Enantio-controlled Route to the Furofuran Lignans: the Total Synthesis of (−)-Sesamolin, (−)-Sesamin, and (−)-Acuminatolide

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The first enantio-controlled route to the furofuran lignans, (−)-sesamolin, (−)-sesamin, and (−)-acuminatolide, has been developed starting from diethyl L-tartrate by employing an intramolecular hetero-Diels–Alder reaction as the key step.

The furofuran lignans are one of the largest groups of lignans[1] whose members show a variety of biological activities.[2] Although interesting syntheses providing these natural products have been developed,[1,3,4] an enantio-controlled route has not hitherto been reported. We present here a novel enantio-controlled route to the furofuran type lignans starting from diethyl L-tartrate (**1**) by employing a highly diastereoselective intramolecular hetero-Diels–Alder reaction[5] as the key step.

The diol (**3**),† prepared from (**1**) and 3,4-methylenedioxycinnamaldehyde *via* sodium borohydride reduction of the acetal (**2**), was treated with di-isobutylaluminium hydride[6] to afford the triol (**4**) which was selectively converted into the 1,2-acetonide (**5**) in 50% overall yield. On sequential *O*-benzylation, deacetalization, and periodate cleavage, (**5**) gave the aldehyde (**8**) in nearly quantitative overall yield. Treatment of (**8**) with Meldrum's acid (2,2,-dimethyl-4,6-dioxo-1,3-dioxane) in methylene chloride in the presence of 4-*N*,*N*-dimethylaminopyridine at 0 °C to room temperature led to spontaneous condensation and intramolecular hetero-Diels–Alder reaction to give the single adduct (**10**), which was refluxed with magnesium chloride in wet dimethylacetamide[7] to afford the δ-lactone (**11**) with a *cis*-ring junction‡ in 58%

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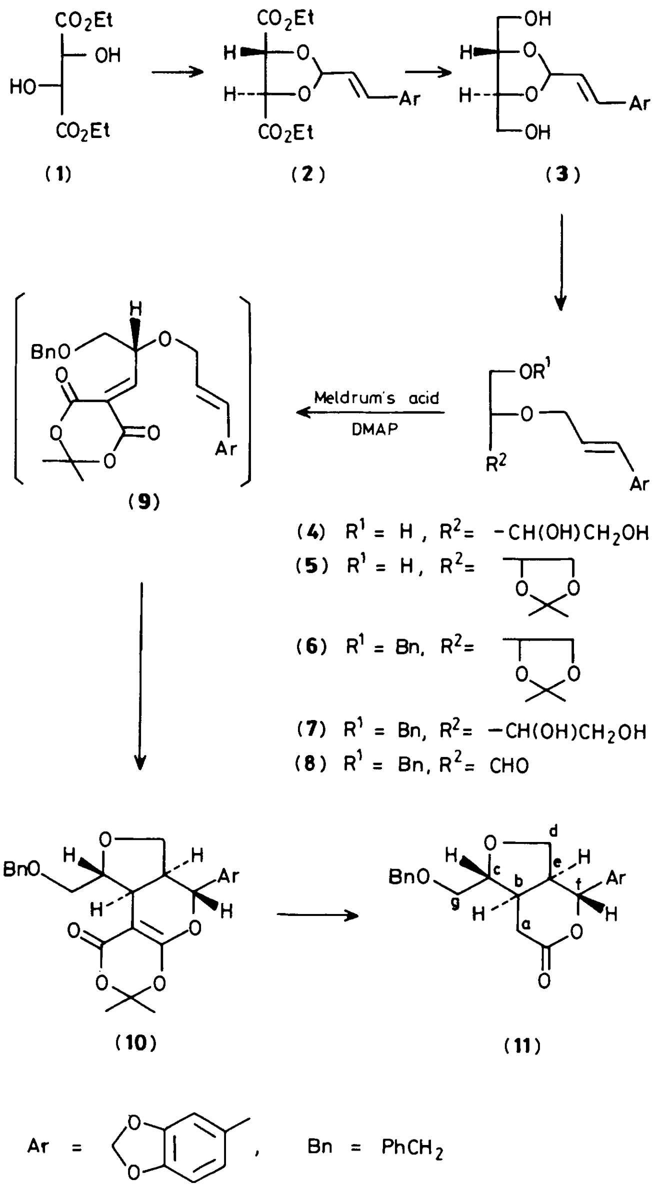
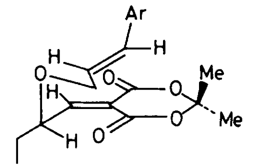
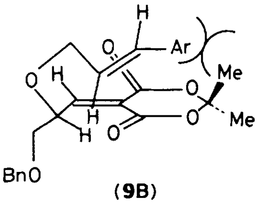
† All new isolated compounds exhibited satisfactory analytical (combustion and/or high resolution mass spectrum) and spectral (i.r., ^{1}H n.m.r., and mass) data.

‡ The lactone moiety of (**11**) is presumed to possess a boat-like conformation with the aromatic group in bowsprit position, this is supported by *X*-ray analysis of a related compound (**11**; Ar = Me): ^{1}H n.m.r. spectrum ($CDCl_3$, 500 MHz) of (**11**) δ 2.51 [dd, *J* 14.6 and 9.8, 1H, $H_a(\beta)$] 2.61 (m, 1H, H_b), 2.75 [dd, *J* 14.6 and 6.1, 1 H, $H_a(\alpha)$], 2.83 (dddd, *J* 11.0, 10.7, 7.9, and 5.2, 1H, H_e), 3.52 [dd, *J* 9.8 and 5.2, 1H, $H_d(\alpha)$], 3.58 (m, 2H, H_g), 3.88 (ddd, *J* 6.1, 5.5, and 4.9, 1H, H_c), 3.93 [DD, *J* 9.8 and 7.9, 1 H, $H_d(\beta)$], 4.57 (s, 2H, $PhCH_2$), 4.96 (d, *J* 11.0, 1H, H_f), 5.90 (s, 2H, methylenedioxy protons), 6.79 (s, 2H, Ar*H*), 6.86 (s, 1H, Ar*H*), 7.28—7.38 (m, 5H, Phenyl *H*).

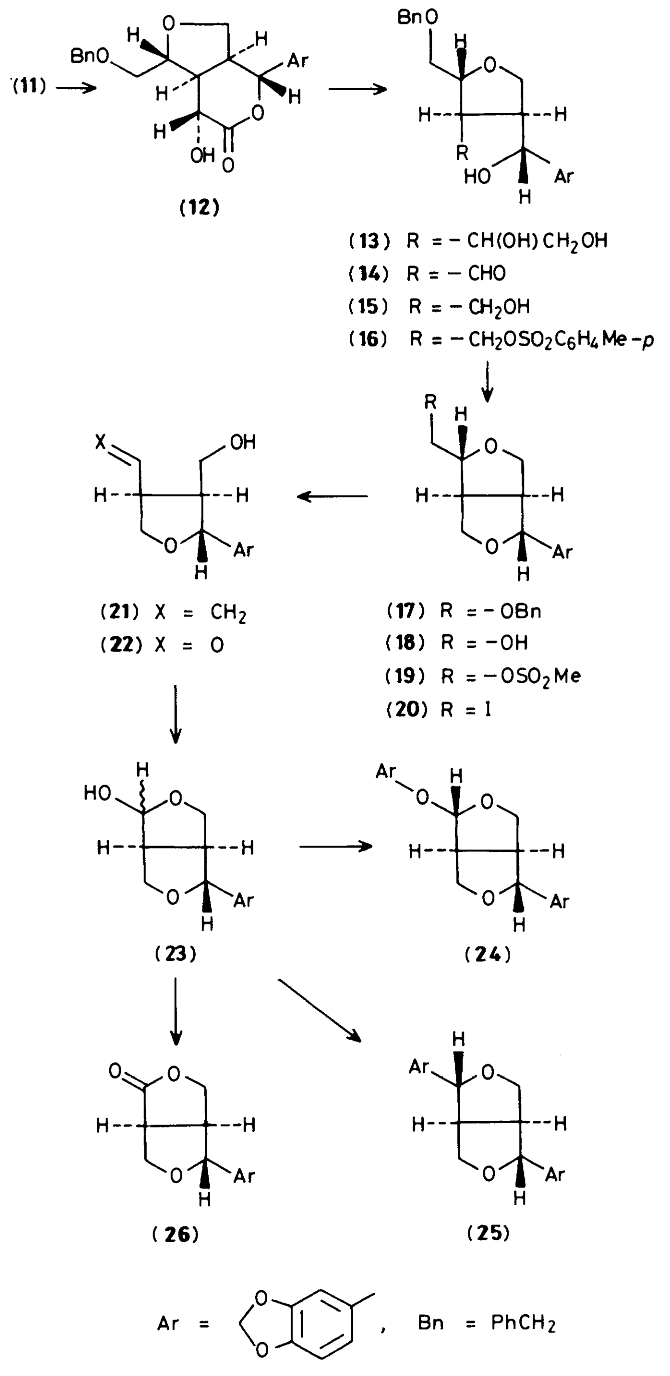


Scheme 1


(9A)


(9B)

overall yield (Scheme 1). The observed highly diastereoselective formation of the adduct (**10**) with a *cis*-ring junction may be attributable to the preferential intervention of the *endo*-active conformer (**9A**) with the bulky benzyloxy group disposed outwards, rather than the *exo*-conformer (**9B**), owing to the considerable non-bonded interaction in (**9B**) between the aryl group on the dienophile and the heterodiene moiety.[7b]



Scheme 2

Hydroxylation of (**11**) with oxidodiperoxy(pyridine)(hexamethylphosphoric triamide)molybdenum (MoOPH)[8,9] in the presence of lithium hexamethyldisilazide afforded the single product (**12**) which was sequentially reduced ($NaBH_4$), oxidized ($NaIO_4$), and reduced ($NaBH_4$) in the same flask to give the diol (**15**) in 53% overall yield. Treatment of (**15**) with toluene-*p*-sulphonyl chloride (1 equiv.) in the presence of n-butyl-lithium (2 equiv.)[10] generated the tetrahydrofuran (**17**) stereoselectively in 91% yield in one stage. On sequential debenzylation [H_2, $Pd(OH)_2$], mesylation (methanesulphonyl chloride, triethylamine), substitution (NaI, methyl ethyl ketone), and reductive ring opening (Zn, MeOH, room temperature), (**17**) furnished the alkene (**21**) in 77% overall yield. Under Lemiuex–Johnson conditions,[11] (**21**) gave samin[12,13] (**23**), $[\alpha]_D^{24}$ −88.18° (*c* 1.1, $CHCl_3$) {lit.[13] for (+)-enantiomer, $[\alpha]_D$ +81.4° (*c* 0.5, $CHCl_3$)}, in 97% yield, *via* (**22**), the enantiomer of which was obtained from naturally occurring (+)-sesamolin[12,13] (**24**) as a degradation product.

Treatment of (**23**) with sesamol (3,4-methylenedioxyphenol) in boiling benzene in the presence of pyridinium toluene-*p*-sulphonate (PPTS) furnished (−)-sesamolin[12] (**24**), m.p. 94.5—95 °C, $[\alpha]_D^{23}$ −216.44° (*c* 0.61, $CHCl_3$) {lit.[12] for (+)-enantiomer, m.p. 93—94 °C, $[\alpha]_D$ +212° ($CHCl_3$)}, in 48% yield. Moreover, (**23**), on treatment with an excess of 3,4-methylenedioxyphenylmagnesium bromide, followed by treatment of the resulting crude diol with PPTS in refluxing methylene chloride, furnished (−)-sesamin[14] (**25**), m.p. 119.5—121.0 °C, $[\alpha]_D^{22}$ −64.51° (*c* 1.05, $CHCl_3$) {lit.[14] m.p. 123—124.5 °C, $[\alpha]_D^{20}$ −64.5° (*c* 1.08, $CHCl_3$)}, in 54% yield, which was isolated from Hydrocotyle plants. On the other hand, oxidation of (**23**) with Fetizon's reagent[15] gave acuminatolide[16] (**26**), m.p. 118—119 °C, $[\alpha]_D^{25}$ −103.82° (*c* 0.31, $CHCl_3$)§ {lit.[16] m.p. 118 °C, $[\alpha]_D^{24}$ −37° (*c* 0.11, $CHCl_3$)}, in 87% yield, which was recently isolated from Australian Helichrysum species. Its absolute structure was not determined previously, but we assume that it is as depicted in Scheme 2.

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§ Although there is a considerable difference between the optical rotation values for the synthetic and natural products, their ^1H n.m.r. spectra are virtually identical.