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Tetrahydrofuran Lignans via Tandem Oxidative Anionic–Radical Processes or Reductive Radical Cyclizations

Ullrich Jahn* and Dmytro Rudakov

Institut für Organische Chemie, Technische Universität Braunschweig, Hagenring 30, D-38106 Braunschweig, Germany

u.jahn@tu-bs.de

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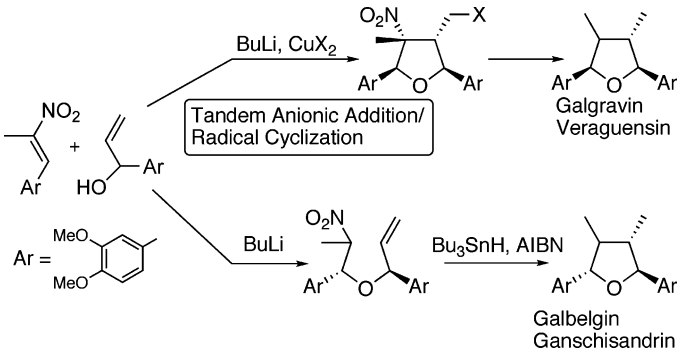
ABSTRACT



Several tetrahydrofuran lignans have become important due to their diverse biological activities. We present initial studies on short syntheses of some of the simplest members of this natural product class. Galgravin and Veraguensin are obtained in only three or four steps from nitroalkenes and allylic alcohols via a new tandem anionic–radical process, and reductive radical cyclizations of *β*-nitro ethers derived from the same precursors are suitable to obtain Galgravin as well as Galbelgin and Ganschisandrin.

2,5-Diaryl-3,4-dimethyltetrahydrofuran lignans are a group of natural products isolated from a variety of South American and East Asian plants such as *Himantandra*, *Ocotea*, *Nectandra*, *Piper*, *Lauraceae*, and *Magnolia* species.[1] A few typical members are presented in Figure 1. Members of this natural product family are constituents of traditional chinese medicines such as Haifengteng.[2] They are antioxidants, phospholipase Cγ1 inhibitors, transcription factor NF-κB inhibitors, DNA topoisomerase I or II inhibitors,[1a] NO production inhibitors,[3a] platelet aggregation factor inhibitors,[3b,c] HIF-1 inhibitors,[3d] melanin biosynthesis inhibitors,[3e] prostaglandin inhibitors,[3f] acetyl-CoA/cholesterol acetyltransferase inhibitors,[3g] neuroprotectors, and potent neurotrophic agents.[3h,i] Moreover, they display trypanocidal,[3j−m] antifungal,[3n] antimalarial,[3o] and a number of additional biological activities.[3p,q] A few members such as Galgravin, Veraguensin, and Galbelgin have been synthesized.[4−6]

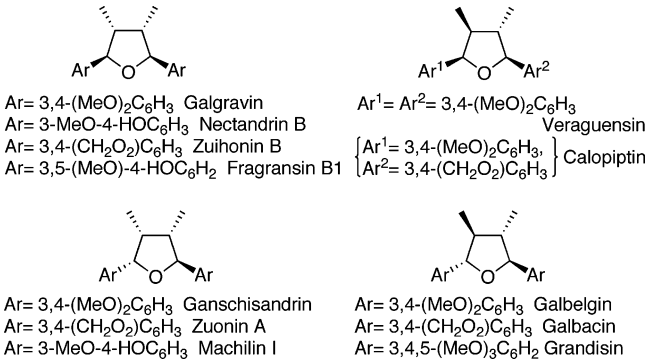


Figure 1. Some 2,5-diaryl-3,4-dimethyltetrahydrofuran lignans.

(1) Reviews: (a) Saleem, M.; Kim, H. J.; Ali, M. S.; Lee, Y. S. *Nat. Prod. Rep.* **2005**, *22*, 696−716. (b) *Phytochem. Rev.* **2003**, *2* (3). (c) Ward, R. S. *Nat. Prod. Rep.* **1995**, *12*, 183−205 and earlier reviews in this series.

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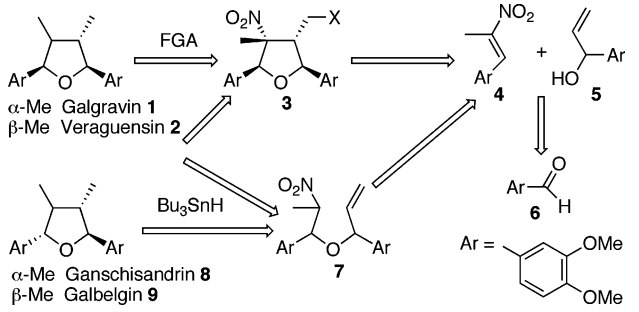
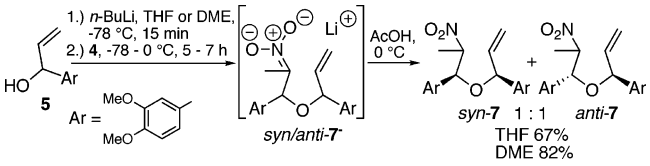
Scheme 1. Retrosynthetic Analysis of Lignans **1**, **2**, **8**, and **9**



During studies toward the design of new oxidative tandem processes involving carbanions, radicals, and carbocations, we developed tandem reactions consisting of alkoxide conjugate addition to nitroalkenes/oxidative radical cyclization/ligand transfer to highly functionalized nitrotetrahydrofurans.[7a] Given the interest in lignans, we decided to apply this methodology to their synthesis. We present here initial results on short three- to four-step total syntheses of Galgravin **1**, Veraguensin **2**, Ganschisandrin **8**, and Galbelgin **9** (Scheme 1).

Scheme 2. Lithium Alkoxide Conjugate Addition to Nitroalkene **4**



The retrosynthetic analyses of Galgravin **1**, Veraguensin **2**, Ganschisandrin **8**, and Galbelgin **9** lead to nitrotetrahydrofurans **3** as central cyclic precursors. The nitro group serves as a removable activating functionality to facilitate the synthesis of **3** (Scheme 1). Further disconnection gives rise to nitroalkene **4** and allylic alcohol **5**, which can be easily synthesized from the common precursor 3,4-dimethoxybenzaldehyde **6**. An attractive feature of this strategy is that the lignans are also accessible from **4** and **5** by reductive radical cyclizations of the β-nitro ether **7** mediated by tributyltin hydride.[8] This allows a direct comparison of the radical cyclization methods and establishes their potential for the synthesis of **1**, **2**, **8**, and **9**.

Starting materials **4** and **5** were synthesized in good yield according to the literature (Supporting Information). Although racemic **5** was used in this study, asymmetric approaches to **5** will be applied in the future.[9]

As a prerequisite to the projected tandem reactions, the efficiency of the alkoxide conjugate addition had to be tested. Addition of **4** to a solution of 2 equiv of the lithium alkoxide of **5** at −78 to 0 °C in THF or DME for 5 h afforded β-nitro ether **7** in good yield as a mixture of four diastereomers (Scheme 2). The diastereomers *syn*- and *anti*-**7** at the ether positions were separable by chromatography. A further separation of the diastereomers differing in the configuration at the nitro group was not possible. The configuration of *syn*- and *anti*-**7** was assigned on the basis of the cyclization results (vide infra).

The tandem alkoxide conjugate addition/radical 5-exo cyclization/ligand transfer reactions were performed as described above for the addition step until **4** was consumed followed by immediate addition of the oxidant at the given temperature (Scheme 3, Table 1).

The results revealed the following features of the tandem process: Both $CuCl_2$ and $CuBr_2$ are convenient SET oxidants and ligand transfer agents in these sequences (entries 1−6). On the other hand, bromine reacted presumably as an electrophile toward the nitronate $\mathbf{7}^-$, providing exclusively β-bromo-β-nitro ether **12b** as a mixture of diastereomers (entry 7). The outcome of the sequences is dependent on the solvent and the temperature of oxidant addition. Compounds **3a**,**b** were formed as predominantly single diastereomers in reasonable yields, based on the diastereomeric composition of **7**, in THF at 0 °C (entries 1 and 5). This means that radical *syn*-**10** cyclized efficiently under the reaction conditions, whereas *anti*-**10** was trapped predominantly as the acyclic β-halo-β-nitro ether *anti*-**12**. In contrast, both *syn*- and *anti*-**10** are reactive enough to cyclize to **3**

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(6) Photochemical carbonyl ylide approach: Clawson, P.; Lunn, P. M.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 153−157.

(7) (a) Jahn, U.; Rudakov, D. *Synlett* **2004**, 1207−1210. For other cyclizations involving α-nitro radicals, see ref 7a and: (b) Hobbs-Mallyon, D.; Whiting, D. A. *J. Chem. Soc., Chem. Commun.* **1991**, 899−900. (c) Snider, B. B.; Che, Q. L. *Tetrahedron* **2002**, *58*, 7821−7827.

Scheme 3

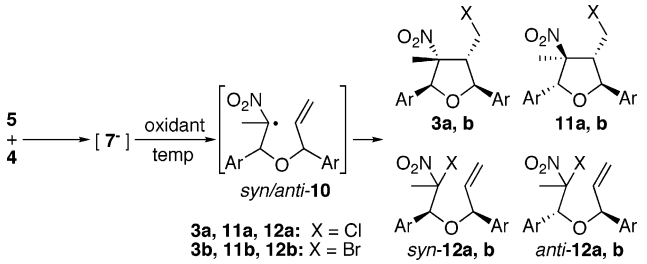


Table 1. Tandem Alkoxide Conjugate Addition/Radical 5-exo Cyclization/Ligand Transfer Reactions

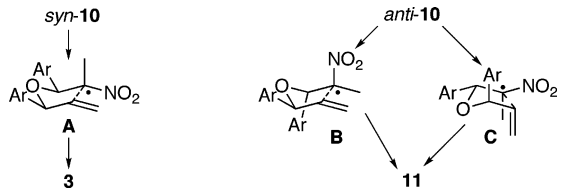
entry	oxidant[a]	solvent	temp [°C]	**3**:**11** [%] (dr)[b]	*syn*-**12**:*anti*-**12** [%] (dr)[b,c]
1	$CuCl_2$	THF	0	**a** 42 (17:1)	**a** 20 (1:7.2)
2	$CuCl_2$	THF	30	**a** 31 (3.6:1)	**a** 16 (1:2.2)
3	$CuCl_2$[d]	DME	0	**a** 52 (2:1)	**a** 19 (1:3)
4	$CuCl_2$[d]	DME	30	**a** 24 (1:1)	**a** 9 (nd)[e]
5	$CuBr_2$	THF	0	**b** 47 (6:1)	**b** 27 (1:5.6)
6	$CuBr_2$	THF	30	**b** 47 (2:1)	**b** 20 (1:3)
7	Br_2[f]	THF	0	**b** 0	**b** 72 (1:1.1)

[a] In one portion was added 2.5 equiv of the anhydrous copper salt. [b] Determined by ^{1}H NMR after isolation. [c] *anti*/*syn* ratio at ether positions. The configuration at the nitro-bearing stereocenter was not determined. [d] In five portions was added 2.5 equiv of $CuCl_2$ to avoid its clotting in the solvent. [e] Not determined. [f] An aliquot of 1.0 equiv of Br_2 as a 0.1 M solution in anhydrous dichloromethane was added dropwise.

and **11** in DME (entries 3 and 4). Here, the cyclization of *anti*-**10** proved also to be highly diastereoselective giving only one diastereomer **11**. An increase of the temperature from 0 to 30 °C led to a general decrease in yield and selectivity of the products (entries 2, 4, and 6). The cyclization rate of *anti*-**10** increased in THF and DME at 30 °C, making the overall tandem reactions less diastereoselective at higher temperature (entries 2, 4, and 6). The configurations of **3** and **11** were assigned by NOE experiments, and the configuration of **12** was assigned on the basis of its cyclization results (vide infra).

The large difference in the cyclization reactivity of the two diastereomeric radicals can be rationalized on the basis of the Beckwith−Houk transition-state model (Scheme 4).[10] Radical *syn*-**10** cyclizes through transition state **A**, where the

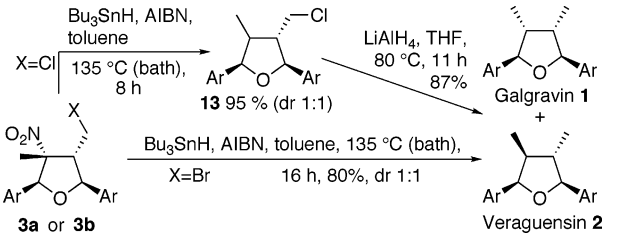
Scheme 4. Transition States for the Radical Cyclizations of **10**



substituents are arranged pseudoequatorially, thus facilitating cyclization. Minimization of allylic strain determines the high simple cyclization diastereoselectivity. In contrast, the diastereomeric radical *anti*-**10** has to cyclize through energetically less favorable chair or boat transition states **B** or **C**, where at least two substituents reside in unfavorable pseudoaxial positions. This decreases the cyclization rate and leads to preferential ligand transfer from the cupric halides to the acyclic radical *anti*-**10** to provide **12a**,**b**. Nonetheless, the cyclization took place at 30 °C affording **11a**,**b** as single diastereomers.

The final reductive halide and nitro group removal from **3** seemed trivial at first glance but proved rather difficult (Scheme 5). Radical reduction of **3a** with excess tributyltin

Scheme 5. Final Steps in the Synthesis of Galgravin **1** and Veraguensin **2**



hydride in toluene provided chloromethyltetrahydrofuran **13** in 95% yield as a 1:1 diastereomeric mixture after 8 h. Chloride reduction was tried with many reagents but was finally only achieved by reaction with $LiAlH_4$ in boiling THF providing Galgravin **1** and Veraguensin **2** as a separable 1:1 mixture in 87% yield.[3b,11] The large reactivity difference of $-NO_2$ vs −Cl reduction may be utilized to synthesize functionalized analogues of the natural products.

The bromomethyl derivative **3b** gave **1** and **2** directly on treatment with excess Bu_3SnH at reflux in toluene in good yield; however, rather long reaction times were necessary to promote complete reduction of the bromide, which is reduced slower than the nitro group.

(8) For radical cyclizations applying nitroalkanes as precursors for alkyl radicals, see: (a) Sosnicki, J. G. *Synlett* **2003**, 1673−1677 and references cited therein. (b) Chen, Y.-J.; Wang, C. Y.; Lin, W.-Y. *Tetrahedron* **1996**, *52*, 13181−13188. (c) Hull (nee Bradley), H. M.; Knight, D. W. *J. Chem. Soc., Perkin Trans. 1* **1997**, 857−863. (d) Crich, D.; Ranganathan, K.; Huang, X. H. *Org. Lett.* **2001**, *3*, 1917−1919. (e) Jang, Y.-J.; Wu, J.; Lin, Y.-F.; Yao, C.-F. *Tetrahedron* **2004**, *60*, 6565−6574. (f) Kamimura, A.; Kadowaki, A.; Nagata, Y.; Uno, H. *Tetrahedron Lett.* **2006**, *47*, 2471−2473.

(9) (a) Tomita, D.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4138−4139. (b) Sprout, C. M.; Richmond, M. L.; Seto, C. T. *J. Org. Chem.* **2005**, *70*, 7408−7417 and references cited therein. (c) Lurain, A. E.; Carroll, P. J.; Walsh, P. J. *J. Org. Chem.* **2005**, *70*, 1262−1268 and references cited therein.

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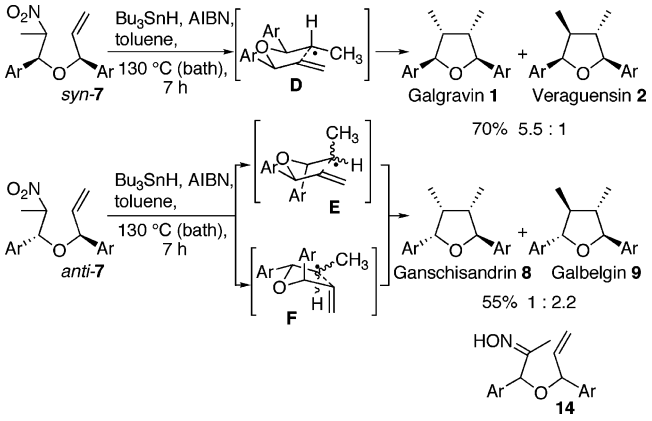
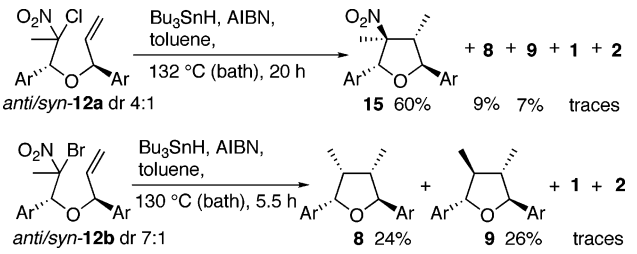
(11) The analytical data of **1**, **2**, **8**, and **9** are in agreement with those of the natural products: (a) Takeya, T.; Matsumoto, H.; Kotani, E.; Tobinaga, S. *Chem. Pharm. Bull.* **1983**, *31*, 4364−4367. (b) Fonseca, S. F.; Barata, L. E. S.; Rúveda, E. A.; Baker, P. M. *Can. J. Chem.* **1979**, *57*, 441−443. (c) Guo, Q.; Fang, H.; Su, W. *Zhongcaoyao* **2004**, *35*, 849−852. (d) Sumathykuttu, M. A.; Madhusudana, J. R. *Phytochemistry* **1991**, *30*, 2075−2076. (e) Yue, J.-M.; Chen, Y.-Z.; Hua, S.-M.; Cheng, J.-L.; Cui, Y.-X. *Phytochemistry* **1989**, *28*, 1774−1776.

Scheme 6. Radical 5-exo Cyclizations of β-Nitro Ethers **7**



Scheme 7. Bu_3SnH-Mediated Synthesis of **8** and **9** from **12a**,**b**



Next, the question arose whether the β-nitro ethers *syn*- or *anti*-**7** are also suitable cyclization precursors in an even more direct approach to lignans **1** and **2** or **8** and **9** (Scheme 6). Moreover, these cyclizations should aid the configuration assignment of **7**. Tributyltin hydride-mediated radical 5-exo cyclization of the nitro ether *syn*-**7** in a 0.036 M refluxing toluene solution provided Galgravin **1** and Veraguensin **2** in a ratio of 5.5:1 in 70% yield. On the other hand, *anti*-**7** gave Ganschisandrin **8** and Galbelgin **9** under identical conditions in 55% yield. Here, the cyclization yield of *syn*-**7** was also better than that of *anti*-**7**, reflecting the more favorable cyclization transition state **D** compared to **E** or **F**. Oxime **14** was detected as a minor byproduct. Thus, nitro ethers **7** may also serve as precursors to the synthesis of tetrahydrofuran lignan natural products.

The rather selective formation of the *anti*-β-halo-β-nitro ethers **12a** and **12b** in the oxidative tandem processes made it mandatory to check their applicability in reductive radical cyclizations to the synthesis of 2,5-*trans*-substituted lignans Ganschisandrin **8** and Galbelgin **9** (Scheme 7). Heating a 4:1 *anti*/*syn* mixture of chloro derivative **12a** with tributyltin hydride at reflux in toluene for 20 h afforded predominantly nitrotetrahydrofuran **15** in 60% yield as a single diastereomer along with 9% and 7% of the separable natural products **8** and **9**. The arrangement of the aryl and nitro groups is thus exclusively *anti* in the cyclization transition state (cf. Scheme 4). The following radical reduction of the nitro group is apparently difficult and unselective giving **8** and **9** in almost equal amounts as was also observed in the radical reduction of **3** (vide supra, cf. Scheme 5). Bromo compound **12b** underwent tributyltin hydride-mediated radical cyclization to Ganschisandrin **8** and Galbelgin **9** in 50% yield in a 1:1.2 diastereomeric ratio. This result confirms that the cyclization of radical *anti*-**10** occurs with high simple diastereoselectivity under mild oxidative (cf. Schemes 3 and 4) as well as much more forcing reductive conditions (Scheme 7).

In summary, the presented methodology allows the three- to four-step syntheses of tetrahydrofuran lignans **1**, **2**, **8**, and **9** by applying oxidative and reductive radical cyclizations of β-nitro ethers. The very different cyclization rates of the diastereomeric β-allyloxy-α-nitro radicals in oxidative tandem alkoxide conjugate addition/radical cyclizations allow an approach to the 2,5-*cis*-substituted lignans Galgravin **1** and Veraguensin **2**. The acyclic halo ethers *anti*-**12** proved to be precursors to the 2,5-*trans*-substituted lignans Ganschisandrin **8** and Galbelgin **9**. Nitro ethers **7** are also suitable precursors for reductive radical cyclizations and may find further applications in radical approaches toward lignans. The presented methodology should be broadly applicable to short total syntheses of other bioactive tetrahydrofuran lignans. Nonnatural analogues should also be accessible. Experimental investigations are underway in these labs.

Acknowledgment. We thank Deutsche Forschungsgemeinschaft and Fonds der Chemischen Industrie for generous funding of this research.

Supporting Information Available: Experimental procedures, spectra, and analytical data for new compounds **1**−**3** and **7**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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