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A stereocontrolled approach for the synthesis of 2,5-diaryl-3,4-disubstituted furano lignans through a highly diastereoselective aldol condensation of an ester enolate with an α-chiral center: total syntheses of (−)-talaumidin and (−)-virgatusin

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Abstract

A general stereocontrolled approach for entry into a family of highly biologically active 2,5-diaryl-3,4-disubstituted furano lignans has been developed. The key step involves a diastereoselective aldol-type condensation of an ester enolate having an α-chiral center with an aromatic aldehyde. The methodology has been illustrated with the total syntheses of (−)-talaumidin and (−)-virgatusin.

Keywords: Aldol reaction; Enantiospecific; Lignans; Stereocontrol

2,5-Diaryl-3,4-disubstituted tetrahydrofurans constitute an important class of lignans[1] comprising a large number of structurally and stereochemically different plant derived metabolites. Structural diversity among the members of this family arises from different types of substituents at the 3,4-positions as well as from the different nature of the aromatic ether substituents. Typical examples include talaumidin **1**[2] and virgatusin **2**.[3] Compounds of this family are associated with a host of interesting biological activities such as anti-tumor, anti-inflammatory, antioxidant, antiviral, neurotrophic, neuoroprotective, and immunosuppressive. For example, (−)-talaumidin **1** exhibits neurotrophic activity in rats while (−)-virgatusin **2** is a potent inhibitor of the endogenous DNA polymerase of hepatitis B virus. Due to their enormous therapeutic potential, furano lignans have recently become the targets of intense synthetic investigation[4–6] (see Fig. 1).

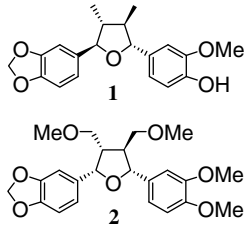

Fig. 1.

The synthesis of these lignans having four contiguous stereocenters either with all trans configuration as in **1** or with cis, trans, trans configuration as in **2** poses a considerable challenge. A number of approaches toward the synthesis of these lignans have been reported. However, these efforts have been directed toward analogues incorporating the 3,4-dimethyl functions as in talaumidin **1**[4] or the corresponding dimethoxymethyl analogues as in virgatusin **2**.[5] We planned to develop a general flexible strategy that would allow an access to lignans of both these series represented by **1** and **2.** Unlike the reported approaches which involve sequential generation of the stereocenters, our approach relies on the synthesis of an acyclic precursor with three contiguous stereocenters with the desired

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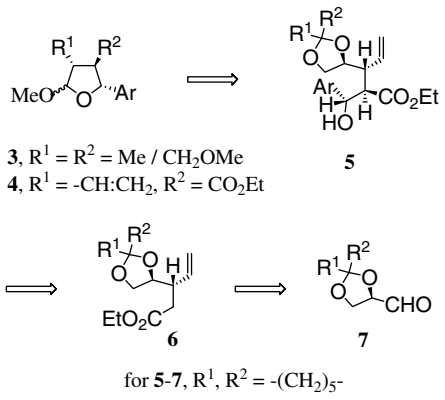
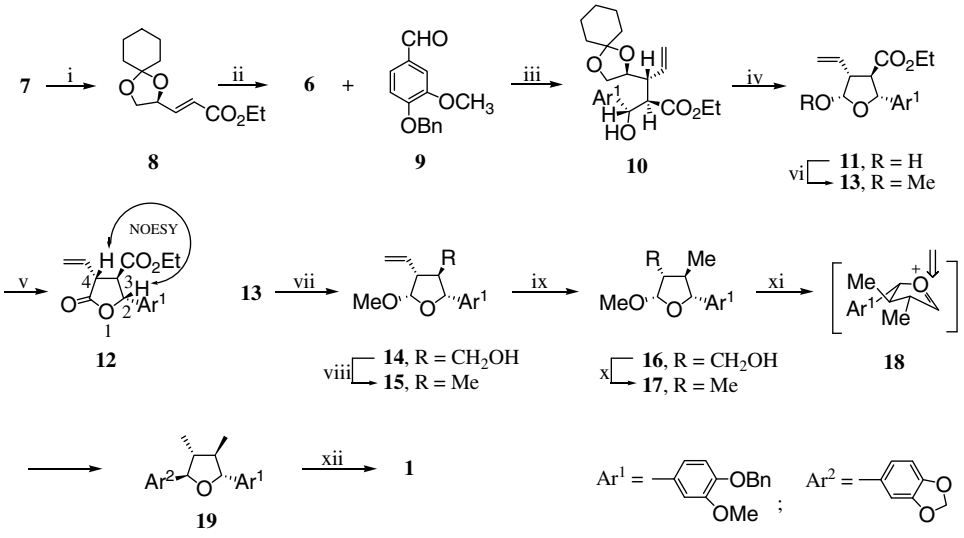


Scheme 1.

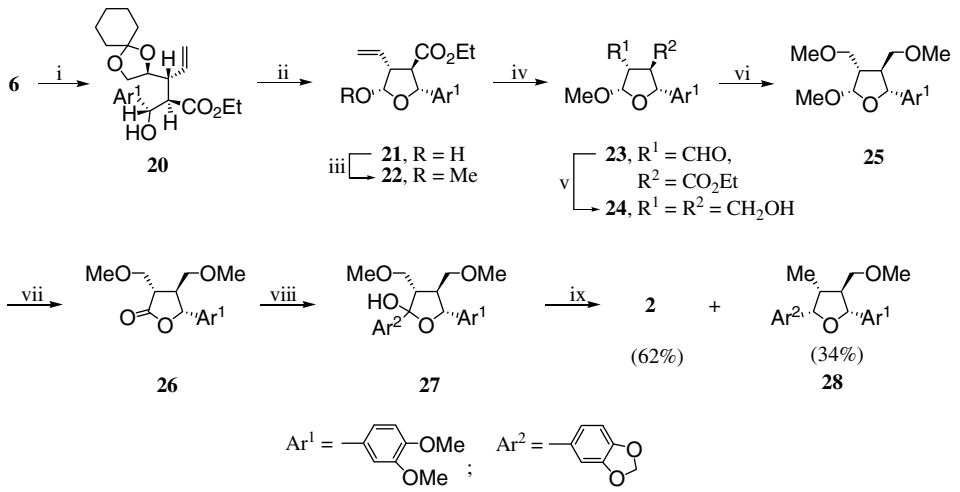
stereochemistry in a single operation prior to cyclization to tetrahydrofurans. We envisaged that **1** or **2** could be obtained through diastereoselective addition of an appropriately substituted aryl unit to acetal **3** or the lactone derived from it (Scheme 1). The latter in turn would be available from acetal **4** in which the carbethoxy and the vinyl groups are masked Me groups for **1** or CH_2OMe groups for **2**. Spontaneous acetalization of the aldehyde, available in situ from ketal **5** would provide oxacycle **4**. Precursor **5** could be obtained from diastereoselective aldol-type reaction of the enolate of ester **6**, available from *R*-(+)-2,3-di-*O*-cyclohexylidine glyceraldehyde **7**. Based on this strategy we herein report the syntheses of (−)-talaumidin and (−)-virgatusin.

The synthesis was started with the preparation of the unsaturated ester **6**.[7] Wittig–Horner reaction of aldehyde **7** with triethyl phosphonoacetate gave the unsaturated ester **8** in 67% yield. The addition of vinylmagnesium bromide to the conjugated ester **8** in the presence of cuprous iodide proceeded stereoselectively to afford the known ester **6**[7] in excellent yield (Scheme 2). Reaction of the lithium enolate derived from ester **6** (LDA) was carried out with 4-benzyloxy-3-methoxybenzaldehyde **9**. Product **10** obtained in 84% yield after chromatographic purification, was found to contain three (ca. 13:1.3:1) (from the intensities of the ^{13}C chemical shifts of the OMe group) of the four possible diastereoisomers with **10**[8] as the major one. As the minor components could not be separated, subsequent steps were carried out with this mixture. Treatment with 60% aqueous acetic acid followed by in situ oxidation with $NaIO_4$ furnished lactol **11** as an anomeric mixture in 68% yield. Jones' oxidation of these lactols delivered the lactone **12** in quantitative yield. Analysis of the NOESY spectrum revealed the cis orientation of the C-2 and C-4 protons confirming the structure of lactone **12**. With the establishment of the structure of the lactone, the structure of the major aldol product was also established as that shown which has the desired configuration at three of the four contiguous stereocenters present in talaumidin.

The next step involved the transformation of the carbethoxy and the vinyl groups to methyl groups. Treatment of the mixture of lactol **11** and its C-5 anomer with MeOH–HCl afforded acetal **13** along with a minor amount of its C-5 anomer. The *syn* stereochemical arrangement of the methoxy group with the vinyl group was ascertained by comparison of the coupling constant ($J = 0$) of the anomeric proton at δ 4.76 with that reported[9] for an analogous compound. The reduction of the ester functionality with LAH afforded alcohol **14** along with two minor isomers in 81% yield with alcohol **14** predominating (ca. 90%).



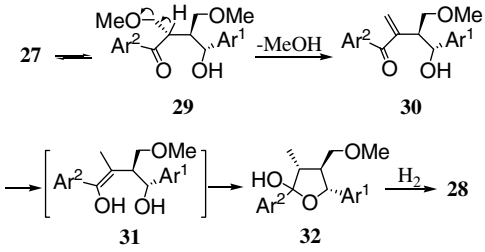
Scheme 2. Reagents and conditions: (i) K_2CO_3, $P(O)(OEt)_2CH_2CO_2Et$, $MeCN/H_2O$ (3:2), 67%; (ii) CH_2:CHMgBr, CuI, TMSCl, −78 °C, THF, 2 h, 80%; (iii) LDA, THF, HMPA, −78 °C, 4 h, 84%; (iv) 60% AcOH, $NaIO_4$, rt, 16 h, 68%; (v) Jones' [O], 10 min, 98%; (vi) MeOH–HCl, rt, 4 h, 87%; (vii) LAH, Et_2O, 0 °C, 1 h, 81%; (viii) a) TsCl, Py, DMAP, rt, 12 h, 85%; b) LAH, THF, rt, 2 h, 80%; (ix) a) OsO_4, $NaIO_4$, THF:H_2O (3:2), 0 °C, 6 h; b) $NaBH_4$, MeOH, 0 °C, 0.5 h, 67% (for 2 steps); (x) a) TsCl, Py, DMAP, rt, 24 h, 85%; b) LAH, THF, rt, 2 h, 80%; (xi) $SnCl_4$, DCM, −78 °C, 3,4-$(OCH_2O)C_6H_4$, 12 h, 80%; (xii) $Pd(OH)_2$, H_2, EtOH, rt, 15 min, 95%.



Scheme 3. Reagents and conditions: (i) LDA, THF, HMPA, −78 °C, veratraldehyde, 4 h, 87%; (ii) 60% AcOH, $NaIO_4$, rt, 16 h, 78%; (iii) MeOH–HCl, rt, 4 h, 88%; (iv) OsO_4, $NaIO_4$, THF–H_2O (3:2), 0 °C, 6 h; (v) LAH, Et_2O, 0 °C, 1 h, 72% (for two steps); (vi) NaH, THF, 0 °C, 1 h, MeI, rt, 4 h, 62%; (vii) (a) AcOH–H_2O (4:1), 60 °C, 2 h; (b) Jones' [O], 82% (for two steps); (viii) 3,4-$(OCH_2O)C_6H_3Li$, Et_2O, −78 °C-rt, 2 h, 70%; (ix) $Pd(OH)_2$, H_2, EtOAc, rt, 1 h, 62%.

The hydroxymethyl group in **14** was then transformed to a methyl group through LAH reduction of its tosylate to produce **15** in excellent yield. Acetal **15** was then treated with OsO_4 (cat)-$NaIO_4$ and the resulting aldehyde on reduction afforded alcohol **16**. The hydroxymethyl group of **16** was converted to a methyl through the reduction of its tosylate to produce the dimethyl derivative **17**. Introduction[4a] of the second aryl unit to **17** was achieved by a Friedel–Crafts type reaction with 1,2-methylenedioxybenzene in the presence of $SnCl_4$ at −78 °C to afford the tetrasubstituted tetrahydrofuran **19** in 80% yield. This reaction is believed[4a] to proceed through the oxocarbenium intermediate **18** generated from **17** on Lewis acid treatment. Steric repulsion between the incoming aryl nucleophile and the adjacent Me group directed addition *anti* to the latter. Finally, hydrogenolysis of **19** in EtOH using $Pd(OH)_2$/C afforded (−)-talaumidin **1** in 95% yield. The spectral data and the specific rotation observed for the compound prepared in this way were found to be closely comparable with those reported in the literature.[4a]

With the completion of the synthesis of talaumidin, efforts were next directed toward the conversion of ester **6** to the dimethoxymethyl analogue virgatusin. The reaction of ester **6** with LDA followed by the condensation of the resulting enolate with veratraldehyde furnished, in 87% yield, a mixture of three diastereoisomers in the ratio 14:1.5:1 (from ^{13}C NMR) (Scheme 3). The major isomer was assigned structure **20** based on analogy with the formation of **10** from **6**. Exposure of this mixture to an aqueous acid followed by treatment of the resulting diol with periodate led to lactol **21** and its anomer as the major product. Treatment of the lactol epimers **21** with MeOH–HCl produced acetal **22**. Attention was next focussed on the conversion of the vinyl and the carbethoxy groups to hydroxymethyl groups. The reaction of **22** with OsO_4 (cat)-$NaIO_4$ provided aldehyde **23** which was reduced with



Scheme 4.

LAH to afford the dihydroxymethyl derivative **24**. Methylation of diol **24** (NaH–MeI) gave the pure dimethyl ether **25** after chromatographic purification in 62% yield. Only at this stage we were able to separate the minor diastereoisomers which were generated during the aldol reaction. Acetal **25** was converted to lactone **26** in 82% yield on acid treatment followed by Jones' oxidation. The addition of 4-lithio-1,2-methylenedioxybenzene to lactone **26** afforded lactol **27**. The lactol thus obtained was subjected to hydrogenolysis using Yamauchi's procedure[5c] (H_2 over $Pd(OH)_2$/C) to give (−)-virgatusin **2** in 62% yield. During hydrogenolysis of the lactol **27**, ether **28** was obtained as a byproduct in 34% yield. The formation of compound **28** may possibly be explained in the following way. Ketol **27** probably exists in equilibrium with the hydroxy-ketone **29**. Elimination of methanol from **29** produces enone **30**. The latter is then reduced in 1,4-manner to enol **31** which eventually cyclizes to give the more stable ketol **32** with Me and CH_2OMe groups *anti* to each other. Finally, the reduction of ketol **32** produces product **28** (see Scheme 4).

In conclusion we have developed a general stereocontrolled route for the synthesis of 2,5-diaryl-3,4-disubstituted tetrahydrofuran lignans. The methodology has been illustrated by the total synthesis of (−)-talaumidin and (−)-virgatusin.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.105.

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8. All new compounds were characterized on the basis of IR, ^{1}H, ^{13}C NMR and HRMS data. Spectral data for selected compounds: Compound **10**: $[\alpha]_D^{25}$ 19.6 (*c* 2.6, $CHCl_3$); IR (neat) 3496, 1724, 1514 cm^{-1}; ^{1}H NMR (from mixture): (300 MHz, $CDCl_3$): δ 7.19–7.34 (5H, m), 6.72–6.87 (3H, m), 5.49–5.54 (1H, m), 5.13–5.14 (2H, m), 5.05 (2H, s), 4.61 (1H, q, $J = 8.5$ Hz), 3.91 (2H, m), 3.83 (1H, m), 3.81 (3H, s), 3.46 (2H, t, $J = 7.8$ Hz), 2.89 (1H, dd, $J = 9.6$, 9.5 Hz), 2.68–2.74 (1H, m), 1.42–1.66 (10H, m), 0.91 (3H, t, $J = 7.1$ Hz, CH_3); ^{13}C (75 MHz, $CDCl_3$): δ 172.3, 149.7, 147.1, 137.0, 135.2, 134.6, 128.5, 127.8, 127.2, 119.0, 118.7, 113.9, 113.8, 110.7, 110.5, 110.2, 74.5, 73.4, 71.1, 68.9, 60.2, 57.6, 56.0, 47.8, 36.4, 35.3, 25.0, 24.1, 14.1; HRMS (ESI) calcd for $C_{30}H_{38}O_7Na$ $(M+Na)^+$, 533.2515; found, 533.2512. Compound **12**: $[\alpha]_D^{25}$ −24.2 (*c* 2.33, $CHCl_3$); IR (neat) 1782, 1732 cm^{-1}; ^{1}H NMR (from mixture): (300 MHz, $CDCl_3$): δ 7.24–7.40 (5H, m), 6.80–6.87 (3H, m), 5.75–5.83 (1H, m), 5.67 (1H, d, $J = 7.6$ Hz), 5.33–5.38 (2H, m), 5.11 (2H, s), 4.07–4.18 (2H, m), 3.85 (3H, s), 3.64 (1H, t, $J = 8.5$ Hz), 3.44 (1H, t, $J = 8.5$ Hz), 1.21 (3H, t, $J = 7.1$ Hz); ^{13}C (75 MHz, $CDCl_3$): δ 174.2, 168.9, 150.0, 148.6, 136.9, 130.1, 128.6, 128.2, 127.3, 121.8, 118.5, 113.8, 109.2, 80.3, 71.0, 61.6, 56.2, 53.4, 47.8, 14.2; HRMS (ESI) calcd for $C_{23}H_{24}O_6Na$ $(M+Na)^+$, 419.1471; found, 419.1472. Compound **1**: $[\alpha]_D^{24}$ −80.8 (*c* 0.9, $CHCl_3$); ^{1}H NMR: (300 MHz, $CDCl_3$): δ 6.75–6.93 (6H, m), 5.94 (2H, s), 5.58 (1H, s), 4.62 (2H, d, $J = 9.0$ Hz), 3.91 (3H, s), 1.74–1.78 (2H, m), 1.04 (3H, d, $J = 5.5$ Hz), 1.02 (3H, d, $J = 5.4$ Hz); ^{13}C (75 MHz, $CDCl_3$): δ 147.9, 147.1, 146.7, 145.2, 136.7, 134.2, 119.8, 119.5, 114.1, 108.7, 108.0, 106.7, 101.0, 88.5, 88.3, 56.1, 51.3, 50.0, 13.96, 13.93; HRMS (ESI) calcd for $C_{20}H_{22}O_5Na$ $(M+Na)^+$, 365.1365; found, 365.1363. Compound **25**: $[\alpha]_D^{25}$ 17.6 (*c* 2.3, $CHCl_3$); ^{1}H NMR: (300 MHz, $CDCl_3$): δ 6.71–6.94 (3H, m), 4.95 (1H, s), 4.64 (1H, d, $J = 9.3$ Hz), 3.87 (3H, s), 3.79 (3H, s), 3.45–3.50 (2H, m), 3.40 (3H, s), 3.34–3.40 (1H, m),3.32 (3H, s), 3.24–3.31 (1H, m), 3.19 (3H, s), 2.64–2.68 (1H, m), 2.50–2.54 (1H, m); ^{13}C (75 MHz, $CDCl_3$): δ 149.2, 148.6, 135.1, 119.5, 110.6, 109.9, 107.8, 84.1, 69.7, 69.6, 59.0, 58.8, 55.9, 55.7, 55.1, 48.1, 47.5; HRMS (ESI) calcd for $C_{17}H_{26}O_6Na$ $(M+Na)^+$, 349.1627; found, 349.1626. Compound **2**: $[\alpha]_D^{25}$ −12.5 (*c* 0.3, $CHCl_3$); ^{1}H NMR: (300 MHz, $CDCl_3$): δ 6.79–7.06 (6H, m), 5.95 (2H, s), 5.08 (1H, d, $J = 7.3$ Hz), 4.73 (1H, d, $J = 7.9$ Hz), 3.92 (3H, s), 3.89 (3H, s), 3.50–3.55 (2H, m), 3.36 (3H, s), 3.09 (3H, s), 3.07 (1H, m), 2.96–3.01 (1H, m), 2.59–2.64 (1H, m), 2.32–2.37 (1H, m); ^{13}C (75 MHz, $CDCl_3$): δ 149.0, 148.6, 147.4, 146.6, 134.2, 132.9, 119.7, 118.8, 111.1, 110.1, 107.9, 107.1, 100.9, 82.7, 81.5, 73.19, 73.15, 59.1, 58.7, 56.0, 55.98, 51.0, 46.6; HRMS (ESI) calcd for $C_{23}H_{28}O_7Na$ $(M+Na)^+$, 439.1733; found, 439.1730.
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