Bioinspired total synthesis of tetrahydrofuran lignans by tandem nucleophilic addition/redox isomerization/oxidative coupling and cycloetherification reactions as key steps†

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A very short three-step approach to trans, trans-2,5-diaryl-3,4-dimethyltetrahydrofuran lignans is reported. The carbon skeleton is assembled in a single step based on an unprecedented tandem reaction consisting of 1,2-addition of aryllithium reagents to α,β-unsaturated aldehydes, ruthenium-catalyzed redox isomerization of the resulting alkoxides to enolates and their dimerization triggered by single electron oxidation. The resulting 2,3-dialkyl-1,4-diketones form with moderate to good d/l-diastereoselectivity and are transformed to the target tetrahydrofuran lignans by reduction and diastereoselective cycloetherification.

Introduction

Tetrahydrofuran lignans I–III are a large class of plant-based natural products (Scheme 1). They display species-specific defined substitution patterns and stereochemistry at the carbon atoms of the tetrahydrofuran rings. All THF lignans are thought to result from the same achiral precursors coniferyl alcohol IV (R = OH) or isoeugenol (R = H). They are subject to oxidatively generate radicals V, which couple to quinone methides VI via presumed arrangement VII in the active site of a dirigent protein. This sets the absolute stereochemistry at C3–C4 and allows subsequent cyclization to pinoresinol VIII, which is enzymatically transformed to lignans of types I and II. In contrast, hydration of dimeric VII provides the diastereomic lignans of type III. It is noteworthy that tetrahydrofuran lignans III with the 3,4-cis- as well as 3,4-trans-dimethyl configuration were isolated and the relative configuration of the 2,5-diaryl units with respect to the 3,4-positions is variable. Even a THF lignan with the sterically most demanding all-cis-configuration has been very recently isolated; thus, all relative and absolute configurations at the tetrahydrofuran ring are found in these natural products showing that the coupling stereochemistry of radicals VI to quinone methides VII varies strongly, and also suggesting strong constraints in the subsequent hydration step from VII to tetrahydrofurans III. Since tetrahydrofuran lignans display diverse and promising biological activities, but nature typically provides only minute quantities, total synthesis is the only way to gain access to larger amounts of the natural products.

Common approaches to THF lignans of type III involve alkylation of enolates B by bromo ketones A, providing d,l-diketones with good selectivity (Scheme 2). Their subsequent reductive cyclization gave predominately cis,trans,trans-2,5-diaryl-3,4-dimethyltetrahydrofurans. Conjugate addition to C and cyclization furnished two diastereomers of tetrahydrofuran lignans with a cis,trans,cis configuration in a 7 : 1 ratio, as well as with trans,trans,trans or cis,trans,trans configuration depending on the configuration of the acyclic precursor, which had to be separated from a 2.5 : 1 diastereomeric mixture before. A conjugate addition/radical cyclization approach of D and E provided tetrahydrofuran lignans with variable 2,5-trans- as well as 2,5-cis-selectivity, but low 3,4-diastereoselectivity. Oxidative coupling reactions of cinnamic acid derivatives gave low yields of 3,4-trans-tetrahydrofuran lignans with variable 2,5-diastereoselectivity. An azonia-Claisen rearrangement of tertiary crotalamines F and propionyl chloride G followed by a twofold addition provided trans,trans,trans-lignans with high diastereoselectivity, but over eight steps.

Recently, we applied redox isomerizations as an atom-economical reactive intermediate switch from alkoxide anions to enolates. They served well in a unique tandem organometallic addition of aryllithium reagents to α,β-unsaturated...
Based on our experience in merging polar and radical processes, we hypothesized that a bioinspired radical-based modular strategy may provide a very short access to tetrahydrofuran lignans II. We envisaged a tandem process consisting of nucleophilic addition of substituted aryllithiums 1 to unsaturated aldehydes 2 and subsequent redox isomerization of resulting alkoxides, thus generating enolates 4. Their single electron oxidation to radicals, similar to that of phenolates IV during biosynthesis (cf. Scheme 1), would trigger dimerization to the lignan carbon framework in a single step.

We report here that such tandem organometallic-radical crossover reactions are indeed an efficient strategy to furnish 1,4-diketones with wide scope, good yield, and surprisingly often good diastereoselectivity. They can be transformed in only two further steps to a number of tetrahydrofuran lignans with reasonable diastereoselectivity.

Results and discussion

An initial screening of new redox isomerization catalysts revealed that the catalyst system consisting of [Ru(p-cymene)Cl2]2 and P(OMe)3 as a ligand is most efficient at accomplishing the critical isomerization of alkoxide 3 to enolate 4 in quantitative yield and the shortest possible reaction time (see the ESI, Table S1†).

With those catalytic conditions at hand, the scope of the tandem addition/isomerization/coupling sequence was explored using ferrocenium hexafluorophosphate as the oxidant (Table 1). Subjecting phenyllithium and aliphatic α,β-unsaturated aldehydes 2 to the sequence gave 1,4-diketones 8a–d in good yields and surprisingly good 6:7:1 diastereoselectivity for the coupling of these rather unbiased systems. THF or DME was used with similar results, but the isomerization is faster in higher boiling DME. Cinnamic aldehyde derivatives with a variable substitution pattern at the aryl ring were also applicable, furnishing 2,3-dibenzylic 1,4-diketones 8e–i with similar good diastereoselectivities. Even polymerization-sensitive acrolein was applicable in the tandem reactions giving 8a,m–p with reasonable yields and diastereoselectivities. Non-commercial aryllithium reagents were conveniently generated by the lithium–halogen exchange of the corresponding commercial aryl bromides with tert-butyl-lithium. They underwent the tandem reaction with similar results providing diketones 8k–p.

For most oxygenated aryllithium substrates it was better to use THF as the solvent, since the enolates tended to precipitate in DME thus thwarting the subsequent SET oxidation. It was noted that additional alkoxy substituents at the arene ring, such as in 8h, 8i and 8l–p, led to somewhat decreased, but still reasonable 3:5:1 diastereoselectivities.

The configuration of the minor 1,4-dicarbonyl compounds meso-8d–g and that of major diastereomers 8h–p were unambiguously determined by X-ray crystallography (Fig. 1). On this basis, the configuration of all other compounds was assigned by NMR spectroscopy.

Scheme 1 Major lignan classes containing the tetrahydrofuran ring and their biosynthesis.
The mechanistic course of the tandem reaction can be rationalized by nucleophilic 1,2-addition of aryllithiums 1 to unsaturated aldehydes 2 generating allylic lithium alkoxides 3 (Scheme 3). In the presence of the ruthenium catalyst, alkoxide 3 transmetalates to ruthenium alkoxide 9, which presumably forms the oxygen-coordinated ruthenium hydride complex 10, which may be in equilibrium with the C-bound hydride complex 11. From both, hydride transfer to the β-position proceeds, generating ruthenium enolate 12, which transmetalates back to the corresponding lithium enolate and regenerates the catalyst. The surprising diastereoselectivity of the dimerization is most likely based on the combination of enolate geometry and aggregation effects. We proved previously that the enolates 4 are formed with an exclusive (Z)-configuration.9 It has also been established that aryl ketone enolates exist in solution as tetrameric aggregates.15 The SET oxidation of the aggregate of 4 leads to a tetrameric radical cation 13, in which three enolate units are positioned to add as nucleophiles. Since rotation around the C-C bond in radical cation 13 is still hindered because of its partial double bond character, d/l-8 results after C-C bond formation and another SET oxidation step (not shown). Minor meso 8c can form by slow rotation to (E)-radical cation 14 and intraaggregate coupling with surrounding enolate units. This proposal is strengthened by Flower’s results, who invoked aggregates in oxidative cross-coupling reactions with simple pinacolone enolates.16 For oxygenated substrates 8m-p, alternative aggregate structures involving the phenolic units can also be envisaged, in which the enolate units are not that well aligned for coupling, thus leading to lower diastereomeric ratios.
The major d/l diastereomers of 1,4-diketones 8m–p are convenient precursors for short total syntheses of tetrahydrofuran lignans (Scheme 4). The reduction of all substrates with excess lithium aluminum hydride in THF gave a crude mixture of diols 15 in quantitative yields as a ca. 1 : 1.5 : 5–6 mixture of symmetrical and unsymmetrical diastereomers (for a stereochemical rationale, see the ESI, Scheme S1†). It must be noted that many reduction and hydrogenation methods were tried, but only LiAlH₄ at room temperature gave diols 15 without competing formation of lactols and derived side products.

When the crude mixture of diols 15m–o was subjected to BF₃ as the Lewis acid at −78 °C, trans,trans-tetrahydrofuran lignans 16 were isolated with 8–10 : 1 diastereoselectivity over diastereomeric cis,trans,trans-17 (Scheme 4; Method A). Dihydronaphthalene lignans 18 were formed competitively in low yields. The formation of lignans under these reaction conditions is irreversible, since resubjecting them to BF₃ under the reaction conditions did not lead to a change in the ratio (not shown).

The diastereoselectivity for the formation of trans,trans,trans-16a–c was considerably lower, when the cycloetherification was performed by mesylation and intramolecular substitution reactions (Method B) and significant amounts of cis,trans,tetrahydrofuran lignans veraguensin (17a), beilschmin B (17b), or unnamed 17c were also isolated. The isolated amounts of dihydronaphthalenes 18a–c did not change significantly compared to Method A.

The methodology was also applicable to the total synthesis of hydroxy group-containing lignans, such as fragransin A₂ (16e), when diketone 8p was used (Scheme 5). Its reduction followed by cycloetherification as described above gave trans,trans,tetrahydrofuran 16d with good diastereoselectivity in the presence of BF₃·OEt₂. In contrast, Method B reproducibly gave low yields of tetrahydrofurans 16d and 17d, but a much larger proportion of dihydronaphthalene 18d. Applying Mitsunobu conditions¹⁸ for the cycloetherification proved to be more effective at giving 16d and 17d in improved yield, but similar low diastereoselectivity as in Method B. The treatment of tetrahydrofurans 16d and 17d with TBAF provided the natural products fragransin A₂ (16e) and odoratisol (17e) in quantitative yield.

The good diastereoselectivity of the cycloetherification reactions mediated by BF₃·OEt₂ despite the low 1 : 1.5 : 5–6 diastereomeric ratio of diols 15 deserves comment (Scheme 6). The results indicate that it proceeds by a stereoconvergent SN₁ mechanism, because the diastereomeric ratio of the starting materials is not reflected in the products 16–18, as would
be expected in an S_N2-type reaction. The Lewis acid BF_3 abstracts hydroxide to form quinoid carbenium ions 19. Whereas minor anti,anti-15 can only cyclize via transition state trans,trans,trans-19, the anti-oriented hydroxy group is apparently predominately activated in unsymmetrical anti,syn-19 and cyclization also proceeds via trans,trans,trans-19 to tetrahydrofuran 16. Only small amounts of THF 17 are formed via transition state cis,trans,trans-19, which is higher in energy because of the cis orientation of the arene and the methyl group in the benzylic alcohol part. The minor dihydronaphthalene 18 likely results from the cyclization of minor syn,syn-15. After the elimination of the hydroxy group, a Friedel–Crafts-type cyclization via strain-free chair-type transition state trans,trans,trans-20 predominates, thus avoiding energetically higher cis-orientations in transition states, such as cis,trans,trans-19. In contrast, the cyclization of anti,anti- and anti,syn-15 to dihydronaphthalenes 18 is less likely, since a cis-orientation of hydroxy and methyl groups in the transition state increases its energy (not shown).

The diastereoselectivity of the cycloetherification via the intermediate mesylate (Method B)\(^ {4,19}\) or using the Mitsunobu conditions (Method C) is in contrast more in line with an S_N2 mechanism, since the configuration of diols 15 is well reflected in the products 16 and 17 (for a rationalization see the ESI, Scheme S2\(^ {7}\)). This reasoning is also supported by the fact that the diastereoselectivity of the cycloetherification remains similar on lowering the temperature to \(-78^\circ\)C and remains significantly different from that of the BF_3-mediated cyclization. These results are important concerning the biosynthetic origin of the stereochemically diverse tetrahydrofuran lignans (cf. Scheme 1), since the results point to the fact that the configuration of the natural products is not determined by the unconstrained conformational preferences of the carbocationic intermediates as described here, but rather by the conformation enforced by the involved dirigent protein or enzyme.\(^ {2,20}\)

**Conclusions**

In summary, a very short, modular and stereoconvergent synthesis of tetrahydrofuran lignans is reported. A key step for the construction of the carbon framework is the new tandem nucleophilic addition/ruthenium-catalyzed isomerization/SET oxidation/radical dimerization resulting in 1,4-dicarbonyl compounds with moderate to good diastereoselectivity, which is traced to the aggregation behavior of the intermediate enolates. The present approach has the potential to generate 1,4-diketones with wider scope than existing methodologies. They are easily transformed into the tetrahydrofuran core by reduction and cyclotrimerization, which proceed with good diastereoselectivity under S_N1 conditions. These results are interesting with respect to the biosynthetic origin of tetrahydrofuran lignans, where carbocations are supposed to be involved as in the presented results, suggesting that the involved proteins enforce the conformation of the cyclizing substrate to the species-specifically formed stereochemically diverse THF lignans.

**Conflicts of interest**

There are no conflicts to declare.

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**Notes and references**


