A concise and diastereoselective total synthesis of *cis* and *trans*-pterocarpans†

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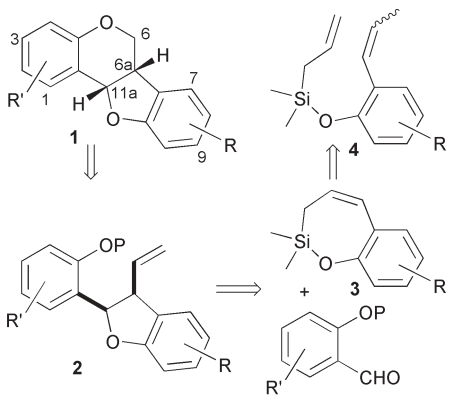
A new strategy for the diastereoselective and convergent synthesis of pterocarpans which is able to control the relative stereochemistry of the molecule through allylation of aromatic aldehydes with cyclic allylsiloxanes is described.

Pterocarpans, the second largest group of natural isoflavonoids, incorporate a *cis* fused benzofuran–benzopyran system in their skeleton.[1] They are produced by plants in response to phytopathogenous fungi infections[2] and their interest is due to their wide range of biological activities, which include antitumoural,[3] anti-HIV,[4] antimalarial,[5] and against snake venoms.[6] This range of activities and their unique structure have attracted the interest of synthetic organic chemists, and several syntheses, most of them in racemic form, have been described.[4b,6,7] However, these methods usually require numerous steps and provide poor yields. The most common strategy starts with the formation of the dihydrobenzopyran ring, and in a latter stage the dihydrobenzofuran ring closure. This pathway only allows the formation of the *cis*-fused system, which is the most stable.[8]

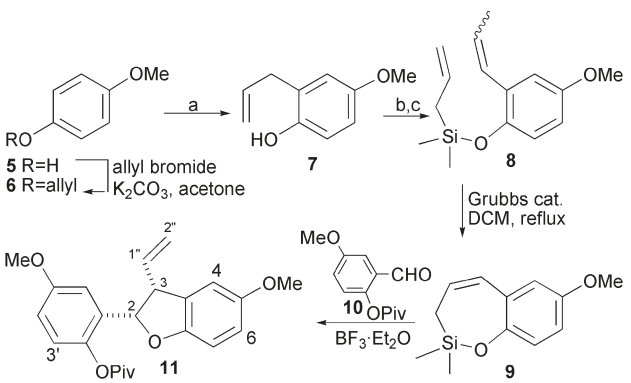
We have developed a new strategy for the diastereoselective and convergent synthesis of pterocarpans (**1**) which is able to control the relative stereochemistry of the molecule in both stereogenic carbons 6a and 11a. In addition, this synthesis ought to be easily adaptable to an asymmetric version. Our retrosynthetic analysis (Scheme 1) is based on the following key disconnections: the dihydrobenzopyran ring could be easily closed through a Mitsunobu reaction from a dihydroxylated intermediate derived from deprotection and degradation of the olefin **2**. This can be obtained by condensation of the benzoxasilepin **3** with aromatic aldehydes in the presence of a Lewis acid (a Sakurai–Hosomi modified reaction). In this stage a dihydrobenzofuran ring is formed and so are the two chiral centres of the molecule. Therefore, the diastereoselectivity of the whole route will be governed in this condensation. **3** can be prepared by ring closing metathesis of allyldimethylsilyl ethers of *o*-propenylphenols (**4**). The preparation of compounds like **4** can be achieved from commercial starting materials in few steps through conventional chemistry.



Scheme 1

Here we describe our first results. Compound **8** was prepared in four steps from *p*-methoxyphenol (**5**) (Scheme 2). Allylation of **5** with allylbromide gave **6** (95%) which was transformed into **7** through a Claisen rearrangement (93%). Treatment with base promoted the migration of the double bond,[9] and final silylation gave the desired diolefin **8** in 87% overall yield as a mixture of geometric isomers (*Z*/*E* 1/12). Ring closing metathesis of **8** in the presence of the commercial Ru-based 1st generation Grubbs catalyst[10] gave **9** in moderate yield (76%), while its imidazolidinylidene analogue (2nd generation Grubbs catalyst)[11] shortened reaction times (from 24 to 1 h) and increased the yield (up to 90%)[12] with a molar ratio substrate/catalyst 200/1.

At this point the second aromatic ring of the pterocapan was introduced through a modified Sakurai–Hosomi condensation of **9** with aldehyde **10**[13] in the presence of $BF_3{\cdot}Et_2O$. High levels of diastereoselectivity have been previously reported for the synthesis of trisubstituted tetrahydrofurans.[14,15] This is the first time that this reaction has been described on a benzo-fused cyclic



Scheme 2 a) *N*,*N*-dimethylaniline, reflux; b) *t*-BuONa, DMSO; c) allylchlorodimethylsilane, NEt_3, DCM.

† Electronic supplementary information (ESI) available: experimental details for the synthesis of all compounds, NMR data and copies of spectra and crystallographic data for **14*cis*** and **14*trans***. See http://www.rsc.org/suppdata/cc/b5/b500919g/

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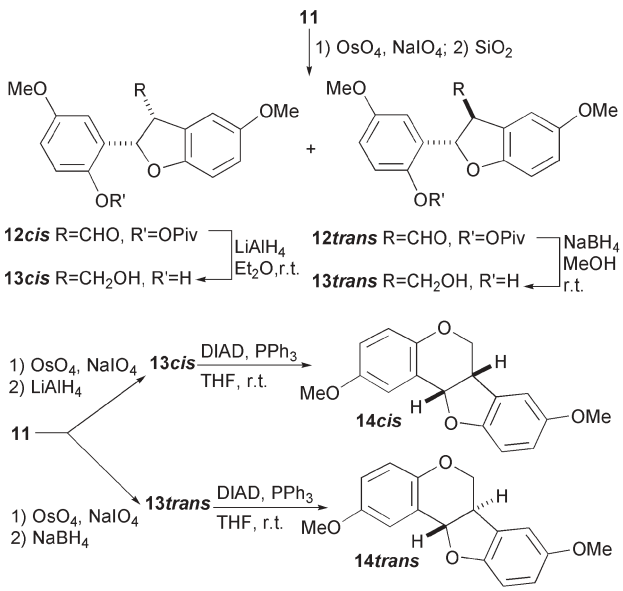
allylsiloxane, and complete diastereoselection was observed, as only the *cis* diastereomer (**11**) was obtained in 68% yield.

In the ^{1}H NMR spectrum of **11** the hydrogen of the oxygenated methine (H2) appears at 5.89 ppm (d, *J* 8.8 Hz) while H-3 gives a dd (*J* 8.8, 7.8 Hz) at 4.22 ppm. The vinyl group originates three signals at 5.37, 5.00 and 4.93 (H-1″ and both H-2″). A relative *cis* stereochemistry was initially proposed in agreement with the intense NOE effect observed between H-2 and H-3. Extensive experimentation on this reaction gave always the same diastereomer. Even on prolonged reaction times in refluxing dichloromethane and excess of $BF_3{\cdot}Et_2O$, we could not detect any amount of the *trans* isomer, and the only by-product that could be isolated was 2-allyl-4-methoxyphenol (produced by protodesilylation of **9**). A possible mechanistic pathway leading to both diastereomeric tetrahydrofurans has been described,[16,17] but the isomerization of the less stable *cis* isomer into the *trans* derivative proposed for tetrahydrofurans was not observed in our system.

The synthesis was completed by the ring closure of the dihydrobenzopyran portion (Scheme 3) through the double bond degradation and Mitsunobu cyclization of the dihydroxy derivative. All attempts of ozonolysis of **11** only gave aromatic ring degradation products. Catalytic osmium tetroxide in excess of $NaIO_4$ gave an aldehyde (**12*cis***) with retention of the relative stereochemistry. However, column chromatography on SiO_2 promoted partial isomerization to the thermodynamically favoured *trans* diastereomer (**12*cis***:**12*trans*** 6:1). To avoid this, the crude mixture of the oxidation was reduced with $LiAlH_4$ in Et_2O, which allowed the formation of **13*cis*** in 68% yield without epimerization. We also took advantage of this easy isomerization of the *cis* aldehyde to prepare a *trans* pterocarpan. Thus, **11** could be transformed into alcohol **13*trans*** (70%) when the oxidation crude was treated with $NaBH_4$ in MeOH, a reagent that reduced the aldehyde and at the same time promoted complete epimerization of C-3. On the other hand, both reductant systems completely removed the pivaloyl protecting group of the phenol, which was needed for the benzopyran ring formation.



Scheme 3

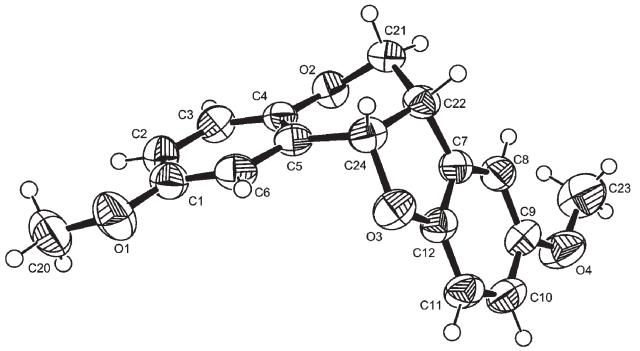


Fig. 1 Crystal structure of **14*cis*** (ORTEP 50%). Selected bond lengths (Å) and bond angles (°): O(3)–C(24) 1.469(3), C(22)–C(24) 1.540(4), C(21)–C(22) 1.504(4), O(2)–C(21) 1.430(3), C(24)–C(22)–H(22) 108.9, C(5)–C(24)–O(3) 108.7(2), O(2)–C(21)–C(22) 113.0(2).

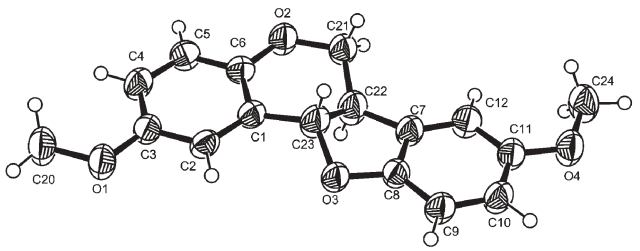


Fig. 2 Crystal structure of **14*trans*** (ORTEP 50%). Selected bond lengths (Å) and bond angles (°): O(3)–C(23) 1.435(3), C(22)–C(23) 1.463(4), C(21)–C(22) 1.476(4), O(2)–C(21) 1.447(3), C(23)–C(22)–H(22) 106.3, C(1)–C(23)–O(3) 118.8(2), O(2)–C(21)–C(22) 111.0(2).

Both pterocarpans **14*cis*** and **14*trans*** were prepared by treatment with PPh_3 and DIAD (diisopropyl azodicarboxylate) of the corresponding alcohols, in yields higher than 70%. The spectroscopic properties of these substances confirm their structural features (see Electronic Supplementary Information†). The main difference between them in their ^{1}H NMR spectra is the coupling constant between H-6a and H-11a, which is 6.6 Hz for the *cis* isomer (in the range of the average values of natural pterocarpans) and 13.4 Hz for the *trans* isomer. The other significant difference is the lower field shift of both hydrogens on C-6 [3.68, 4.29 (*cis*) and 4.47, 4.88 (*trans*)]. Appropriate crystals for X-ray diffraction could be prepared from both final products, thus confirming the proposed relative stereochemistry. This is the first time that an X-ray crystallographic analysis of a *trans* pterocarpan has been described.‡

In conclusion, we have achieved a diastereoselective total synthesis of pterocarpans in eight steps from commercial aldehydes or phenols. We are now applying the strategy to the preparation of a series of natural and unnatural pterocarpans in order to evaluate their biological activities. Looking ahead, we foresee that if the Sakurai reaction could be carried out with a chiral acid, there would be an extraordinarily simple way to make the route enantioselective.

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Notes and references

‡ Crystal data for **14*cis***. $C_{17}H_{16}O_4$, M = 284.30, triclinic, space group $P\bar{1}$, a = 4.7090(7), b = 8.2955(12), c = 9.1628(13) Å, α = 92.006(2)°, β = 94.865(2)°, γ = 104.989(3)°, V = 343.9(9) Å^3, T = 273 K, Z = 1, μ(Mo–Kα) = 0.098 mm^{-1}. A total of 1568 reflections were collected, 1200 unique reflections (R_{int} = 2.23) which were used in all calculations. The final wR (F^2) was 0.0697 (all data). Crystal data for **14*trans***. $C_{17}H_{16}O_4$, M = 284.30, triclinic, space group $P\bar{1}$, a = 8.0941(8), b = 8.7487(8), c = 10.2094(10) Å, α = 78.617(2)°, β = 82.940(2)°, γ = 77.161(2)°, V = 688.65(11) Å^3, T = 273 K, Z = 2, μ(Mo–Kα) = 0.097 mm^{-1}. A total of 3775 reflections were collected, 2407 unique reflections (R_{int} = 2.37) which were used in all calculations. The final wR (F^2) was 0.1901 (all data). CCDC 260556 & 260557. See http://www.rsc.org/suppdata/cc/b5/b500919g/ for crystallographic data in CIF or other electronic format.

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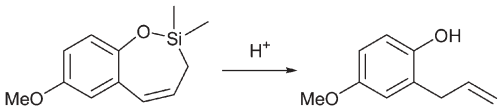

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