compound **8a** (0.38 g, 80%, viscous oil) was prepared from **2c** (0.30 g, 1.27 mmol) and allyl alcohol by following the same procedure as described for **1a**. [Found: C, 51.42; H, 5.69. $C_{16}H_{21}O_5Br$ requires C, 51.47; H, 5.67%]; $\nu_{max}$ (neat) 3078, 2981, 2935, 2837, 1743, 1595, 1515, 1465, 1421, 1371, 1336, 1261, 1240 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 1.36 (t, $J$=7.2 Hz, 3H), 3.76–3.82 (m, 1H), 3.87–3.98 (m, 1H), 3.89 (s, 6H, 2×OC*H*$_3$), 4.23 (d, $J$=10 Hz, 1H), 4.29–4.37 (m, 2H), 4.67 (d, $J$=10 Hz, 1H), 5.12–5.21 (m, 2H), 5.75–5.80 (m, 1H), 6.85–6.95 (m, 3H, Ar*H*). $^{13}C$ NMR $\delta$ 14.4, 48.3, 56.2, 56.4, 62.4, 70.8, 82.0, 110.5, 111.1, 117.8, 121.6, 129.9, 134.4, 149.5, 149.8, 169.3.

### 3.2. Typical procedure for the radical cyclisation of the bromoethers 1b–8b

**3.2.1. Preparation of ethyl (2*R*,3*R*)-2-(3,4-methylendioxyphenyl)-4-methylenetetrahydrofuran-3-carboxylate 1b.** A solution of the bromoether **1a** (150 mg, 0.42 mmol) and EPHP (380 mg, 2.11 mmol) in dry benzene (12 mL) was refluxed in the presence of AIBN (10 mg, added in two portions at an interval of 30 min) under nitrogen. After completion of the reaction (monitoring by TLC) the reaction mixture was allowed to come to room temperature and was diluted with ether (50 mL). The organic part was separated, washed successively with 2N HCl (10 mL), saturated aqueous $NaHCO_3$ (2×10 mL) and dried ($Na_2SO_4$). Solvent was removed under reduced pressure and the residue obtained was purified by column chromatography over silica gel (30% ethyl acetate/petroleum ether) to afford the cyclised product **1b**[4b] (93 mg, 80%) as a viscous oil.

**3.2.2. Preparation of ethyl (2*R*,3*R*)-2-(3,4-dimethoxyphenyl)-4-methylenetetrahydrofuran-3-carboxylate 2b.** Compound **2b** (0.09 g, 78%, viscous oil),[4b] was prepared from **2a** (0.15 g, 0.40 mmol) by the same procedure as described for **1b**.

**3.2.3. Preparation of ethyl (2*R*,3*R*)-2-(3-methoxy-4-benzyloxyphenyl)-4-methylenetetrahydro-furan-3-carboxylate 3b.** Compound **3b** (0.11 g, 89%, viscous oil) was prepared **3a** (0.15 g, 0.34 mmol) by the same procedure as described for **1b**. [Found: C, 71.41; H, 6.73. $C_{22}H_{24}O_5$ requires C, 71.72; H, 6.57%]; $\nu_{max}$ (neat) 3064, 3031, 2979, 2935, 2871, 1732, 1664, 1593, 1515, 1463, 1421, 1371, 1340, 1263, 1232 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 1.25 (t, $J$=7.4 Hz, 3H), 3.45–3.49 (m, 1H), 3.88 (s, 3H, OC*H*$_3$), 4.12–4.27 (m, 2H), 4.57 (q, $J$=13.0 Hz, two peaks further split, $J$=2.1 Hz, 2H), 4.47 (dd, $J$=13.0, 2.2 Hz, 1H), 4.62 (dd, $J$=13.0, 2.2 Hz, 1H), 5.09 (d, $J$=2.1 Hz, 1H), 5.14 (s, 2H, OC*H*$_2$Ph), 5.14–5.18 (m, 2H), 6.84 (s, 2H, Ar*H*), 6.96 (s, 1H, Ar*H*), 7.25–7.43 (m, 5H, Ar*H*). $\delta_C$ (75 MHz, $CDCl_3$) 14.6, 56.4, 57.4, 61.5, 71.4, 71.9, 83.8, 106.7, 110.0, 114.0, 119.0, 127.6, 128.3, 129.0, 133.3, 137.5, 147.0, 148.4, 150.1, 171.2.

**3.2.4. Preparation of 1-[(2*R*,3*R*)-2-(3,4-dimethoxyphenyl)-4-methylenetetrahydrofuran-3-yl] ethanone 4b.** Compound **4b** (46 mg, 75%, viscous oil) was prepared from **4a** (80 mg, 0.24 mmol) by the same procedure as described for **1b**. [Found: C, 68.48; H, 6.98. $C_{15}H_{18}O_4$ requires C, 68.68; H, 6.92%]; $\nu_{max}$ (neat) 2999, 2937, 2837, 1710, 1593, 1520, 1465, 1419, 1357, 1263, 1236 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 2.02 (s, 3H), 3.43–3.46 (m, 1H), 3.62 (s, 3H, OC*H*$_3$), 3.64 (s, 3H, OC*H*$_3$), 4.54 (q, $J$=13.2 Hz, two peaks further split, $J$=2.1 Hz, 2H), 4.86 (dd, $J$=16.8, 2.1 Hz, 2H), 4.97 (d, $J$=6.9 Hz, 1H), 6.54–6.65 (m, 3H, Ar*H*). $\delta_C$ (75 MHz, $CDCl_3$) 29.7, 55.9, 65.8, 72.0, 83.4, 107.6, 109.4, 111.4, 118.8, 133.2, 147.2, 149.3, 149.6, 205.9.

**3.2.5. Preparation of methyl (2*R*,3*R*)-2-(4-methoxyphenyl)-4-methylenetetrahydrofuran-3-carboxylate 5b.** Compound **5b** (0.1 g, 87%, viscous oil) was prepared from **5a** (0.15 g, 0.46 mmol) by the same procedure as described for **1b**. [Found: C, 67.24; H, 6.81. $C_{14}H_{16}O_4$

requires C, 67.73; H, 6.50%]; $\nu_{max}$ (neat) 2999, 2952, 2912, 1735, 1612, 1515, 1458, 1436, 1301, 1249 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 3.48–3.54 (m, 1H), 3.74 (s, 3H, OC$H_3$), 3.80 (s, 3H, OC$H_3$), 4.55 (q, $J$=12.0 Hz, two peaks further split, $J$=3.0 Hz, 2H), 5.10 (dd, $J$=18.0, 3.0 Hz, 2H) 5.17 (d, $J$=6.0 Hz, 1H), 6.84–6.92 (m, 2H, Ar$H$), 7.26–7.33 (m, 2H, Ar$H$). $\delta_C$ (75 MHz, $CDCl_3$) 52.7, 55.7, 57.4, 71.9, 83.7, 106.8, 114.3, 127.9, 132.2, 146.9, 159.9, 171.7.

**3.2.6. Preparation of 1-[(2*R*,3*R*)-2-(2-methoxyphenyl)-4-methylenetetrahydrofuran-3-yl]ethanone 6b.** Compound **6b** (0.09 g, 81%, viscous oil) was prepared **6a** (0.15 g, 0.48 mmol) by the same procedure as described for **1b**. [Found: C, 72.11; H, 6.99. $C_{14}H_{16}O_3$ requires C, 72.39; H, 6.94%]; $\nu_{max}$ (neat) 3078, 2999, 2939, 2839, 1712, 1664, 1602, 1490, 1461, 1438, 1357, 1244 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 2.23 (s, 3H), 3.43–3.46 (m, 1H), 3.69 (s, OC$H_3$), 4.53 (q, $J$=12.6 Hz, two peaks further split, $J$=2.1 Hz, 2H), 4.93 (dd, $J$=4.2, 2.1 Hz, 1H), 5.04 (dd, $J$=4.2, 2.1 Hz, 1H), 5.45 (d, $J$=6 Hz, 1H), 6.76–6.92 (m, 2H, Ar$H$), 7.15–7.21 (m, 1H, Ar$H$), 7.36–7.38 (m, 1H, Ar$H$). $\delta_C$ (75 MHz, $CDCl_3$) 28.0, 55.2, 65.3, 72.0, 79.4, 107.5, 110.4, 121.0, 125.8, 128.9, 130.0, 147.3, 156.0, 205.7.

**3.2.7. Preparation of 3-methylenehexahydro-4*H*-furo[2,3-*b*]pyran 7b.** Compound **7b** (0.08 g, 63%, viscous oil)[3d,e] was prepared from **7a** (0.2 g, 0.91 mmol) by the same procedure as described for **1b**.

**3.2.8. Preparation of ethyl (2*R*,3*R*)-2-(3,4-dimethoxyphenyl)-4-methyltetrahydrofuran-3-carboxylate 8b.** Compound **8b** (0.08 g, 84%, viscous oil) was prepared from **8a** (0.12 g, 0.32 mmol) by the same procedure as described for **1b**. [Found: C, 74.93; H, 7.52. $C_{16}H_{22}O_5$ requires C, 65.29; H, 7.53%]; $\nu_{max}$ (neat) 2968, 2937, 2875, 2837, 1728, 1593, 1517, 1463, 1421, 1377, 1350, 1263, 1236 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 1.07 (d, $J$=7 Hz, 3H), 1.27 (t, $J$=7.2 Hz, 3H), 2.71–2.81 (m, 1H) 3.00 (t, $J$=8.4 Hz, 1H), 3.65 (dd, $J$=8.1, 6.7 Hz, 1H), 3.86 (s, 3H, OC$H_3$), 3.88 (s, 3H, OC$H_3$), 4.11–4.23 (m, 2H), 4.27 (dd, $J$=8.1, 6.7 Hz, 1H), 5.05 (d, $J$=8.7 Hz, 1/5H), 5.19 (d, $J$=7.7 Hz, 4/5H), 6.81–6.90 (m, 3H, Ar$H$); $\delta_C$ (75 MHz, $CDCl_3$) 14.3, 14.7, 37.5, 56.2, 57.0, 60.8, 75.5, 82.1, 84.3, 109.4, 111.5, 118.6, 134.6, 148.9, 149.4, 172.3.

**3.2.9. Synthesis of dihydrosesamin (10).** The bromo-alcohol **9**[4d] on radical cyclisation reaction under identical reaction conditions as described for **1b** for 72 h afforded a mixture of two isomers in a ratio of 5:3 in 70% isolated yield (5.5% of starting material **9** recovered). The major isomer was separated by preparative TLC (20% ethyl acetate/petroleum ether) to afford **10**[4d,6] in 50% yield. $\delta_H$ (300 MHz, $CDCl_3$)) 1.60 (br s, O$H$), 2.32–2.38 (m, 1H $C_3$–$H$), 2.55 (dd, $J$=13.3 and 10.3 Hz, 1H, $C'_4$–$H$), 2.63–2.76 (m, 1H, $C_4$–$H$), 2.87 (dd, $J$=13.3 and 5.2 Hz, 1H, $C'_4$–$H$), 3.69–3.78 (m, 2H, $C'_3$–$H$), 3.89 (dd, $J$=10.5 and 6.8, 1H, $C_5$–$H$), 4.04 (dd, $J$=8.4 and 6.5 Hz, 1H, $C_5$–$H$), 4.78 (d, $J$=6.5 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$H$); $\delta_C$ (75 MHz, $CDCl_3$) 33.4, 42.4, 52.5, 60.8, 72.8, 82.8, 100.7, 100.9, 106.4, 108.1, 108.3, 108.8, 119.1, 121.5, 134.3, 137.0, 145.8, 146.7, 147.8, 147.8.

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