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A novel, stereoselective and convergent synthesis of aryltetralins†

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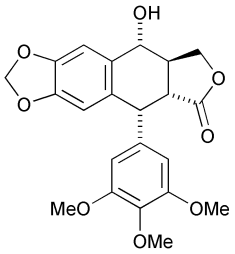
A novel one-pot, two-component condensation reaction between readily available allylsiloxanes 5 and electron-rich aldehydes 6 generates aryltetralins 7 with complete control of stereochemistry.

Natural products containing the aryltetralin skeleton exhibit diverse and interesting biological activities.[1] Members of the podophyllotoxin family of compounds **1** and semi-synthetic derivatives are employed clinically as anti-tumour agents, and many synthetic approaches to these compounds have been developed.[2] The *trans*-fused lactone is crucial for the activity of the podophyllotoxins, but many compounds containing the *cis*-fused lactone are also biologically active, for example β-norconidendrin **2** is a potent and selective inhibitor of HIV integrase.[3] Structures containing the isomeric lactone are also known, *e.g.* picropolygamain **3** exhibits activity against a range of human cancer cell lines.[4] Further, semi-synthetic derivatives of natural aryltetralins lacking the lactone have been prepared and show interesting cytotoxic[5] or immunosuppressive[6] activity.



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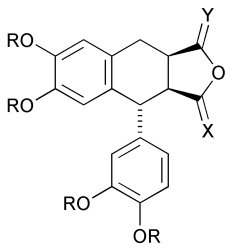


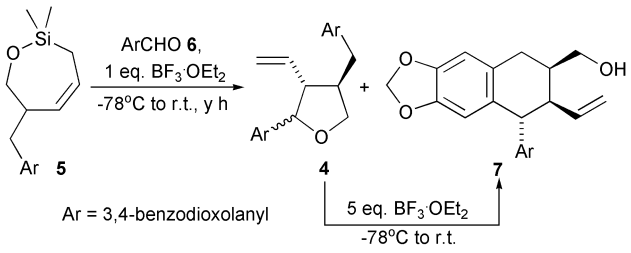
2 R = H, X = O, Y = H_2
3 R = -CH_2-, X = H_2, Y = O

During the course of recent work on the synthesis of lignan-related tetrahydrofurans[7] **4** by a Lewis acid-mediated condensation of cyclic allylsiloxanes **5**[8] with aryl aldehydes **6**, we observed small quantities (7%) of a by-product which was subsequently characterised as the aryltetralin **7**. Compound **7** was formed as a single isomer whose stereochemistry was proven by extensive NOE experiments.

We felt that if the reaction could be optimised to deliver **7** as the major product, then the convergent and highly stereoselective nature of the process would render it a highly attractive approach to the aryltetralin skeleton. Further, the presence of the hydroxymethyl and ethenyl substituents should allow conversion through to either isomeric series of lactones exemplified by compounds **2** and **3**. We describe herein the results of these studies.

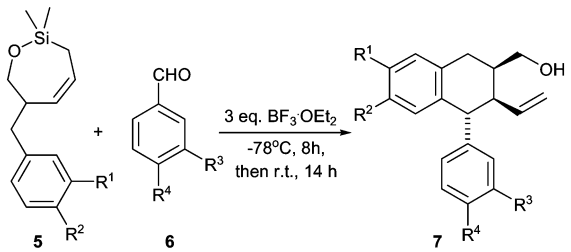
We suspected that aryltetralin **7** arose through a Lewis-acid mediated isomerisation of the initially formed tetrahydrofuran **4**.[9] Our first experiments verified that **4** could indeed act as a source of **7**. As shown in Scheme 1, exposure of **4** (as a 92 : 8 mixture of 2,3-*cis* to 2,3-*trans* isomers) to excess boron trifluoride etherate at room temperature led cleanly to **7** as a single isomer in 90% yield (with 10% recovered **4**). Tellingly, compound **7** could also be isolated as a single stereoisomer in quantitative yield when a 50 : 50 mixture of diastereomers of **4** was employed, supporting the notion that ionisation of the benzylic C–O bond is the trigger for the reaction.

While the isomerisation of the isolated THFs to the aryltetralins is in itself a useful process, a one-pot conversion of allylsiloxanes **5** and aldehydes **6** to the aryltetralins would constitute a significant synthetic advantage. Pleasingly, modification of the reaction conditions for tetrahydrofuran formation by increasing the quantity of Lewis acid to three molar equivalents and prolonging the reaction times at ambient temperature did indeed lead to the predominant formation of **7**. The application of these conditions to the reaction of five allylsiloxanes **5a–e** with a range of aryl aldehydes was then investigated (Table 1‡).



Scheme 1 Initial observation of aryltetralin formation.

Table 1 Scope and limitations of aryltetralin formation‡



Entry	R^1	R^2	R^3	R^4	Yield
1	–OCH_2O–		–OCH_2O–		66%
2	–OCH_2O–		H	OMe	57%
3	–OCH_2O–		OMe	OMe	53%
4	–OCH_2O–		OMe	OH	60%
5	OMe	H	–OCH_2O–		46%
6	OMe	H	H	OMe	48%
7	OMe	OMe	–OCH_2O–		62%
8	OMe	OMe	H	OMe	59%
9	–OCH_2O–		H	OMe	54%[a]
10	–OCH_2O–		H	H	0%[b]
11	H	H	–OCH_2O–		0%[b]

[a] TMS-OTf (1 eq.) as Lewis acid, CH_2Cl_2, −78 °C, 4 h, then r.t. [b] 68–73% yield of tetrahydrofurans **4** formed instead.

† Electronic supplementary information (ESI) available: compound data and copies of NMR spectra for compounds **7**. See http://www.rsc.org/suppdata/cc/b4/b409528f/

DOI: 10.1039/b409528f

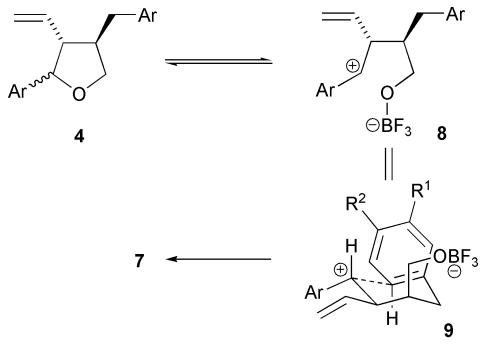


Fig. 1 Proposed mechanism for aryltetralin formation.

We found that the reaction works in good to excellent yield with a range of siloxanes and aldehydes bearing oxygenation patterns found in natural aryltetralins (Table 1, entries 1–8). Notably, the reaction is tolerant of unprotected phenolic functionality in the aldehyde component (entry 4), a motif found in many natural aryltetralins but not tolerated without protection in most other synthetic approaches to this skeleton. Trimethylsilyl triflate was also found to be a suitable Lewis acid for the transformation (entry 9). In all cases, the aryltetralin was formed as a single stereoisomer. The reaction appears general provided that both aromatic rings are electron rich. As demonstrated by entries 10 and 11, substitution of either aryl group by a simple phenyl group is sufficient to curtail the reaction at the tetrahydrofuran stage, with no aryltetralin being observed.

Mechanistically, the reaction presumably involves the reversible Lewis acid-mediated opening of the initial tetrahydrofuran product **4** to the stabilised benzylic cation **8**, which then cyclises by an intramolecular Friedel–Crafts alkylation through the chair-like transition state **9** to yield **7** (Fig. 1). Similar mechanisms have been proposed for the isomerisation of natural lignans to aryltetralins under protic or Lewis acidic conditions.[9,10] The proposal is supported by the observation that mixtures of stereoisomeric tetrahydrofurans converged to a single isomeric aryltetralin, and also that replacement of either aryl ring by a simple phenyl ring curtails the reaction by either preventing the formation of **8** or its nucleophilic capture by the second aryl ring.

In summary, a one-pot, two-component condensation reaction between allylsiloxanes and electron-rich aldehydes generates aryltetralin skeleta with complete control of stereochemistry using mild, non-toxic and functional group tolerant reagents. The chemistry provides an extremely rapid *de novo* entry into this biologically important class of compounds which will enhance the range of available target structures compared to semi-synthetic approaches. Applications in target synthesis are underway in our laboratories.

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Notes and references

‡ General procedure for aryltetralin formation: To a solution of the cyclic allylsiloxane (0.112 mmol) in DCM (2.5 mL) at −78 °C was added boron trifluoride diethyletherate (0.336 mmol). After 5 min the aldehyde (0.112 mmol in 0.2 mL DCM) was added dropwise. The solution was stirred at −78 °C for 8 h, then warmed slowly to room temperature with stirring over the next 14 h before the addition of brine (2 mL) and Et_2O (2 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 2 mL). The combined organic phases were washed with water (2 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (Et_2O–hexane) yielded the aryltetralin **7** as a white solid.

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