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An asymmetric route to total synthesis of the furano lignan (+)-veraguensin

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ABSTRACT

Total synthesis of the furano lignan (+)-veraguensin is described. The key steps involve a diastereoselective aldol-type condensation of an ester enolate having an α-chiral center with an aromatic aldehyde and a novel isomerization of the *syn* vicinal substituents on the furan ring via a ring opening–ring closing protocol.

Lignans[1] having 2,5-diaryl-3,4-disubstituted tetrahydrofurans constitute 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. Talaumidin **1**,[2] veraguensin **2**,[3] galgravin **3**[4], and ganschisandrin **4**[5] are representative examples that illustrate the structural and stereochemical diversity present among compounds of this family (Fig. 1). A host of interesting biological activities, such as anti-tumor, anti-inflammatory, antioxidant, antiviral, neurotrophic, neuroprotective, immunosuppressive etc. are associated with compounds of this family. Due to their enormous therapeutic potential, furano lignans have recently become the targets of intense synthetic investigation[6,7] culminating in the total synthesis of several members of this family including veraguensin.[6a,c,d]

The synthesis of these lignans having four contiguous stereocenters with various stereochemical dispositions of the substituents poses considerable challenge. Although a number of approaches toward the synthesis of some of these lignans have been reported, some of these approaches lack generality and are directed to synthesis of lignans with a particular stereochemical orientation of the substituents. We planned to develop a general flexible strategy that would allow access to lignans **1**–**4**. 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 stereochemistry in a single operation prior to cyclization to tetrahydrofurans. We envisaged that all these compounds could be obtained from acetal **5** or the lactone derived from it on diastereoselective addition of an appropriately substituted aryl unit. The benzyl group in **5** on hydrogenolysis at a late stage would generate the phenolic OH required for **1** while its methylation would provide the aryl moiety present in the lignans **2**–**4**. Acetal **5** could be obtained from **6**, which in principle should be available from coupling of the enolate of the ester **7** with the aldehyde **8** (Scheme 1). Based on this idea we herein report a stereocontrolled synthesis of veraguensin.

Reaction of the lithium enolate derived from the known ester **7**[8] (LDA) was carried out with 4-benzyloxy-3-methoxybenzaldehyde

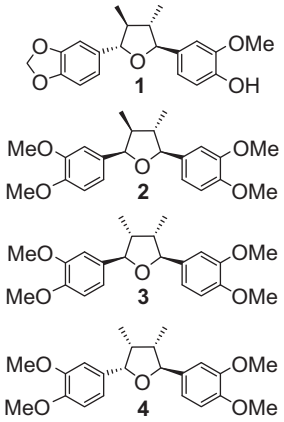

Figure 1. Representative examples of tetrahydrofurano lignans.

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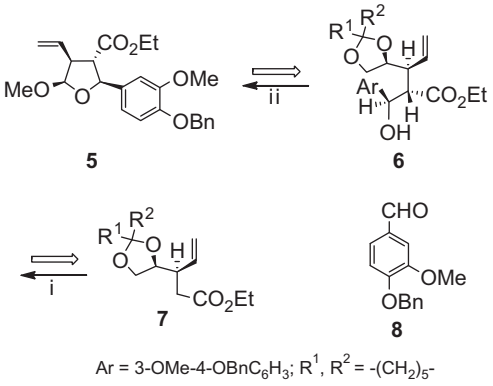
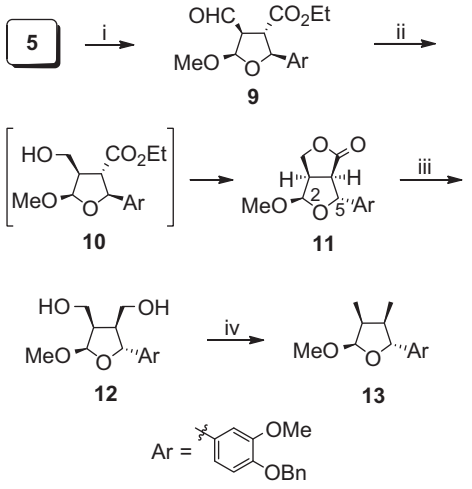


Scheme 1. Synthesis of acetal **5**. Reagents and conditions: (i) LDA, THF, HMPA, −78 °C, 4 h, 82%; (ii) (a) 60% AcOH, $NaIO_4$, rt, 16 h, 70%; (b) MeOH-HCl, rt, 4 h, 85%.



Scheme 2. Synthesis of dimethyl acetal **13**. Reagents and conditions: (i) OsO_4, $NaIO_4$, THF/H_2O (3:2), 0 °C to rt, 6 h; (ii) $NaBH_4$, MeOH, 0 °C, 1 h, silica gel, 50% (2 steps); (iii) $LiAlH_4$, THF, 0 °C, 1 h, 85%; (iv) (a) MsCl·Et_3N, DCM, 0 °C, 2 h, 86%; (b) $LiAlH_4$, THF, rt, 12 h, 78%.

8. The product **6** obtained in 82% yield after chromatographic purification, was found to contain the four possible diastereoisomers in ca. 25:4:1.5:1 ratio (from the intensities of the ^{13}C chemical shifts of the CO group) with **6** as the major one. The minor components could not be separated by column chromatography. So we decided to carry out the synthesis with this mixture. Treatment of this mixture with 60% aqueous acetic acid followed by in situ oxidation with $NaIO_4$ produced the corresponding lactol mixture. Subsequent treatment of the lactol mixture thus obtained with MeOH-HCl provided after purification through column chromatography the acetal **5** as the major product in 85% yield (Scheme 1). The stereochemical assignment to it was based on analogy to the formation of the corresponding enantiomeric acetal obtained from aldol condensation of the aldehyde **8** with C-3 epimeric ester **6**.[7] The acetal **5** has the desired configuration at three of the four contiguous stereocenters present in (+)-veraguensin and (+)-talaumidin. Indeed we have recently demonstrated that *ent*-acetal **5** could be converted to (−)-talaumidin. However, for the synthesis of the lignans **3** and **4** it is now required to transform the vinyl and the carbethoxy groups into dimethyls with change in stereochemical disposition of the 3,4-substituents from *trans* to *cis*.

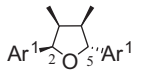
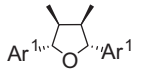
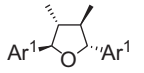
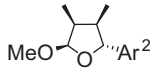
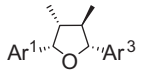
Toward this end acetal **5** was treated with OsO_4 (cat)-$NaIO_4$ in aqueous THF to afford aldehyde **9** which without further purification and characterization was reduced with $NaBH_4$ in MeOH (Scheme 2). Attempted purification of the expected hydroxy-ester **10** through column chromatography over silica gel afforded lactone **11** in 50% yield (in two steps). For stereochemical assignment, lactone **11** was converted to acetal **13** as follows. Lactone **11** was reduced with $LiAlH_4$ to afford diol **12**. Diol **12** was then transformed to the dimesylate reduction, which afforded acetal **13**. The stereochemical assignment to acetal **13** is based on comparison of the chemical shifts[9] of the C_3-, C_4-Me's as well as the coupling constants of the C_2- and C_5-H's with those observed for the naturally occurring lignans (Table 1). It may be noted from the Table 1 that chemical shifts of the Me groups as well as those of C-2 and C-5 H′s are greatly influenced by the relative orientation of the aromatic rings on the adjacent carbons. Thus, Me's *anti* to Ar's are deshielded and appear at δ 1.01–1.05 while Me *syn* to Ar is shielded and appears at δ 0.62 (entries 1–3). Further, C-2 H and C-5 H *anti* to each other have identical chemical shift. However, the C-2 H is deshielded by ~0.8 ppm when it is *syn* to the C-3 H (entry 1). In acetal **13** C-4 Me appeared at δ 1.01 which is comparable to the chemical shifts (1.01–1.05) of C-4 Me's in compounds in entries 1–3. This clearly indicates that C-4 Me and C-5 Ar are *anti* to each other in **13**. This is again supported by the chemical shift (δ 4.50) of C-5 H. Further, the coupling constant (J) between C_5-H and C_4-H′s, which are *anti* to each other in the lignans (entries 1–3), is 6.4–9.3 Hz. The C-5 H in **13** appeared as a doublet at δ 4.50 with J = 9.6 Hz. This also indicates that C-4 Me and C-5 Ar are *anti* to each other in the acetal **13** (entry 4). On the other hand the coupling constant between the *syn* C-2 H and C-3 H in ganischisandrin (entry 1) was found to be much lower (J = 4.4 Hz) compared to that observed between the C-5 H and C-4 H. In acetal **13** C_2-H appeared as a singlet clearly indicating that OMe and Me are *syn* to each other in **13**. Thus comparison of the ^1H NMR spectral data of **13** with those reported for the lignans (entries 1–3) ruled out the formation of the other diastereoisomers. With the establishment of the structure of acetal **13**, structures of the compounds **11** and **12** from which **13** was derived were established. This structural assignment to **13** was further confirmed by its transformation to the known lactone **18**[6f] (Scheme 4).

It may be noted that during silica gel column chromatography not only the carbethoxy group epimerized that led to spontaneous lactonization but interestingly the configuration of the C-5 aryl substituent was also inverted. The formation of lactone **11** from **10** may be attributed to the following (Scheme 3). Initially the ring oxygen of **10** is protonated to provide **14**. The latter then underwent ring opening to form the unsaturated ester **15**. Oxy Michael addition then takes place to form the intermediate **17** in which the aryl group occupies the more stable pseudo equatorial position rather than the species **16** which is energetically high due to the presence of unfavorable 1,3-diaxial interaction between OMe and Ar group. Finally protonation of the enolate proceeds with epimerization at C-4 followed by lactonization to lead to **11**. It is probably the lactonization that drives the reaction to follow this course.

The compound **13**, which has the desired relative stereochemical orientation at C-3, C-4, and C-5 centers for the lignans **3** and **4**, was subjected to Friedel–Crafts reaction with 3,4-dimethoxy benzene. A number of Lewis acids, such as $SnCl_4$, $BF_3{\cdot}Et_2O$ etc were used. Unfortunately, this reaction led to an intractable mixture.

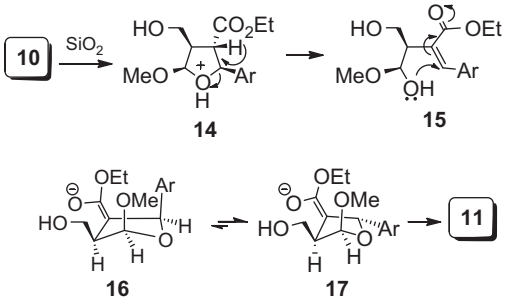
Acetal **13** was then transformed to the known lactone **18**[6f] by treating it with aqueous acetic acid followed by Jones oxidation. Lactone **18** was then allowed to react with 3,4-dimethoxyphenyl lithium to produce the cyclic hemiacetal **19** as a distereomeric mixture. This without further purification was subjected to hydrogenolysis to produce phenol **20**. Methylation of the phenol finally completed the synthesis of (+)-veraguensin (Scheme 4). The NMR spectral data for the compound **2** synthesized in this way matched exactly with those reported in literature[6c,d] and the specific rotation observed [$[\alpha]_D^{25}$ 33.9 (c 1.75, $CHCl_3$)] for **2** was also

Table 1

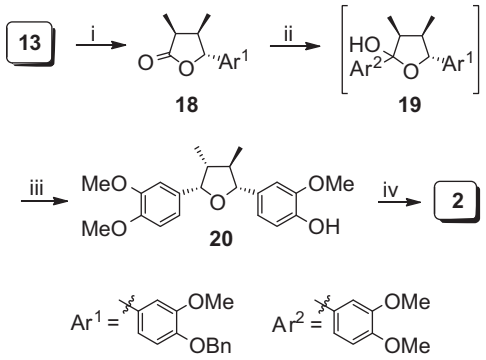
Entry	Compound	δ (ppm)				J (Hz)	
		C_3-Me	C_4-Me	C_2-H	C_5-H	C_2-H	C_5-H
1	 Ganschisandrin	0.62	1.01	5.47	4.67	4.4	9.1[a]
2	 Galgravin	1.05	1.05	4.52	4.52	6.4	6.4[a]
3	 Galbelgin	1.05	1.05	4.66	4.66	9.3	9.3[a]
4	 **13**	0.92	1.01	4.70	4.51	0	9.6
5	 **20**	0.66	1.07	5.12	4.40	8.6	9.3

Ar^1 = 3,4-$(OMe)_2C_6H_3$, Ar^2 = 4-OBn-3-$OMeC_6H_3$, Ar^3 = 4-OH-3-$OMeC_6H_3$

[a] Ref. 6c.



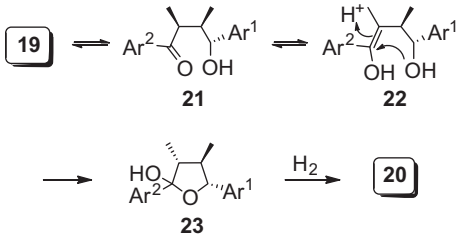
Scheme 3.



Scheme 4. Synthesis of veraguensin **2**. Reagents and conditions: (i) (a) 60% AcOH, rt; (b) Jones [O], 88% (2 steps); (ii) 3,4-dimethoxyphenyl lithium, Et_2O, −78 °C to rt, 3 h; (iii) $Pd(OH)_2$, H_2, EtOAc, rt, 54% (2 steps); (iv) NaH, MeI, rt, 3 h, 80%.

found to be comparable with the reported value [$[\alpha]_D^{25}$ 34.2 (*c* 1.10)].[3]

The isomerization of the 3,4-*cis*-dimethyl groups in **19** to 3,4-*trans*-dimethyls during hydrogenolysis may be explained as follows (Scheme 5). The cyclic hemiacetal **19** probably remains in equilibrium with the hydroxy-ketone **21** which through its enol



Scheme 5.

22 undergoes cyclization to give a new cyclic hemiacetal **23** in which 3,4-dimethyl groups remain *trans* oriented to avoid steric interaction arising out of vicinal *cis*-dimethyl groups in **19**. Deoxygenation on hydrogenolysis then produces **20**. A comparison of the chemical shifts of the C-3 and C-4 Me's as well as those of C-2 and C-5 H's along with their coupling constants with those of the lignans (Table 1, entries 1–3) confirmed the stereochemical assignment as depicted in structure **20**. Alternatively, the Me group next to the lactone carbonyl may isomerize under the reaction condition prior to addition of aryl lithium to lead to **23**.

In conclusion we have developed a new route for the synthesis of furano lignan (+)-veraguensin. Although the approach was targeted to the synthesis of *cis*-dimethyl furano lignans **3** and **4**, an interesting isomerization of the 4,5-substituents via a ring opening–ring closing reaction took place.

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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.2010.10.136.

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9. All new compounds were characterized on the basis of IR, ^{1}H, ^{13}C NMR and HRMS data. Spectral data for selected compounds: *Compound* ***13***. $[\alpha]_D^{25}$ −20.8 (*c* 3.7, $CHCl_3$); IR ν_{max} (liquid film) 1658, 1515 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.25 (5H, m), 6.99 (1H, s), 6.83–6.75 (2H, m), 5.14 (2H, s), 4.70 (1H, s), 4.50 (1H, d, *J* = 9.6 Hz), 3.90 (3H, s), 3.48 (3H, s), 2.42 (1H, dd, q, *J* = 9.6, 7.2, 6.6), 2.25 (1H, q, *J* = 7.1 Hz), 1.00 (3H, d, *J* = 7.3 Hz), 0.91 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9 (C), 147.8 (C), 137.4 (C), 135.5 (C), 128.6 (CH) (x2), 127.8 (CH), 127.3 (CH) (x2), 119.4 (CH), 113.5 (CH), 111.0 (CH), 110.4 (CH), 87.8 (CH), 71.1 (CH_2), 55.9 (CH_3), 54.9 (CH_3), 44.2 (CH), 42.9 (CH), 11.4 (CH_3), 10.9 (CH_3); HRMS (ESI) calcd for $C_{21}H_{26}O_4Na$ (M+Na)$^+$: 365.1729. Found: 365.1729. *Compound* ***18***: $[\alpha]_D^{25}$ 15.6 (*c* 1.8, $CHCl_3$); IR ν_{max} (liquid film) 2928, 1770, 1516, 1456 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.30 (5H, m), 6.86 (1H, d, *J* = 8.3 Hz), 6.85 (1H, d, *J* = 2.0 Hz), 6.77 (1H, dd, *J* = 1.8, 8.1 Hz), 5.15 (2H, m), 4.98 (1H, d, *J* = 6.8 Hz), 3.89 (3H, s), 2.78 (1H, q, *J* = 7.7 Hz), 2.53 (1H, sixtet, *J* = 7.0 Hz), 1.22 (3H, d, *J* = 7.5 Hz), 1.07 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8 (CO), 150.1 (C), 148.5 (C), 137.0 (C), 131.3 (C), 128.7 (CH) (x2), 128.0 (CH), 127.4 (CH) (x2), 118.3 (CH), 113.9 (CH), 109.3 (CH), 85.8 (CH), 71.2 (CH_2), 56.2 (CH_3), 42.2 (CH), 38.5 (CH), 12.6 (CH_3), 10.3 (CH_3); HRMS (ESI) calcd for $C_{20}H_{22}O_4Na$ (M+Na)$^+$: 349.1416. Found: 349.1418. *Compound* ***20***: $[\alpha]_D^{25}$ 18.0 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (1H, d, *J* = 1.3 Hz), 7.0–6.85 (5H, m), 5.62 (1H, br s), 5.12 (1H, d, *J* = 8.6 Hz), 4.40 (1H, d, *J* = 9.3 Hz), 3.91 (3H, s), 3.87 (3H, s), 3.85 (3H, s), 2.28–2.20 (1H, m), 1.84–1.74 (1H, m), 1.05 (3H, d, *J* = 6.5 Hz), 0.66 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7 (C), 148.2 (C), 146.6 (C), 145.3 (C), 133.9 (C), 132.9 (C), 119.4 (CH), 119.3 (CH), 114.3 (CH), 110.8 (CH), 110.5 (CH), 109.5 (CH), 87.5 (CH), 83.1 (CH), 56.0 (CH_3) (x2), 55. 9 (CH3), 47.9 (CH), 46.1 (CH), 15.0 (CH_3) (x2); HRMS (ESI) calcd for $C_{21}H_{26}O_5Na$ (M+Na)$^+$: 381.1678. Found: 381.1675. *Compound* ***2***: $[\alpha]_D^{25}$ 33.9 (*c* 1.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07–7.02 (2H, m), 6.89–6.82 (4H, m), 5.13 (1H, d, *J* = 8.5 Hz), 4.42 (1H, d, *J* = 9.2 Hz), 3.90 (3H, s), 3.89 (3H, s), 3.87 (3H, s), 3.85 (3H, s), 2.25 (1H, m), 1.79 (1H, m), 1.07 (3H, d, *J* = 6.5 Hz), 0.66 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1 (C), 148.72 (C), 148.71 (C), 148.2 (C), 133.9 (C), 133.6 (C), 119.3 (CH), 118.8 (CH), 111.1 (CH), 110.8 (CH), 110.5 (CH), 110.1 (CH), 87.4 (CH), 83.1 (CH), 56.08 (CH_3), 56.00 (CH_3) (x2), 55.94 (CH_3), 48.0 (CH), 46.1 (CH), 15.18 (CH_3), 15.11 (CH_3); HRMS (ESI) calcd for $C_{22}H_{28}O_5Na$ (M+Na)$^+$: 395.1834. Found: 395.1835.