Approaches to synthetic neolignans

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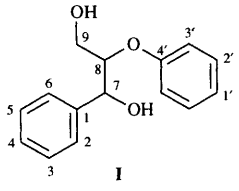
COMMUNICATION

Several synthetic approaches to neolignans with a C(8)–O–C(4′) linkage are described. Although direct introduction of a chiral aryloxy ether bond at the 8-position of protected phenylpropane derivatives was not successful, an efficient method for the synthesis of a chiral aryloxy ether bond has been developed, starting from a tartrate derivative.

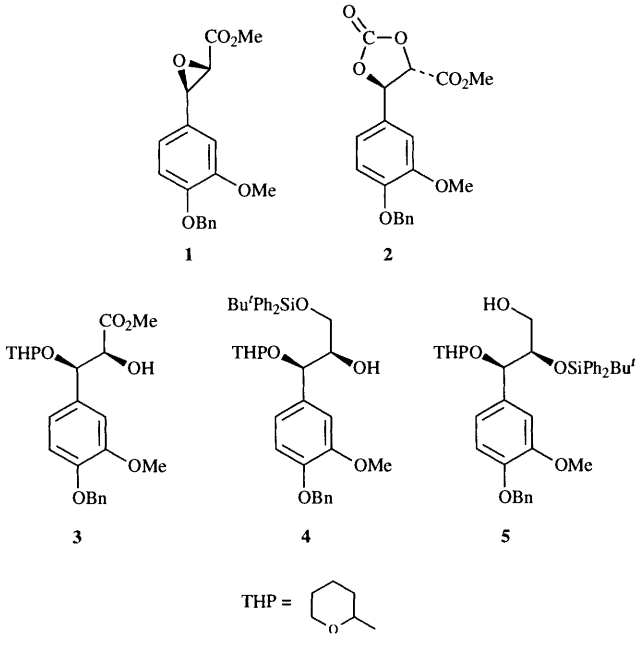
Neolignans are a group of natural products having very broad structural variation and a large number of neolignans have been isolated and characterized in recent years.[1] One of the major classes of neolignans contains a chiral aryloxy C(8)–O–C(4′) ether linkage (**I**), and this type of neolignan is structurally



I

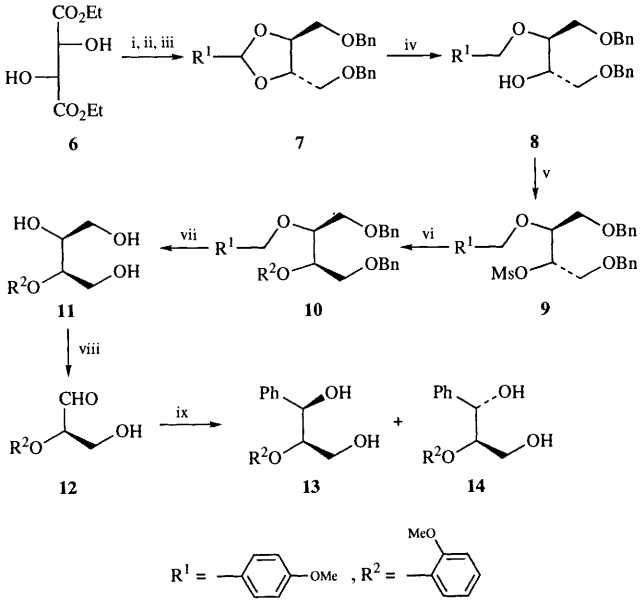
analogous to the major interunit linkage of lignin. Whereas lignans and neolignans are optically active small molecules (typically dimers), lignin is an optically inactive polymer. The biosynthetic relationship among lignans, neolignans and lignin is still relatively unclear. Due to this current lack of understanding and the biological activity of numerous lignans and neolignans, we have begun a research programme directed at developing asymmetric syntheses of several neolignans. In this communication our efforts to prepare C(8)–O–C(4′) linked neolignans are described.

Several methods to directly introduce a chiral aryloxy ether bond at the 8-position of phenylpropane derivatives have been attempted. The reaction of **1**[2,3] with sodium 2-methoxyphenolate under various reaction conditions only provided an uncharacterized mixture of products, although ring-opening of an epoxide analogous to **1** with sodium 2-methoxyphenolate has been reported to occur exclusively at the 8-position.[4] Another method was inspired by a recent report in which a cyclic carbonate analogous to **2**[5] was treated with thiophenol and triethylamine to afford a ring-opening product exclusively at the 8-position.[6] However, compound **2** did not react with 2-methoxyphenol using triethylamine or imidazole as a base. In light of these setbacks, we next employed a Mitsunobu reaction to synthesize the chiral alkyl aryl ether.[7] Unfortunately, the Mitsunobu reaction of **3** with 2-methoxyphenol provided an uncharacterized mixture. Submission of **4** to the Mitsunobu reaction with 2-methoxyphenol resulted in silyl migration to provide **5** in 62% yield.



1 **2** **3** **4** **5**

Due to the difficulty associated with construction of a chiral aryloxy ether bond at the 8-position of the phenylpropanoid side chain, our attention turned to the initial synthesis of a chiral aryloxy ether bond, then introduction of an aromatic ring at the 7-position (Scheme 1). A three step reaction sequence



6 **7** **8** **9** **10** **11** **12** **13** **14**

Scheme 1 *Reagents and conditions:* i, 4-methoxybenzaldehyde dimethyl acetal, *p*-TsOH, DMF; ii, $LiAlH_4$, THF; iii, BnBr, KOH, toluene; iv, DIBAL-H, toluene; v, $MeSO_2Cl$ (MsCl), pyridine; vi, caesium 2-methoxyphenolate, 18-crown-6; vii, H_2, Pd–C, MeOH–HCO_2H (9:1); viii, $Pb(OAc)_4$, benzene; ix, PhLi, THF

involving diol protection, reduction and benzylation (without purification of the intermediate compounds) provided **7** from **6** in 65% yield.[8,9] The reductive ring-opening of **7** provided **8** in 97% yield.[10] Compound **8** was mesylated to provide **9** in 98% yield. Only a trace amount of **10** was detected by thin layer chromatography (TLC) after a mixture of **9** and sodium 2-methoxyphenolate in dry benzene was refluxed for 30 h. The

addition of 18-crown-6 to the mixture accelerated the reaction, and TLC showed that about 30% of **9** was converted to **10** after refluxing the above mixture for 30 h. However, **9** was completely converted to **10** by refluxing the mixture of **9**, caesium 2-methoxyphenolate and 18-crown-6 in benzene for 24 h. Hydrogenation of **10** with Pd–C in methanol–formic acid (9:1) provided **11** in 76% yield based on **9**. Diol cleavage of **11** with lead tetraacetate in dry benzene provided **12**, which was submitted to the next step without purification. The reaction of **12** with excess phenyllithium at 0 °C provided equal amounts of two diastereoisomers, **13** and **14**, in 72% yield based on **11**. The separation of **13** and **14** was achieved by ion-exchange chromatography (QAE-Sephadex A-25) using 0.06 M $K_2B_4O_7$ *in acetone*–water (1:4) as the eluent.[11] Compounds **13** and **14** have greater than 96% ee as determined by NMR of the Mosher bis(esters) of **13** and **14**.

In conclusion, several synthetic routes to neolignans with C(8)–O–C(4′) linkages have been investigated. Direct introduction of an aryloxy ether bond at the 8-position of a phenylpropane sidechain was not successful. As an alternative, an efficient method for the synthesis of a chiral aryloxy ether bond has been established, using caesium phenolate and 18-crown-6. This had led to the preparation of two optical neolignans in high enantiomeric excess. Through utilization of these protocols, the synthesis of several neolignans with C(8)–O–C(4′) linkages will be reported in the near future.

Experimental

(2*R*,3*S*)-1,4-Dibenzyloxy-3-(4-methoxybenzyloxy)-2-(2-methoxyphenoxy)butane

Caesium 2-methoxyphenolate (4.77 g, 18.6 mmol) and 18-crown-6 (3.90 g, 14.8 mmol) were added to a solution of **9** (4.10 g, 7.45 mmol) in dry benzene (40 ml). The reaction mixture was stirred, refluxed at 80 °C for 24 h, filtered through Celite and the solvent evaporated at reduced pressure to provide a syrup. The syrup was purified by silica gel chromatography (hexane–ethyl acetate; 6:1) to provide **10** (3.91 g, 85–90% purity). The byproducts were difficult to remove by silica gel column chromatography; however, these byproducts were readily eliminated after the subsequent deprotection step. A small amount of pure **10** was obtained by preparative TLC (hexane–ethyl acetate; 6:1); $[\alpha]_D$ −13.8 (*c* 1.44, $CHCl_3$); δ_H[400 MHz, $(CD_3)_2CO$] 3.72 (1 H, dd, $J_{3,4a}$ 5.5, $J_{4a,4b}$ 10.4, 4a-H), 3.76 (3 H, s, OCH_3), 3.78 (3 H, s, OCH_3), 3.80 (1 H, dd, $J_{1a,2}$ 5.2, $J_{1a,1b}$ 10.5, 1a-H), 3.84 (1 H, dd, $J_{3,4b}$ 4.1, $J_{4a,4b}$ 10.4, 4b-H), 3.87 (1 H, dd, $J_{1b,2}$ 3.6, $J_{1a,1b}$ 10.5, 1b-H), 4.03 (1 H, dt, $J_{3,4b}$ 4.1, $J_{3,4a}$, $J_{3,2}$ 5.5, 3-H), 4.44–4.55 (4 H, m, benzylic H), 4.60–4.70 (3 H, m, H-2, benzylic H), 6.81–7.30 (18 H, aromatic H); δ_C[100 MHz, $(CD_3)_2CO$] 55.42 and 56.13 (OCH_3), 69.92 (C-1), 70.74 (C-4), 72.94 and 73.65 (benzylic C), 78.30 (C-3), 79.78 (C-2), 113.56, 114.28, 118.14, 121.56, 122.73, 128.07, 128.24, 128.26, 128.98, 130.13, 131.86, 139.65, 139.69, 148.91, 151.64 and 160.05 (aromatic C).

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