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Cite this: *RSC Adv.*, 2013, **3**, 22834

A diastereoselective route to 2,5-diaryl-3,4-disubstituted tetrahydrofuran lignans: protection free synthesis of (+)-galbelgin and (+)-galbacin†

Received 22nd August 2013
Accepted 25th September 2013

DOI: 10.1039/c3ra44573a

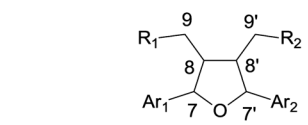
www.rsc.org/advances

Sunit Hazra‡ and Saumen Hajra*

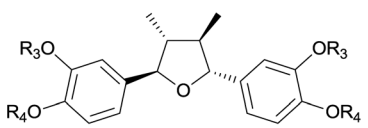
An efficient and protection free asymmetric synthesis has been reported for all-*trans* variant 2,5-diaryl-3,4-disubstituted tetrahydrofuran lignans in seven steps from *N*-succinyl-2-oxazolidinone. (+)-Galbelgin and (+)-galbacin were synthesized in very good overall yields by this route where diastereoselective aldol reaction, stereoselective *C*-alkylation over *O*-alkylation and Friedel–Crafts reaction serve as key steps.

The 2,5-diaryl-3,4-disubstituted tetrahydrofuran motif is present in a host of lignans which display a wide variety of biological activities, namely antitumor, antibacterial, antifungal and antioxidant activities.[1] The substitution pattern on aryl groups, nature of alkyl substituent along with the relative and absolute stereochemistry about the four contiguous stereocenters add structural diversity in this lignan subclass (Fig. 1). Of the six possible diastereomeric classes of 2,5-diaryl-3,4-disubstituted THF lignans four have been isolated,[2] among which the all-*trans* and *cis–trans–trans* isomers have promising biological profile, represented by galbelgin[3] **1** and galbacin[3] **2** in the former class and virgatusin[4] **3** and urinaligran[5] **4** in the later. Galbelgin and galbacin show antioxidant and antiviral activity whereas virgatusin and urinaligran show antifungal and antibacterial activity. In spite of being small in size, the challenging structural features and strong biological profile of the all *trans* 2,5-diaryl-3,4-dimethyl tetrahydrofuran lignans have attracted organic chemists for the asymmetric synthesis of these molecules.[6,7] However, most routes either require a significant number of steps or suffer from poor stereoselctivity. Thus asymmetric synthesis of 2,5-diaryl-3,4-dimethyl tetrahydrofuran lignans remains an active area of research. Our continuous interest[8] towards research on butyrolactone derived natural products prompted us to develop an efficient general method for 2,5-diaryl-3,4-disubstituted tetrahydrofuran lignan synthesis. Herein we report our efforts for the synthesis of the all *trans* 2,5-diaryl-3,4-dimethyl tetrahydrofuran lignans (+)-galbelgin and (+)-galbacin.

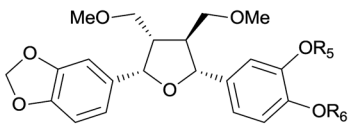
The overall structural feature of the target natural products **1** and **2** suggests that advanced intermediate **5** would give rise to the target 2,5-diaryl-THFs (Scheme 1). Hence, the sequence consisting α-functionalization of lactone **5**, stereoselective alkylation and *trans*-stereoselective incorporation of aryl group



R_1, R_2 = H, OMe, OEt, OAc
Ar_1, Ar_2 = mono-, di-, tri-oxygenated phenyl



R_3 = R_4 = Me, (-)-Galbelgin **1**
R_3 = R_4 = -CH_2-, (-)-Galbacin **2**



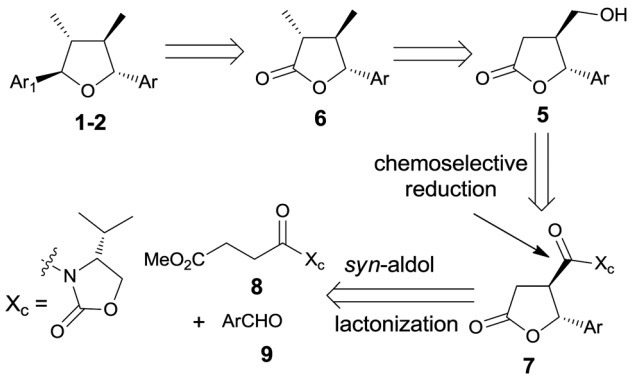
R_5 = R_6 = Me, (-)-Virgatusin **3**
R_5 = R_6 = -CH_2-, (+)-Urinaligran **4**

Fig. 1 General structure of 2,5-diaryl-3,4-disubstituted THF lignans and common subclasses.

Department of Chemistry, Indian Institute Technology Kharagpur, Kharagpur 721302, India. E-mail: shajra@chem.iitkgp.ernet.in; Fax: +91-3222282252; Tel: +91-3222283340

† Electronic supplementary information (ESI) available: Detailed experimental procedure, analytical data of synthesized compounds along with 1H and 13C spectra of compounds **7**, **12**, **13**, **6**, **14**, **1** and **2** are provided. See DOI: 10.1039/c3ra44573a

‡ Present address: Centre for Applied Chemistry, Central University of Jharkhand, Jharkhand 835205, India. E-mail: sunit16h@gmail.com

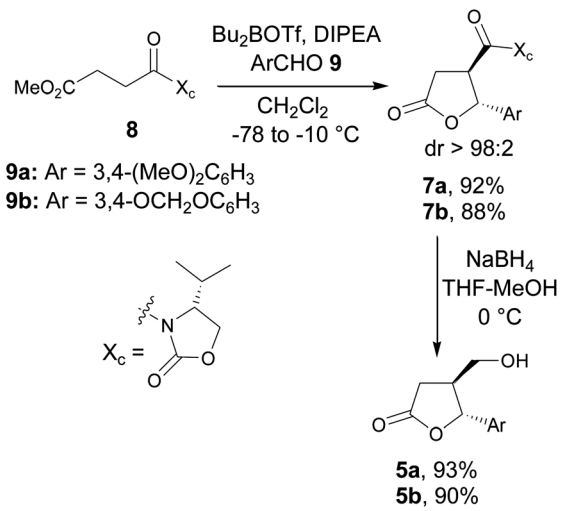


Scheme 1 Retrosynthetic analysis of 2,5-diaryl-THF lignans **1–2**.

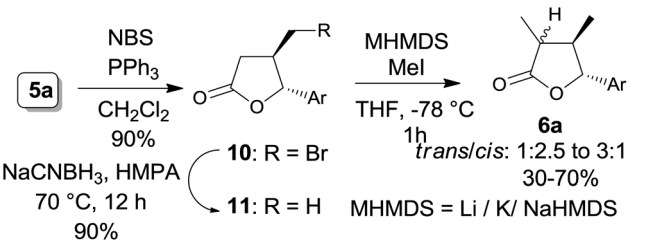
made up the essence of our investigation. The intermediate **5** was thought to be obtainable from lactone **7** by chemoselective reductive elimination of chiral auxiliary and the lactone **7** arising from *syn*-aldol reaction of *N*-succinyl oxazolidinone **8** with aldehyde **9** *via in situ* lactonization.

The study began with boron triflate mediated *syn*-aldol reaction of *N*-succinyl oxazolidinone substrate[8a] **8** with veratraldehyde and piperonal and *in situ* lactonization to get the *trans*-lactones **7a** and **7b** in 92% and 88% yields, respectively, with high diastereoselectivity (>98 : 2) (Scheme 2). The lactones **7** were treated with 1.3 equiv. of $NaBH_4$ in THF–MeOH (4 : 1) at 0 °C to get lactone alcohols **5a** and **5b**, respectively, in excellent yields. Compounds **5a** and **5b** were then used as intermediates for the synthesis of galbelgin and galbacin.

We started with the synthesis of galbelgin **1**. Our initial plan was to deoxygenate the C-3 hydroxymethyl group of **5a** to a methyl group and then attempt an alkylation with MeI. For that purpose, lactone **5a** was reacted with NBS and PPh_3 in CH_2Cl_2 solvent to get a bromo intermediate **10** which was converted to methyl lactone **11** by $NaCNBH_3$ reduction[9] (Scheme 3). With lactone **11** in our hand, we submitted it to base mediated methylation at −78 °C (Scheme 3). But our plan faced a setback when base mediated alkylation of **11** gave a mixture of **6a** and its



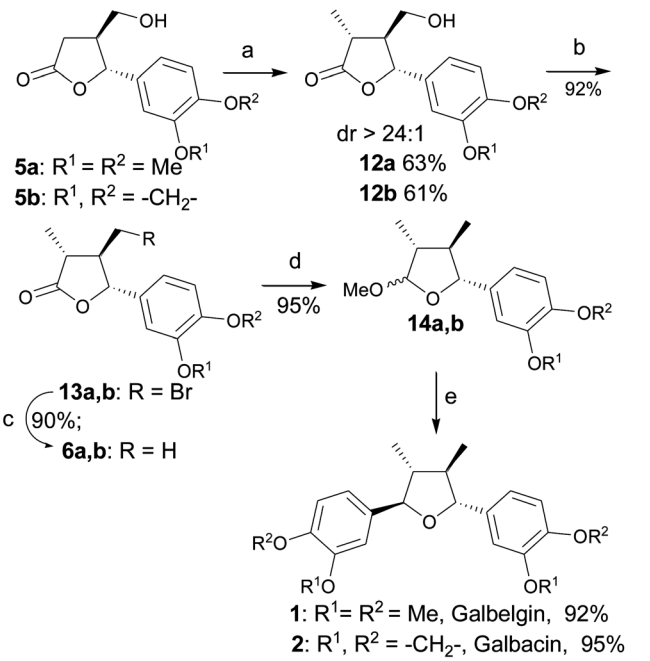
Scheme 2 Synthesis of common intermediate lactone **5a,b**.



Scheme 3 Initial route to galbelgin **1**.

C-3 epimer, which could not be separated by column chromatography. Inconsistent results were obtained with different bases used. KHMDS showed 1.5 : 1 preference for **6a**. With NaHMDS, only 30% conversion could be achieved with a 3 : 1 preference for desired isomer, whereas LHMDS gave 1 : 2.5 selectivity for desired compound.

In a revised plan, requisite conversion of CH_2OH group to CH_3 was postponed until the incorporation of a methyl group at C-3 of **5a** and **5b**. Thus protection of hydroxymethyl group, methylation, followed by deprotection and conversion of CH_2OH group to CH_3 could be an alternate path of action. However, we exploited differential reactivity of primary OH and C-3 of **5a** and **5b** to secure selective *C*-alkylation over *O*-alkylation to avoid the extra protection and deprotection steps. After several combinations, with 2.1 equiv. of LDA and 1.0 equiv. of MeI at −30 °C, we were able to get the desired *C*-methylated products **12a** and **12b** from **5a** and **5b** in 63% and 61% yields, respectively, as single isomers along with 30% recovery of



Reagents: a) LDA, MeI, THF, -30 °C; b) NBS, Ph_3P, CH_2Cl_2; c) $NaCNBH_3$, HMPA, 70 °C, d) i) DIBAL-H, THF, -78 °C, 1h; (ii) MeOH,$CH_3C(OMe)_3$, PTSA, rt; ; e) Ar-H, BF_3-OEt_2, CH_2Cl_2, -78 °C to -20 °C;

Scheme 4 Asymmetric synthesis of (−)-galbelgin **1** and galbacin **2**.

lactone alcohols **5a** and **5b**, thereby making our route as protection free method (Scheme 4). Chelation of metal–enolate with oxygen bearing a negative charge of the C-4 hydroxymethyl group might control the high diastereoselectivity of this alkylation step.

Compounds **12** *via* the intermediacy of corresponding bromo-compounds **13a** and **13b** were converted to 3,4-dimethyl lactones **6a** and **6b** by $NaCNBH_3$ reduction in 83% yields over two steps. Methyl acetals **14a** and **14b** were prepared[7b] in one pot from **6a** and **6b** by DIBAL-H reduction at −78 °C, quenching with MeOH and then reacting with trimethylorthoacetate in presence of catalytic amount of PTSA at room temperature. Finally BF_3–Et_2O mediated Friedel–Craft reaction[7b] of **14a** with 3,4-dimethoxybenzene and **14b** with 3,4-methylenedioxybenzene at low temperature (2 h at −78 °C then 10 h at −20 °C) completed the synthesis of (+)-galbelgin **1** {$[\alpha]_D^{28}$ = +80.0 (c 0.5, $CHCl_3$), lit.[7b] $[\alpha]_D^{28}$ = +80.7 (c 0.55, $CHCl_3$), lit.[1c] $[\alpha]_D^{28}$ = +83.4 (c 0.47, $CHCl_3$)}, and (+)-galbacin **2** {$[\alpha]_D^{28}$ = +110 (c 1.0, $CHCl_3$), lit.[3] $[\alpha]_D^{28}$ = +117 ($CHCl_3$)} in 39% and 36% overall yields in seven steps from *N*-succinyl-2-oxazolidinone **8** (Scheme 4). Spectral data of synthesized **1** and **2** were in good agreement with literature reports.[1c,3,7b] Unlike other literature reports,[7b,d] no epimerization was observed during the Friedel–Craft reaction of methyl acetals **14a,b**. Interestingly, this route could provide recently isolated hybrid THF-lignans having 9′-OH/OMe and 9-deoxy units (R_1 = H, R_2 = OH, OMe).[10]

In conclusion, a notably brief and diastereoselective tactic has been reported for the synthesis of all *trans*- variant of 2,5-diaryl-3,4-disubstituted tetrahydrofuran lignans from readily available reagents. The sequence utilizes boron-mediated *syn*-aldol reaction, which diastereoselectively adds the *N*-succinyl oxazolidinone to electron rich aromatic aldehydes. The chirality generated in this reaction guides the formation of four consecutive stereocenters found in target compounds **1** and **2**. The protection free total synthesis of (+)-galbelgin and (+)-galbacin has been completed with overall yields of 39% and 36%, respectively. This is the first asymmetric synthesis of (+)-galbacin.

Acknowledgements

CSIR, New Delhi is gratefully acknowledged for financial support. S. Hazra thanks UGC, New Delhi for his fellowship.

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