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Stereocontrolled Assembly of Tetrasubstituted Tetrahydrofurans: A Concise Synthesis of Virgatusin

Tito Akindele,[†] Stephen P. Marsden,*[,†] and John G. Cumming[‡]

School of Chemistry, University of Leeds, Leeds LS2 9JT, U.K., and AstraZeneca, Mereside, Alderley Park, Macclesfield SK10 4TG, U.K.

s.p.marsden@leeds.ac.uk

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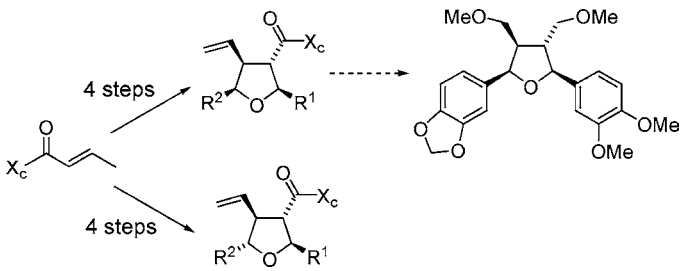
ABSTRACT

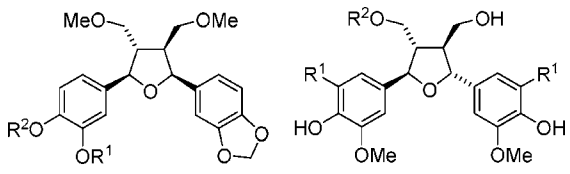


The condensation of substituted allylsiloxanes with aldehydes leads to the highly stereoselective construction of 2,3,4,5-tetrasubstituted tetrahydrofurans. With electron-rich aryl and α,β-unsaturated aldehydes as substrates, the stereochemical outcome at C5 can be dictated by appropriate choice of Lewis acid. The reaction has been applied to a concise (nine step) synthesis of (+)-virgatusin (*ent*-1).

Among the diverse skeleta of the lignan family of natural products, the 2,5-diaryl-3,4-di(alkoxymethyl)tetrahydrofuran skeleton has been observed to occur in several natural products. These have been isolated from a range of plant sources, many of which are used in traditional herbal medicines to treat a range of ailments. Representatives of four of the six possible diastereoisomeric classes of these compounds have been isolated. The *cis,trans,trans* and all-*trans* isomers are the most populous, exemplified by virgatusin **1**[1] and urinaligran **2**[2] in the former class and icariol A_2 **3**,[3] neo-olivil **4**,[4] and taxumairin **5**[5] in the latter (Figure 1).

Members of the *cis,trans,cis*[6] and *trans,cis,trans*[7] classes are also known. Further, glycosylated derivatives of the parent lignans have been isolated, either as *O*-arylglycosides[8] or with the sugars appended to the hydroxymethyl substituents.[7,9]

Given the diversity of these structures and the enormous breadth of biological activity associated with lignan natural products in general,[10] these compounds are desirable targets for synthesis. To our knowledge, synthetic approaches to just one member of this class have been reported. Yoda synthesized (−)-virgatusin **1** in 17 steps from dihydroxyacetone



1 $R^1 = R^2 = Me$
2 $R^1, R^2 = -CH_2-$
3 $R^1 = OMe, R^2 = H$
4 $R^1 = R^2 = H$
5 $R^1 = H, R^2 = Et$

Figure 1. Representative tetrasubstituted lignan natural products.

[†] University of Leeds.
[‡] AstraZeneca.

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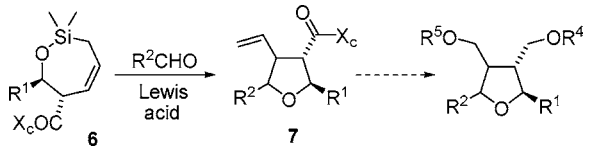
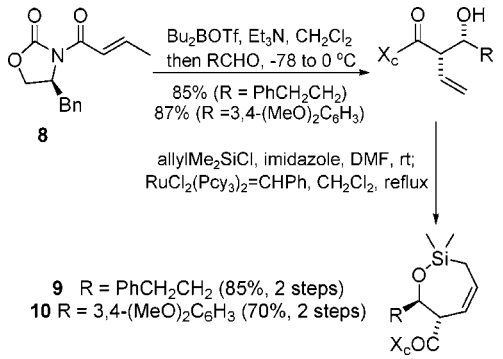


Figure 2. Planned synthetic approach to tetrasubstituted lignans.

dimer,[11] while more recently Yamauchi reported the synthesis of both enantiomers of virgatusin in 15 steps from (*R*)-benzyloxazolidinone.[12] Both syntheses feature as a key step a diastereoselective reduction of a cyclic hemiacetal to access the fully substituted tetrahydrofuran. Stevenson has reported stereoselective racemic routes to *cis*,*trans*,*trans* and all-*trans*-2,5-diaryl-3,4-dimethyltetrahydrofuran natural products which employ the corresponding hydroxymethyl derivatives as precursors.[13,14] The key transformation is an $FeCl_3$-mediated dimerization of substituted cinnamates and could in principle be used to access racemic compounds of type **1**−**5**. Pohmakotr described the synthesis of all-*cis*-2,5-diaryl-3,4-di(hydroxymethyl)tetrahydrofurans by reaction of dilithiated α-aroylsuccinates with aldehydes,[15] although this stereochemical motif has not yet been found in natural materials.

We[16] and others[17] have reported the stereocontrolled synthesis of tetrahydrofurans by condensation of metathesis-derived cyclic allylsiloxanes with aldehydes or acetals. The substitution patterns accessed so far have primarily been 2,3,5-[16a,17] and 2,3,4-trisubstituted,[16b] but Cossy reported two examples of the synthesis of 2,3,4,5-tetrasubstituted products, utilizing an allylsiloxane derived from crotonylation of an aldehyde.[17] We felt that the method could provide rapid access to target structures of type **1**−**5** if more highly functionalized, enantiomerically enriched precursor allylsiloxanes of type **6** were utilized (Figure 2). The C3 carboxyl substituent and C4 ethenyl group of the resulting tetrahydrofuran **7** serve as latent hydroxyalkyl groups, which can be unmasked simultaneously or sequentially as required, allowing access to the nonsymmetrically substituted natural products such as **5**. We now report the attainment of these

Scheme 1



goals, including the ability to tune the C5-stereochemistry by judicious choice of Lewis acid and the application of the method in the shortest synthesis to date of virgatusin **1**.

The requisite allylsiloxanes of type **6** have previously been prepared by Taylor and co-workers,[18] using a deconjugative aldol reaction of a crotonyl oxazolidinone, followed by silylation of the aldol adduct with allylchlorodimethylsilane and ring-closing olefin metathesis. Application of this procedure to benzyloxazolidinone **8** with dihydrocinnamaldehyde and veratraldehyde gave the allylsiloxanes **9** and **10**, respectively, in excellent yield over the three steps (Scheme 1). These building blocks contain two of the asymmetric centers present in the tetrahydrofuran targets, and the relative stereochemistry corresponds to the establishment of a 2,3-*trans* relationship in the tetrahydrofuran.

With these materials in hand, we then commenced an examination of their condensation reactions with a range of aldehydes. Initially, our efforts focused on the alkyl-substituted siloxane **9** under the standard conditions we had previously developed, namely the use of boron trifluoride etherate as Lewis acid, commencing the reaction at −78 °C and allowing the mixture to warm to room temperature. Under these conditions, we were delighted to find that the reaction worked with a range of aldehyde substrates, and the results are outlined in Table 1.

Condensation with aliphatic aldehydes gave good to excellent yields of the corresponding adducts **11a**/**12a** as a single diastereoisomer (entries 1 and 2). This was assigned the given stereochemistry on the basis of NOE studies on **11a**. Reaction with benzaldehyde for 23 h gave a 65% yield of a mixture of two diastereoisomers **13a** and **13b**. Attempts to achieve higher yields by prolonged reaction times at room temperature (entry 4) or at reflux (entry 5) did indeed lead to slightly higher yields but at the expense of diastereoselectivity: reduced selectivity in favor of **13a** was seen, and a third diastereoisomer **13c** could now be detected in the ^{1}H NMR spectrum. Reaction with piperonal (entry 6) gave a 91:9 mixture of products, with the all-*trans* isomer **14b** now dominating over **14a**. This stereochemical assignment was made on the basis of the observed upfield chemical shift of

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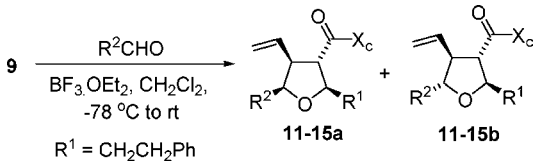
Table 1. Condensation of Allylsiloxane **9** with Aldehydes



entry	R^2	product	yield (%)	dr (**a**/**b**/**c**)
1	$BnCH_2$	**11a**	91	100:0:0
2	$BnOCH_2$	**12a**	65	100:0:0
3	Ph	**13a**,**b**	65	93:7:0
4[a]	Ph	**13a**−**c**	78	80:12:8
5[b]	Ph	**13a**−**c**	74	73:15:12
6	piperonyl	**14a**,**b**	37	9:91:0
7	(*E*)-styryl	**15a**−**c**	39	11:78:11
8[c]	(*E*)-styryl	**15a,b**	25	78:12:0
9	EtO_2C		0	

[a] Extended reaction time at room temperature. [b] Reaction from −78 °C to reflux. [c] Reaction held at −78 °C.

the C5-proton in **14b** (4.75 ppm, cf. 5.22 ppm in **14a**), which correlates with trends seen in our previous studies[16b] and presumably arises from anisotropic shielding by the C4-vinyl group in **14b**. A similar outcome was seen with cinnamaldehyde (entry 7) where isomer **15b** was the dominant of three isomeric products. Attempted reactions with the electron-deficient aldehyde ethyl glyoxylate gave no product (entry 9), and likewise, the dimethyl acetals of methyl glyoxylate and pyruvaldehyde failed to yield any tetrahydrofuran.

The stereochemical outcome of the reaction follows from our previously proposed model,[16] whereby cyclization through a chairlike transition state leads to the formation of isomers **11**−**15a** (Figure 3). With electron-donating unsaturated aldehydes, subsequent Lewis acid mediated epimerization[19] through a stabilized allylic or benzylic cation leads to the more stable all-*trans* isomer **11**−**15b**. In support of this proposition, exposure of diastereomerically pure **14a** (vide infra) to boron trifluoride etherate returns predominantly **14b**. At this stage, we do not know the identity of the third isomeric component **13**/**15c**, but suspect that epimerisation may be occurring at C3 by enolization of the carboxyl group,

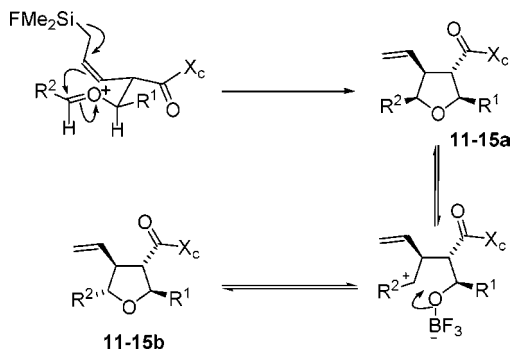
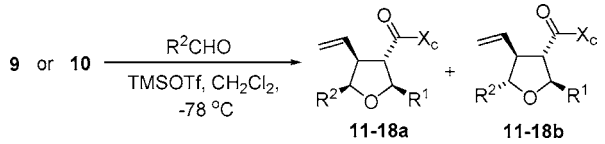


Figure 3. Rationale of stereochemical outcome.

Table 2. Condensation of Allylsiloxanes **9** and **10** with Aldehydes



entry	R^1	R^2	product	yield	dr
1	$BnCH_2$	$BnCH_2$	**11a**	86	100:0
2	$BnCH_2$	$BnOCH_2$	**12a**	76	100:0
3	$BnCH_2$	Ph	**13a**	81	100:0
4	$BnCH_2$	piperonyl	**14a**	72	100:0
5	$BnCH_2$	(*E*)-styryl	**15a**,**b**	95	97:3
6	veratryl	$BnCH_2$	**16a**	41	100:0
7	veratryl	Ph	**17a**	34	100:0
8	veratryl	piperonyl	**18a**,**b**	63	91:9
9	veratryl	(*E*)-styryl		0	

or at C2 by a β-elimination/Michael addition pathway. Again, exposure of diastereomerically pure **13a** to boron trifluoride etherate leads to the appearance of minor signals in the ^{1}H NMR due to **13c**, supporting the notion that the latter is an isomer of the former.

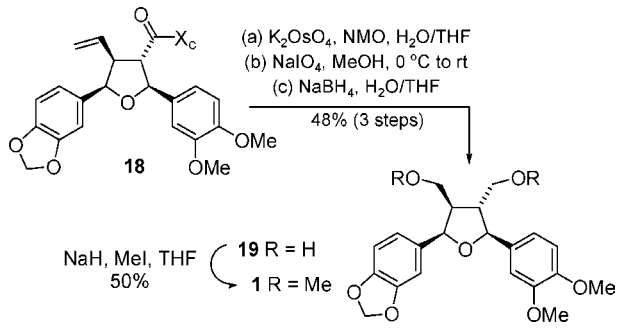
We had previously shown that the epimerisation pathway operates only at higher temperatures,[16b] and indeed carrying out the reaction with cinnamaldehyde for a prolonged period at −78 °C returned a 78:12 mixture of isomers **15a** to **15b**, albeit in a reduced yield (entry 8). Using trimethylsilyl trifluoromethanesulfonate as the activating agent[16b,17] the reactions proceed smoothly at −78 °C, allowing high conversions under conditions where the isomerization is minimized. The application of these conditions to the reactions of siloxanes **9** and **10** was investigated, and the results are outlined in Table 2.

We were pleased to find that the condensation reactions of siloxane **9** were uniformly high yielding under these conditions and further that a single isomer corresponding to the kinetic product was formed in all cases except for reaction with cinnamaldehyde, where 3% of the isomeric product was observed. We then turned our attention to the more exacting case of the veratraldehyde-derived siloxane **10**. The reactions here are complicated both by the potential for cleavage of the labile benzylic C−O bond in the siloxane (or intermediates therefrom) during the reaction, and by the presence of a second labilizing group which may cause fragmentation/isomerization in the product tetrahydrofurans.

In the event, reaction of **10** with dihydrocinnamaldehyde and benzaldehyde gave modest yields of single diastereomeric products **16**/**17a**. More interestingly still, reaction with piperonal gave the tetrahydrofuran skeleton with electron-rich aryl groups at both the C2 and C5 positions in good yield and as an inseparable 91:9 mixture of diastereomers **18a**/**b**.

(19) For an example of Lewis acid-mediated isomerisation of lignan skeleta, see: Aldous, D. J.; Dalencon, A. J.; Steel, P. G. *J. Org. Chem.* **2003**, *68*, 9159.

Scheme 2



Compound **18a** contains the necessary aryl groups and relative stereochemistry for a synthesis of the unnatural antipode of the natural product virgatusin **1**. We were able to complete this synthesis according to the final steps in Scheme 2.

Chemoselective oxidative cleavage of the C4-olefin in the presence of the electron-rich aromatics was achieved by dihydroxylation/periodate cleavage to give a C4-aldehyde. This was subsequently reduced with sodium borohydride, with concomitant reductive cleavage of the oxazolidinone auxiliary, to give diol **19** as a ca. 3:1 mixture of diastereomers, the enrichment in the minor isomer possibly being a result of partial chromatographic resolution. Finally a double Williamson etherification with iodomethane returned (+)-**1**, as an inseparable ca. 3:1 mixture with its C5 epimer. The ^{1}H NMR and ^{13}C NMR data for the major component matched that reported for (−)-**1**,[1] and the optical rotation of the mixture displayed an opposite sign and similar magnitude to that for the natural compound. It should be noted that the synthesis compares extremely favorably in terms of length (9 steps from (*S*)-benzyloxazolidinone) with those reported by Yoda[11] and Yamauchi.[12]

In summary, a concise route to the synthesis of enantiomerically pure tetrasubstituted tetrahydrofurans has been outlined. With electron-rich conjugated aldehydes, control of the C5-stereochemistry is possible through appropriate choice of Lewis acid. The potential of the chemistry has been demonstrated through the shortest synthesis of virgatusin to date, and further applications of the method are in hand.

Acknowledgment. We thank the EPSRC and AstraZeneca for an Industrial CASE award (T.A.).

Supporting Information Available: Experimental details for the cyclocondensation reactions and the synthesis of virgatusin are provided, along with ^{1}H NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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