Synlett B. B. Mane et al. Letter

Enantioselective Total Synthesis of Ligraminol D and Ligraminol E

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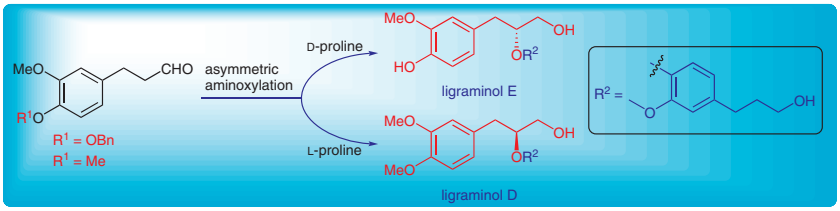

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Abstract As a part of our ongoing research on the synthesis of bioactive constituents or molecules by using an organocatalytic approach, enantioselective total syntheses of ligraminol D and ligraminol E were achieved starting from a commercially available nonchiral aldehyde. Key steps in this synthesis were an asymmetric α-aminoxylation of an aldehyde and a Mitsunobu reaction.

Key words asymmetric synthesis, total synthesis, aminoxylation, ligraminols, Mitsunobu reaction, asymmetric catalysis

Lignans and neolignans are a diverse class of pharmacologically active phenylpropanoid oligomers that occur naturally in various plants.[1] Lignans act as antioxidants and phytoestrogens with estrogenic and antiestrogenic activities.[2,3] The action of lignans on the human body can reduce the risk of breast or prostate cancer.[4] Researchers have focused their attention on syntheses of natural products, which has led to the discovery of various important anticancer drugs, such as vinblastine, vincristine, paclitaxel, and the lignin-derived etoposide, etopophos, and teniposide.

Lignans are the main bioactive constituent of *Acorus gramineus*, commonly known as Japanese sweet flag, which usually grows in wetlands or shallow water in Japan, the Korean peninsula, and eastern Asia. The plant spreads aggressively by rhizomes, which have been used in traditional Chinese medicine as a remedy for cognitive problems and for sedation, enhancing brain function, and analgesia.[5] Phytochemical investigations on species of this genus led to the isolation of various compounds of biological importance.[6] Phytochemical studies on *A. gramineus* have identified several active phenolics, such as α-asarone, β-asarone, and phenylpropenes that exhibit antibacterial, antifungal, anthelmintic, and pesticidal activities.[7–9] On 2011, Lee and co-workers isolated the lignans ligraminol A–E (Figure 1) from *A. gramineus*; these compounds showed antiproliferative activities toward human normal and cancer cell lines and inhibitory effects on nitric oxide (NO) production in lipopolysaccharide-activated BV-2 cells, a microglial cell line.[10]

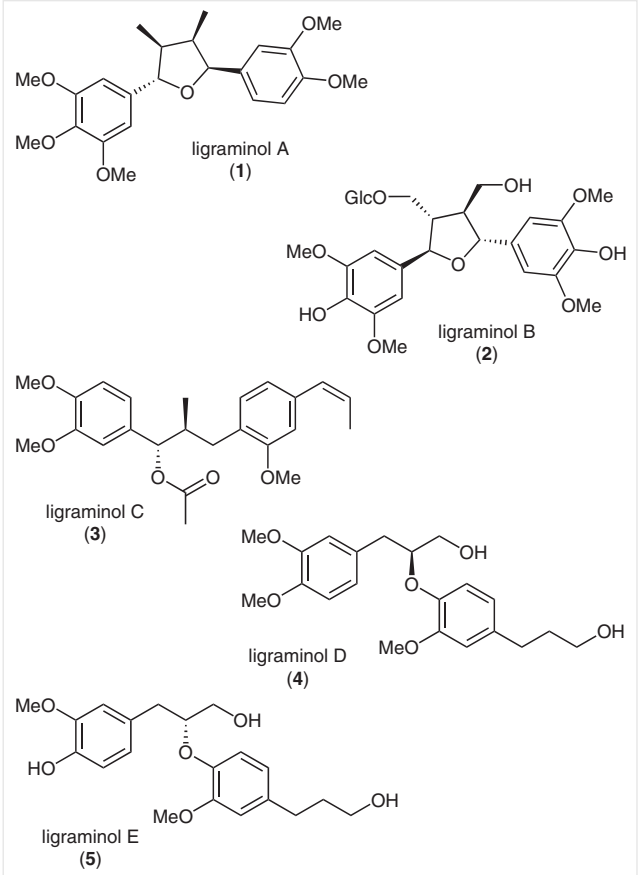

Figure 1 Ligraminols A–E isolated from *Acorus gramineus*; Glc = glucosyl

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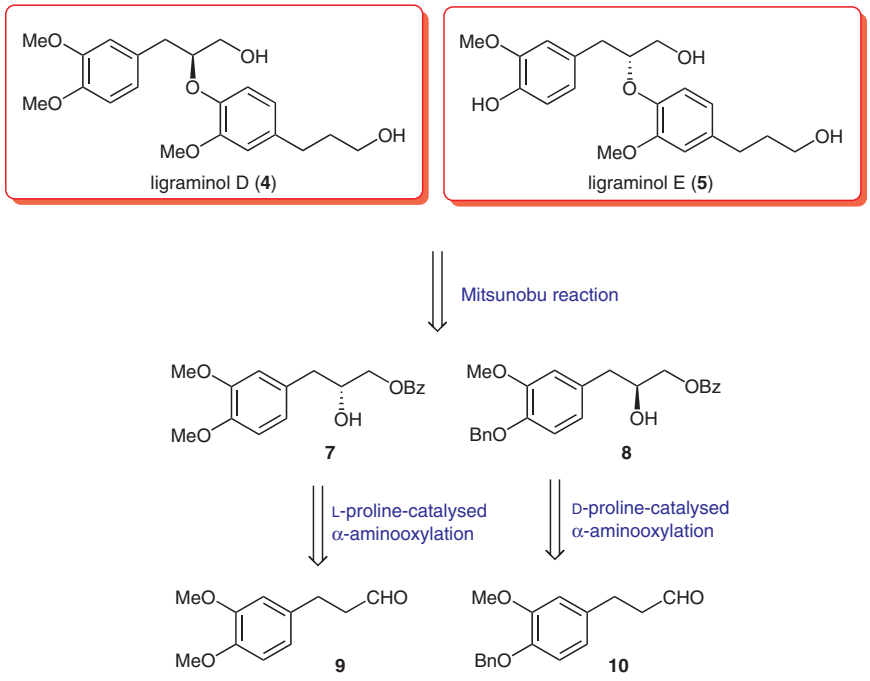
The natural-product synthetic approach and the development of new lignan derivatives as anticancer drugs is an attractive and promising avenue. Two total syntheses of ligraminol E and one of ligraminol D have previously been reported in the literature.[11] The synthesis of ligraminol E (**5**) reported by Gangar et al. was accomplished by using a chiral auxiliary and gave an overall yields of 23.9% over eight steps.[11a] A recent approach by Muthukrishnan and coworkers relied on a regioselective ring opening of a chiral epoxide with a Grignard reagent.[11b]

Over the past few years, the field of asymmetric organocatalysis has become an emerging area of research in the synthesis of chiral compounds with high optical purity.[12] Among various organocatalysts, proline is readily available in both its D- and L-forms, and is a bifunctional amino acid.[12a,13] Asymmetric aminoxylation is an attractive method for introducing chirality from nonchiral aldehydes.[14] As part of our research program on the development of new strategies for the enantioselective syntheses of biologically active compounds and their key chiral intermediates based on proline-catalyzed asymmetric α-aminoxylation of aldehydes,[15] we have developed enantioselective syntheses of ligraminol D (**4**) and ligraminol E (**5**) involving an organocatalytic asymmetric α-aminoxylation of an aldehyde and a Mitsunobu reaction as key steps.

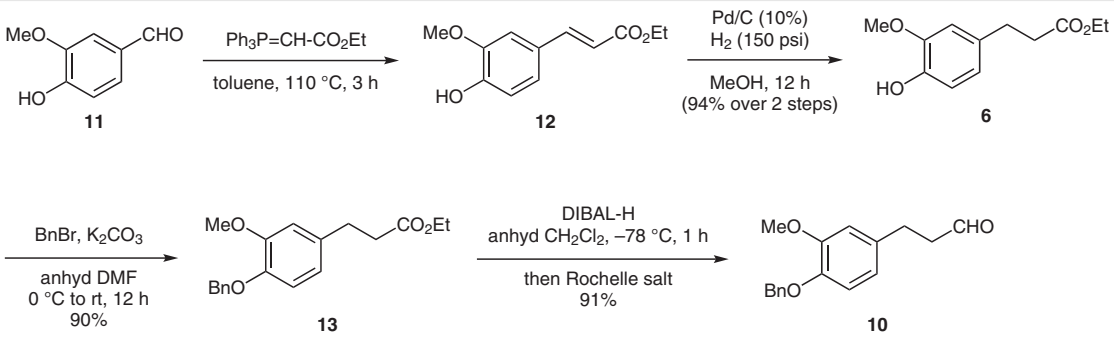
Our retrosynthetic analysis for ligraminol D (**4**) and ligraminol E (**5**) is outlined in Scheme 1. We envisaged short and efficient syntheses of ligraminol D (**4**) and ligraminol E (**5**) from the chiral *sec*-alcohols **7** and **8**, respectively, through Mitsunobu reaction with ethyl 3-(4-hydroxy-3-methoxyphenyl)propanoate (**6**). To obtain enantiomerically pure *sec*-alcohols **7** and **8**, the nonchiral aldehydes **9** and **10** could be subjected to L- or D-proline-catalyzed asymmetric α-aminooxylation, respectively, followed by protection with benzoyl chloride.

Our synthesis of ligraminol E (**5**) started from commercially available vanillin (**11**), which was subjected to Wittig olefination followed by double-bond reduction through catalytic hydrogenation in methanol to give ester **6** in 94% yield over the two steps (Scheme 2). The phenolic group of ester **6** was protected by treatment with BnBr in anhydrous DMF to afford the O-benzylated ester **13** in 90% yield. Ester **13** was reduced with DIBAL-H in CH_2Cl_2 to deliver the corresponding aldehyde **10** in 91% yield.[16]

Aldehyde **10** was treated with nitrosobenzene in the presence of ecofriendly D-proline, which catalyzed an α-aminooxylation reaction[15] in MeCN at –10 °C. This was followed by in situ reduction of the aldehyde group with $NaBH_4$ in MeOH to afford the aminooxy alcohol **14** (Scheme 3). This crude aminooxy alcohol intermediate **14** was treated with 30 mol% of $Cu(OAc)_2{\cdot}H_2O$ in MeOH to cleave the O–N bond and give the chiral diol **15** {$[\alpha]_D^{20}$ –16.4 (*c* 0.55, MeOH)} in 72% yield over the two steps. The enantiomeric excess was 97.3%, as determined by HPLC on a Chiralpak IA column. Selective benzoylation of the primary hydroxy functionality of diol **15** was carried out by using benzoyl chloride and triethylamine in CH_2Cl_2 at –10 °C to give the secondary alcohol **8** in 90% yield. Secondary alcohol **8** was subjected to a Mitsunobu reaction[17] with ester **6** in the presence of DEAD and PPh_3 in refluxing dry THF to give



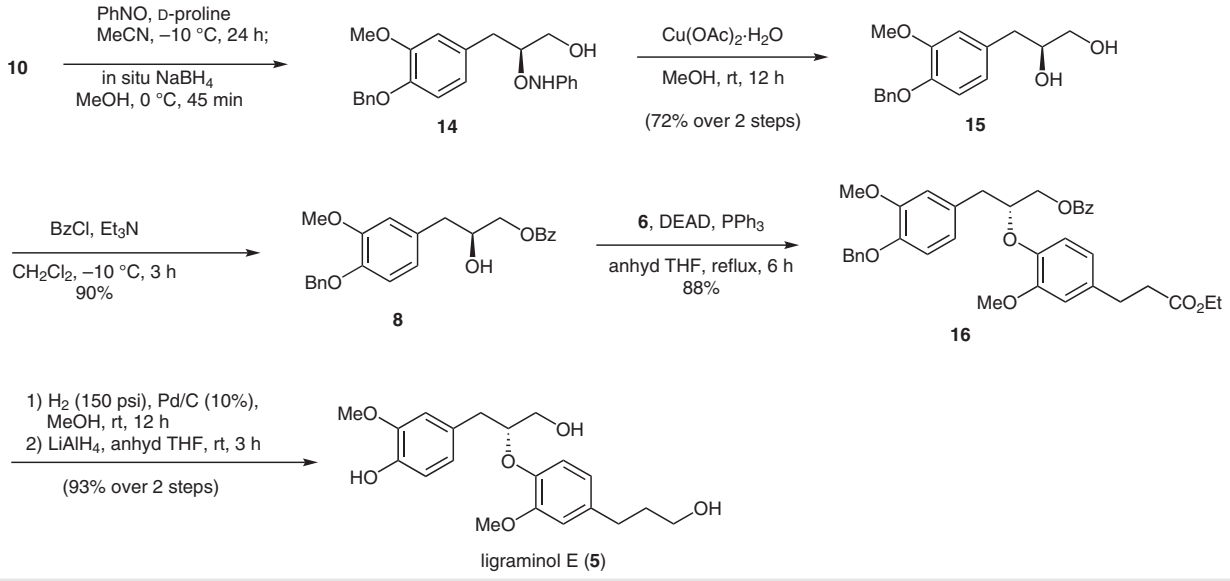
Scheme 1 Retrosynthetic analysis for ligraminol D and ligraminol E



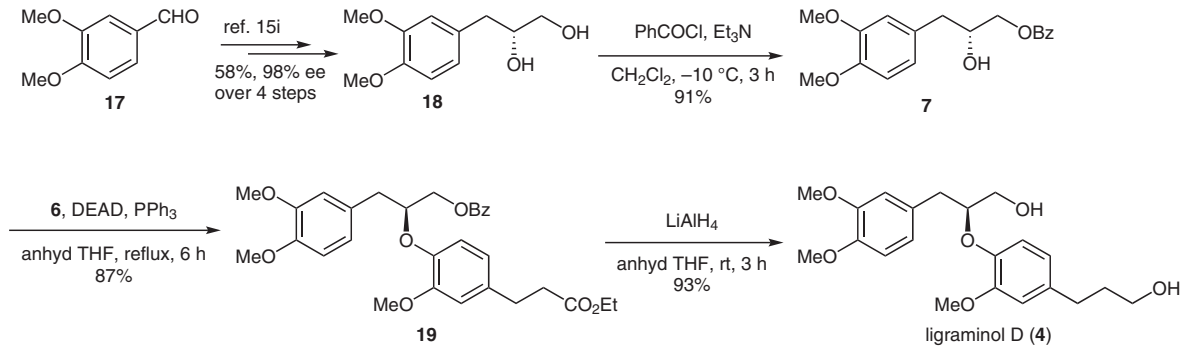
Scheme 2 Synthesis of the key intermediate aldehyde **10**

ether **16** in 88% yield. Debenzylation of ether **16** by hydrogenation in the presence of 10% Pd/C in MeOH, followed by global reduction with $LiAlH_4$ in dry THF gave ligraminol E (**5**).

We then turned our attention to the synthesis of ligraminol D (**4**) (Scheme 4). We realized that our previously reported (*R*)-diol **18**[15i] might serve as a suitable precursor with the required C-3 stereocenter of ligraminol D (**4**). Se-



Scheme 3 Synthesis of ligraminol E (**5**) from intermediate aldehyde **10**



Scheme 4 Synthesis of ligraminol D (**4**) from diol **18**

lective benzoylation of the primary hydroxy group of diol **18** was carried out by using benzoyl chloride and triethylamine in CH_2Cl_2 at –10 °C. Finally both fragments, the diol **18** and the ester **6**, were coupled under Mitsunobu conditions[17] to afford ether **19** in 87% yield. This was successfully reduced by $LiAlH_4$ in dry THF to afford ligraminol D (**4**) in 93% yield. The spectral data were in good agreement with those reported in the literature.[11b]

In conclusion, we have achieved a concise enantioselective total synthesis of ligraminol D in seven steps with 42.6% overall yield and that of ligraminol E in ten steps with 40.8% overall yield through proline-catalyzed asymmetric α-aminoxylation of aldehydes.[18] High yields, the ready availability of the starting material, and high enantioselectivity are among the salient features of our synthetic approach. The reported procedure provides the shortest known route to the synthesis of the title compound from nonchiral starting materials.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690249.

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(18) **4-{(2*R*)-3-Hydroxy-2-[4-(3-hydroxypropyl)-2-methoxyphenoxy]propyl}-2-methoxyphenol (Ligraminol E) (5)**
To a solution of ether **16** (0.190 g) in MeOH (10 mL) was added 10% Pd/C (0.05 g), and the mixture was stirred for 12 h under H_2 (150 psi; 1.03 MPa). The catalyst was filtered off and the filtrate was concentrated under reduced pressure. A solution of the resulting crude ether (0.154 g, 0.30 mmol) in anhyd THF (5 mL) was added dropwise to a cold (0 °C) suspension of $LiAlH_4$ (0.025 g, 0.66 mmol) in anhyd THF (5 mL), and the suspension as stirred for 3 h at rt, then cooled to 0 °C. The reaction as quenched with sat. aq NH_4Cl (2 mL), and mixture was diluted with EtOAc (10 mL), filtered through a Celite pad under vacuum, and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel, EtOAc–hexane (3:7)] to give a sticky colourless liquid; yield: 0.119 g (93%; two steps); $[\alpha]_D^{25}$ +17.5 (*c* 0.103, MeOH) [Lit.[11b] +18.3 (*c* 0.10, MeOH)].
IR (neat): 3387, 2923, 2852, 1602, 1509, 1261, 1026, 798 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.87–6.83 (m, 1 H), 6.81–6.76 (m, 3 H), 6.74–6.69 (m, 2 H), 4.24–4.18 (m, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.71–3.63 (m, 4 H), 3.06 (dd, *J* = 13.9, 6.7 Hz, 1 H), 2.90 (dd, *J* = 13.9, 6.9 Hz, 1 H), 2.66 (t, *J* = 6.9 Hz, 2 H), 1.91–1.84 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.9, 146.5, 145.6, 144.3, 137.3, 129.7, 122.1, 121.0, 119.8, 114.4, 112.4, 112.2, 85.14, 63.4, 62.1, 55.9, 55.8, 37.3, 34.2, 31.8. HRMS (ESI, +): *m/z* [M +

Na]$^+$ calcd for $C_{20}H_{26}NaO_6$: 385.1627; found: 385.1628.

(2*S*)-3-(3,4-Dimethoxyphenyl)-2-[4-(3-hydroxypropyl)-2-methoxyphenoxy]propan-1-ol (Ligraminol D) (4)

A solution of ether **19** (0.115 g, 0.23 mmol) in anhyd THF (5 mL) was added dropwise to a cold (0 °C) suspension of $LiAlH_4$ (0.018 g, 0.48 mmol) in dry THF (5 mL) and the suspension was stirred for 3 h at r.t, then cooled to 0 °C. The reaction was quenched with sat. aq NH_4Cl (3 mL), and the mixture was diluted with EtOAc (10 mL), filtered through a Celite pad under vacuum, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 25% EtOAc–hexane) to give a sticky liquid; yield: 0.077 g (93%), $[\alpha]_D^{25}$ –24.3 (*c* 0.154, MeOH); {Lit.[11b] –29.0 (*c* 0.1, MeOH); Lit.[11a] +9.5 (*c* 0.1, MeOH)}

IR (neat): 3402, 2945, 1605, 1510, 1036 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82 (br s, 3 H), 6.76 (br s, 1 H), 6.68 (d, *J* = 0.9 Hz, 2 H), 4.25–4.19 (m, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.69–3.67 (m, 4 H), 3.08 (dd, *J* = 13.9, 6.7 Hz, 1 H), 3.01–2.88 (m, 2 H), 2.66 (t, *J* = 6.7 Hz, 2 H), 1.91–1.84 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.9, 148.9, 147.7, 145.5, 137.3, 130.5, 121.5, 121.0, 119.8, 112.8, 112.4, 111.3, 85.1, 63.5, 62.1, 55.9, 55.9, 55.9, 37.3, 34.2, 31.8. HRMS (ESI, +): *m/z* [M + Na]$^+$ calcd for $C_{21}H_{28}NaO_6$: 399.1784; found: 399.1781.