Radical cyclisation route to furanolignans: short and stereoselective synthesis of (±)-dihydrosesamin and (±)-lariciresinol

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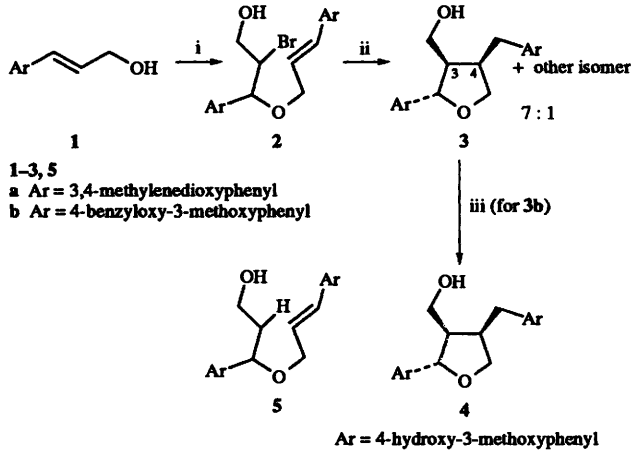
The furanolignans, (±)-dihydrosesamin **3a** and (±)-lariciresinol **4** have been synthesised by a very short and stereoselective route in good overall yield using a radical cyclisation as the key step. The radical precursor **2**, prepared from the easily accessible cinammyl alcohol **1**, on radical cyclisation in the presence of Bu_3SnH and a catalytic amount of AIBN, furnished **3** along with a second isomer in a ratio of 7:1. The product **3a** was identical with natural dihydrosesamin. The lariciresinol dibenzyl ether **3b**, on controlled catalytic hydrogenation, afforded (±)-lariciresinol **4** in excellent yield.

Due to their widespread occurrence in nature and broad range of biological activities,[1] lignans have attracted considerable attention from organic chemists. A major subgroup of lignans is comprised of tri- and tetra-substituted tetrahydrofurans, the synthesis of which pose interesting and often unsolved problems of stereocontrol. Very few synthetic strategies for the furanolignans have been reported[2] and the radical cyclisation is still unexplored. Carbon–carbon bond formations by radical reactions have been well documented in the literature,[3] especially for the construction of complex natural products.

Our recent work on an intramolecular radical cyclisation in connection with the synthesis of 3,7-dioxabicyclo lignans[4] led us to undertake the present work. We now report in detail[5] an exceptionally short and highly stereoselective synthesis of (±)-dihydrosesamin **3a**[6] and (±)-lariciresinol **4**[7] in good overall yield, involving a tin hydride-mediated intramolecular radical cyclisation as the key step. Dihydrosesamin was isolated from *Daphane tangutica Maxim.* and has been used in the treatment of rheumatism and toothache.[6] Lariciresinol was isolated from *Dirca Occidentalis* and *Wikstroemia elliptica* and is significantly active against the P-388 lymphocytic leukaemia.[7]

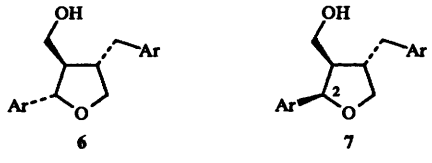
Results and discussion

Treatment of an excess of the readily available cinnamyl alcohol **1** with NBS (*N*-bromosuccinimide, 0.4 equiv.) in methylene dichloride afforded the bromohydrin **2** (Scheme 1) in excellent yield as a viscous oil. The C-2 benzylic proton appeared as a doublet in the ^1H NMR spectrum at δ 4.52 (J 8) for **2a** and at δ 4.62 (J 8) for **2b**. Although it was not possible to predict from the ^1H NMR spectrum whether **2** was a pure isomer or a mixture of *threo* and *erythro* compounds this was not important since, as a result of loss stereochemistry about the radical centre during cyclisation, it is not relevant to the stereochemical properties of the product. Radical cyclisation of the crude bromo alcohol **2a** with Bu_3SnH and AIBN (azoisobutyronitrile, cat.) in refluxing benzene (0.02 mol dm^{-3}) gave the 5-*exo-trig* cyclised product **3a** together with a second isomer (total 80%; in a ratio of 7:1), and the reduced product **5a** (10%). The ratio of the two isomers was determined from the ^1H NMR spectrum of the crude reaction mixture. The C-2 benzylic proton appeared as a doublet at δ 4.79 (J 6.2) for the major isomer and at δ 4.58 (J 8) for the minor isomer. The major isomer was separated by preparative TLC (20% ethyl acetate in light petroleum) in 60% yield. The spectral data of the major isomer **3a** were identical with those of (±)-dihydrosesamin.[2a] Since neither the minor isomer nor a derivative formed by reaction of its hydroxy group could be separated chromatographically in pure form its stereochemistry



Scheme 1 *Reagents and conditions:* i, NBS (0.4 equiv.), CH_2Cl_2, −15 °C–room temp., 20 h; ii, Bu_3SnH, AIBN (cat.), benzene, reflux, 10 h; iii, H_2, Pd–C (10%), EtOH, 1 h

remains uncertain. Comparison of the ^1H NMR spectrum of **3a** with that of the mixture revealed three distinct signals for the minor isomer at δ 1.93 (m, 4-H_2), 3.61 (d, J 5.5, 5-H_2) and 4.58 (d, J 8.0, 2-H). These are in agreement with those of the isomers **6** or **7**, synthesised by Whiting and Stevens,[2a] who reported



that it was not possible to deduce with complete confidence which isomer had which stereochemistry.

Similarly, the bromo alcohol **2b** under identical radical reaction conditions furnished an isomeric mixture of 5-*exo-trig* cyclised products (90%; 7:1) as a crystalline solid but no reduced product **5b**. Although the major isomer **3b** was separated by fractional crystallisation (ethyl acetate–light petroleum) in 65% yield, mp 118 °C, this was not so for the minor isomer. The alcohol **3b**, on catalytic hydrogenation over 10% palladium on charcoal in ethanol afforded finally (±)-lariciresinol **4**[7] as a resin in 85% yield.

The reasons for the high diastereoselectivity in the described radical cyclisations may be attributed to the models proposed by Beckwith,[8] and Houk and Spellmeyer.[9]

Experimental

The compounds described are all racemates. Mps were determined in open capillary tubes and are uncorrected. IR spectra of solids (KBr) and liquids (neat) were recorded on a Perkin-Elmer PE-298 instrument. ^{1}H NMR spectra were recorded at 200 MHz on a Varian Associates XL-200 spectrometer with $SiMe_4$ as internal standard; J values are given in Hz. ^{13}C NMR spectra were recorded at 25 MHz on a JEOL FX-100 spectrometer. The organic extracts were dried over anhydrous Na_2SO_4. Column chromatography was performed on silica gel (60–120 mesh). Preparative TLC was performed using Merck pre-coated silica 60 F 254 plates (0.2 mm). Methylene dichloride was distilled from phosphorus pentoxide. Elemental analyses were performed by Mr P. P. Bhattacharya and Mr S. Sarkar of this laboratory. Light petroleum of boiling range 60–80 °C was used for chromatography.

General procedure for the preparation of the bromo alcohols 2a, b

2-Bromo-3-(3,4-methylenedioxyphenyl)-3-[3-(3,4-methylenedioxyphenyl)prop-2-enyloxy]propan-1-ol 2a. To a magnetically stirred solution of the cinnamyl alcohol **1a** (1 g, 5.6 mmol) in dry CH_2Cl_2 (10 cm^3) at −15 °C (ice–salt bath) was added dropwise a solution of NBS (392 mg, 2.2 mmol) in dry CH_2Cl_2 (10 cm^3) under a nitrogen atmosphere during 1 h. The reaction mixture was stirred at −15 °C for a further 2 h and at room temperature for 30 h. It was then diluted with CH_2Cl_2 (50 cm^3), washed with 1 mol dm^{-3} aqueous NaOH (3 × 15 cm^3), brine (2 × 15 cm^3) and finally dried. The solvent was removed under reduced pressure and the residue was purified by flash chromatography over silica gel (240–400 mesh) (30% ethyl acetate in light petroleum) to furnish the pure title compound **2a** (465 mg, 80% based on unchanged starting alcohol **1a**) as a faint yellow viscous oil (Found: C, 55.4; H, 4.5. $C_{20}H_{19}O_6Br$ requires C, 55.18; H, 4.39%); ν_{max}/cm^{-1} 3440, 2900, 1610 and 1500; δ_H(200 MHz; $CDCl_3$) 2.57 (1 H, br s, OH), 3.81–4.18 (5 H, m, 2 × OCH_2 and CHBr), 4.52 (1 H, d, J 8, OC*H*Ar), 5.93 (2 H, s, OCH_2O), 5.97 (2 H, s, OCH_2O), 5.98–6.11 (1 H, m, =CH), 6.38 (1 H, d, J 16, =C*H*Ar) and 6.63–6.90 (6 H, m, ArH).

2-Bromo-3-(4-benzyloxy-3-methoxyphenyl)-3-[3-(4-benzyloxy-3-methoxyphenyl)prop-2-enyloxy]propan-1-ol 2b. A solution of the cinnamyl alcohol **1b** (2.0 g, 7.4 mmol) in CH_2Cl_2 (25 cm^3) was treated with NBS (527 mg, 2.96 mmol) according to the general procedure to afford the bromo alcohol **2b** (715 mg, 78% based on unchanged starting alcohol **1b**) as a viscous oil (Found: C, 65.7; H, 5.7. $C_{34}H_{35}O_6Br$ requires C, 65.91; H, 5.66%); ν_{max}/cm^{-1} 3500, 2940, 1600 and 1515; δ_H(200 MHz; $CDCl_3$) 2.72 (1 H, br s, OH), 3.87 (6 H, s, 2 × OCH_3), 3.75–4.30 (5 H, m, CHBr, 2 × OCH_2) 4.62 (1 H, d, J 8, OC*H*Ar), 5.15 (4 H, s, 2 × OCH_2Ph), 6.0–6.20 (1 H, m, =CH), 6.42 (1 H, d, J 16, =C*H*Ar), 6.75–7.0 (6 H, m, ArH) and 7.22–7.50 (10 H, m, PhH).

General procedure for the preparation of the tetrahydrofurans 3a, b

(2*S,3*R**,4*R**)-3-Hydroxymethyl-2-(3,4-methylenedioxyphenyl)-4-[(3,4-methylenedioxyphenyl)methyl]tetrahydrofuran 3a (dihydrosesamin).** A mixture of the bromohydrin **2a** (500 mg, 1.14 mmol), Bu_3SnH (0.4 cm^3, 1.37 mmol) and AIBN (10 mg) in dry benzene (70 cm^3) was refluxed on a preheated oil bath (90–100 °C) under a nitrogen atmosphere for 10 h. Volatiles were removed under reduced pressure and the residue was chromatographed over silica gel (35% ethyl acetate in light petroleum) to afford a mixture of two isomers (327 mg, total 80%) in a ratio of 7:1. The major isomer **3a** was separated by preparative TLC (20% ethyl acetate in light petroleum) as a resinous mass (240 mg, 60%), ν_{max}/cm^{-1} 3420, 2900, 1610 and 1500; δ_H(200 MHz; $CDCl_3$) 1.72 (1 H, br s, OH), 2.28–2.42 (1 H, m, 3-H), 2.52 (1 H, dd, J 13 and 10, C*H*HAr), 2.66–2.84 (1 H, m, 4-H), 2.88 (1 H, dd, J 13 and 5, CH*H*Ar), 3.70–4.0 (3 H, m, CH_2OH and 5-H), 4.13 (1 H, dd, J 8.5 and 7, 5-H), 4.79 (1 H, d, J 6.2, 2-H), 5.93 (2 H, s, OCH_2O), 5.94 (2 H, s, OCH_2O) and 6.61–6.92 (6 H, m, ArH); δ_C(25 MHz; $CDCl_3$) 33.0 (t), 42.2 (d), 52.4 (d), 60.4 (t), 72.7 (t), 82.7 (d), 100.7 (t), 100.8 (t), 106.1 (d), 107.9 (d), 108.1 (d), 108.9 (d), 119.0 (d), 121.3 (d), 134.1 (s), 137.0 (s), 146.0 (s), 146.7 (s), 147.6 (s) and 147.6 (s); m/z 356 (M$^+$, 40%), 165 (68), 149 (40) and 135 (100).

(2*S,3*R**,4*R**)-3-Hydroxymethyl-2-(4-benzyloxy-3-methoxyphenyl)-4-[(4-benzyloxy-3-methoxyphenyl)methyl]-tetrahydrofuran 3b.** Following the general procedure a solution of the bromohydrin **2b** (700 mg, 1.13 mmol), Bu_3SnH (3.7 cm^3, 1.35 mmol) and AIBN (10 mg) in benzene (68 cm^3) was refluxed to furnish a mixture of two isomers in a ratio of 7:1 as a solid (550 mg, total 90%). The major isomer **3b** (396 mg, 65%) was separated by fractional crystallisation (ethyl acetate–light petroleum) as a crystalline solid, mp 118 °C (Found: C, 75.7; H, 6.8. $C_{34}H_{36}O_6$ requires C, 75.53; H, 6.71%); ν_{max}/cm^{-1} 3440, 2930, 1590, 1510 and 1460; δ_H(200 MHz; $CDCl_3$) 2.35–2.55 (1 H, m, 3-H), 2.60 (1 H, d, J 13, one peak further split, C*H*HAr), 2.62–2.85 (1 H, m, 4-H), 2.94 (1 H, dd, J 13 and 5, CH*H*Ar), 3.70–3.85 (2 H, m, CH_2OH), 3.85–3.98 (1 H, m, 5-H), 3.88 (3 H, s, OCH_3), 3.90 (3 H, s, OCH_3), 4.05 (1 H, dd, J 8 and 7, 5-H), 4.80 (1 H, d, J 6.6, 2-H), 5.15 (2 H, s, CH_2Ph), 5.18 (2 H, s, CH_2Ph), 6.15–6.95 (6 H, m, ArH) and 7.30–7.50 (10 H, m, PhH).

(2*S,3*R**,4*R**)-3-Hydroxymethyl-2-(4-hydroxy-3-methoxyphenyl)-4-[(4-hydroxy-3-methoxyphenyl)methyl]-tetrahydrofuran 4 (lariciresinol).**
A solution of the tetrahydrofuran **3b** (260 mg, 0.48 mmol) in dry ethanol (25 cm^3) was stirred in the presence of 10% Pd–C and hydrogen under normal pressure at room temperature for 1 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (65% ethyl acetate in light petroleum) to afford lariciresinol **4** (147 mg, 85%) as a resinous mass, ν_{max}/cm^{-1} 3400, 1610, 1515, 1470, 1450 and 1430; δ_H(200 MHz; $CDCl_3$) 1.70 (1 H, br s, OH), 2.25–2.42 (1 H, m, 3-H), 2.51 (1 H, d, J 13, one peak further split, C*H*HAr), 2.55–2.75 (1 H, m, 4-H), 2.88 (1 H, dd, J 13 and 5, CH*H*Ar), 3.60–3.75 (2 H, m, CH_2OH), 3.83–3.89 (1 H, m, 5-H), 3.80 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 3.98 (1 H, dd, J 8.6 and 6.4, 5-H), 4.72 (1 H, d, J 6.6, 2-H), 5.52 (1 H, br s, ArO*H*), 5.60 (1 H, br s, ArO*H*) and 6.60–6.83 (6 H, m, ArH); δ_C(25 MHz; $CDCl_3$) 33.1 (t), 42.3 (d), 52.4 (d), 55.8 (q), 55.8 (q), 60.6 (t), 72.7 (t), 82.7 (d), 108.5 (d), 11.4 (d), 114.3 (d), 114.5 (d), 118.6 (d), 121.1 (d), 132.2 (s), 134.7 (s), 143.9 (s), 145.0 (s), 146.7 (s) and 146.7 (s); m/z 360 (M$^+$, 63%), 236 (20), 194 (30), 151 (43) and 137 (100).

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References

1 (*a*) D. A. Whiting, *Nat. Prod. Rep.*, 1985, **2**, 191; 1987, **4**, 499; 1990, **7**, 349; (*b*) R. S. Ward, *Nat. Prod. Rep.*, 1993, **10**, 1; (*c*) G. M. Massanet, E. Pando, F. Rodriguez-Luis and E. Zubia, *Fitoterapia*, 1989, **LX**, 3.
2 (*a*) D. R. Stevens and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1990, 425; 1992, 633; (*b*) J. Mitra and A. K. Mitra, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1285.
3 (*a*) B. Giese, *Radicals in Organic Synthesis, Formation of Carbon–*

Carbon bonds, Pergamon Press, Oxford, 1986; (*b*) M. Ramaiah, *Tetrahedron*, 1987, 3541; (*c*) A. Srikrishna, *Current Science*, 1987, **56**, 392; (*d*) D. P. Curran, *Synthesis*, 1988, 417 and 489; (*e*) W. B. Motherwell and D. Crich, *Free Radical Chain Reactions in Organic Synthesis*, Academic Press, Orlando, 1991.
4 (*a*) S. Adhikari and S. C. Roy, *Tetrahedron Lett.*, 1992, **33**, 6025; (*b*) S. C. Roy and S. Adhikari, *Tetrahedron*, 1993, **49**, 8415.
5 A portion of this work appeared in a preliminary communication: G. Maiti, S. Adhikari and S. C. Roy, *Tetrahedron Lett.*, 1994, **35**, 3985.
6 Z. Lin-Zen, O. Seligmann, H. Lotter and H. Wagner, *Phytochemistry*, 1983, **22**, 265.
7 C.-Y. Duh, C. H. Phoebe, Jr., J. M. Pezzuto, A. D. Kinghorn and N. R. Farnsworth, *J. Nat. Prod.*, 1986, 706.
8 A. L. J. Beckwith, C. J. Easton, T. Lawrence and A. K. Serelis, *Aust. J. Chem.*, 1983, **36**, 545.
9 D. C. Spellmeyer and K. N. Houk, *J. Org. Chem.*, 1987, **52**, 959.

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