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Asymmetric aldol approach to dibenzylbutyrolactone lignans: synthesis of (−)-(7′*S*)-hydroxymatairesinol and (−)-(7′*S*)-hydroxyarctigenin

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ABSTRACT

A competent and general asymmetric synthesis of 7′-hydroxydibenzylbutyrolactone lignans such as (7′*S*)-hydroxymatairesinol and (7′*S*)-hydroxyarctigenin has been reported from *N*-succinyl-2-oxazolidinone in six steps where diastereoselective aldol reaction and stereoselective alkylation serve as the key steps.

Dibenzylbutyrolactone lignans constitute an important subclass of the lignan[1] family and show a broad range of biological activities such as immunoregulatory,[2] neuroprotective,[3] anticancer,[4] antitumor,[5] and anti-HIV[6] properties. In this subclass of lignans, only six compounds having hydroxyl functionality at the C-7′ position are known. Among these, (7′*S*)- and (7′*R*)-hydroxymatairesinols **3** and **4**, (7′*R*)-hydroxyarctigenin **5** and (−)-(7′*R*)-parabenzlactone **6** are plant lignans,[7] whereas (7′*R*)- and (7′*S*)-hydroxyenterolactones **7** and **8** are mammalian lignans.[8] The C-7′-epimer of compounds **5** and **6** that is, (7′*S*)-hydroxyarctigenin **9** and (7′*S*)-parabenzlactone **10**, respectively, are non-natural compounds. Among the (7′-deoxy)dibenzylbutyrolactone lignans, matairesinol **1** and arctigenin **2** (Fig. 1) are reported to be potent cytostatic agents against human leukemic HL-60 cells, with IC_{50} values of less than 100 ng/mL. In recent studies, 7′-hydroxymatairesinols are found to be the precursors to mammalian lignans, enterolactone, and hydroxyenterolactones, which display antiestrogenic and anticarcinogenic activities among other biological profiles.[9,10] Hydroxymatairesinols are also the dominant lignans in many daily cereals. Compounds **3–10**, in particular hydroxymatairesinols, have been under extensive biological and clinical studies[10,11] due to their pharmaceutical importance.

Besides their significant biological activities, these compounds have also been recognized as intermediates in the synthesis of other classes of lignans.[12] Consequently, they have been acknowledged as interesting targets by synthetic and medicinal chemists. Although the reports of the synthesis of (7′-deoxy)dibenzylbutyrolactone lignans abound in the literature,[13] the synthesis of 7′-hydroxydibenzylbutyrolactone lignans has received less effort.[14] The Sherburn group developed an elegant and general convergent synthesis of 7′-hydroxydibenzylbutyrolactone lignans via a domino radical cyclization though the synthesis of the key intermediate itself takes seven steps and uses thiophosgene.[14a] Wähälä et al. reported a general synthesis of 7′-hydroxydibenzylbutyrolactone lignans utilizing a Michael addition of lithiated dithiane to Feringa's chiral 5-menthyloxybutenolide[15] as the key step.[14b] Recently, we developed efficient methods for the asymmetric synthesis of butyrolactones[16,17] and applied these methods to synthesize a choice of butyrolactone natural products.[18] In a further application of our method,[16a] herein, we report an efficient and general synthetic protocol for the synthesis of 7′-hydroxydibenzylbutyrolactone lignans via an asymmetric aldol reaction of chiral *N*-succinyl-2-oxazolidinone and a stereoselective alkylation as the key steps

Biogenetically lignans are derived from two cinnamyl (ArC_3) units coupled by a β–β′ (8–8′) linkage. From a synthetic point, this Ar_2C_6 unit can be raised from two Ar-C and one C_4 units. Thus chiral succinyl substrate **11** was chosen as the C_4 precursor, where the first Ar-C could be introduced by an asymmetric aldol reaction with ArCHO to provide stereoselectively the C7′-hydroxy functionality and the desired stereochemistry of the lactone ring. The second Ar-C unit can be attached by a stereoselective alkylation with $Ar'CH_2X$ of the lactone obtained from the aldol product by chemoselective reduction of COX_c and lactonization (Scheme 1).

To start with the synthesis of target molecules **3** and **9**, dialkylboron-triflate-mediated *syn*-aldol reactions of *N*-succinyl-

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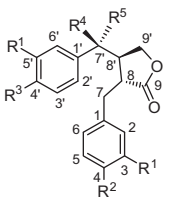


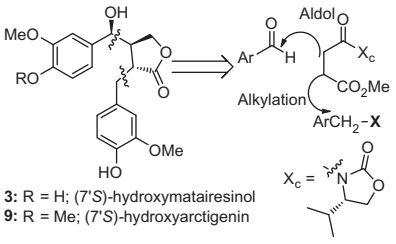
1 R^1 = OMe; R^2 = R^3 = OH; R^4 = R^5 = H matairesinol
2 R^1 = R^3 = OMe; R^2 = OH; ; R^4 = R^5 = H arctigenin
3 R^1 = OMe; R^2 = R^3 = OH; R^4 = OH; R^5 = H (7′*S*)-hydroxymatairesinol
4 R^1 = OMe; R^2 = R^3 = OH; R^4 = H; R^5 = OH (7′*R*)-hydroxymatairesinol
5 R^1 = R^3 = OMe; R^2 = OH; R^4 = H; R^5 = OH (7′*R*)-hydroxyarctigenin
6 R^1- R^2 = R^1- R^3 = OCH_2O; R^4 = H; R^5 = OH (7′*R*)-parabenzlactone
7 R^1 = OH; R^2 = R^3 = R^5 = H; R^4 = OH (7′*S*)-hydroxyenterolactone
8 R^1 = OH; R^2 = R^3 = OH; R^4 = H; R^5 = OH (7′*R*)-hydroxyenterolactone
9 R^1 = R^3 = OMe; R^2 = OH; R^4 = OH; R^5 = H (7′*S*)-hydroxyarctigenin
10 R^1- R^2 = R^1- R^3 = OCH_2O; R^4 = OH; R^5 = H (7′*S*)-parabenzlactone

Figure 1. 7′-Hydroxydibenzylbutyrolactone lignans and their 7′-deoxy analogues.

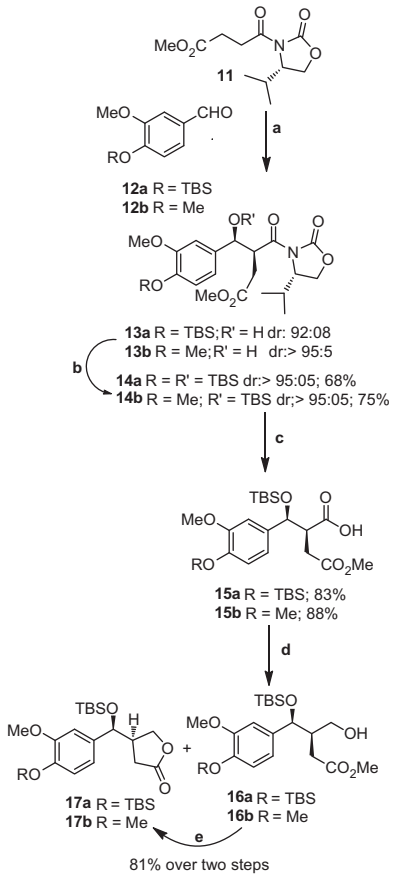
2-oxazolidinone[16a] **11** were carried out with *O*-silyl vanillin **12a** and veratraldehyde **12b**. Costly *n*-Bu_2BOTf, which afforded high diastereoselectivity (dr >95:5) for both aldehydes **12**, was replaced with cheap and easily accessible (*cy*-Hex)$_2$BOTf (prepared in the laboratory[19]) and provided the corresponding *syn*-aldol products **13a,b** with 92:8 and >95:5 diastereoselectivities, respectively (Scheme 2). The aldols **13a,b** were found to undergo lactonization with time at rt. Hence, after filter column the compounds **13a,b** were immediately protected with TBSOTf in the presence of 2,6-lutidine in CH_2Cl_2 at 5 °C to obtain the corresponding *O*-silyl aldols **14a** and **14b** as a single diastereomer after column chromatographic purification in 68% and 75% yields over two steps, respectively. Chemoselective reduction of the COX_c unit of **14** either with $NaBH_4$ or $LiBH_4$ was not successful. This problem was overcome by a two-step method. At first, the chiral auxiliary of **14a,b** was removed via $LiOH–H_2O_2$ mediated chemoselective hydrolysis in $THF–H_2O$ (5:1) to provide the corresponding acids **15a,b** in 83% and 88% yields, respectively. Acids **15a,b** were then chemoselectively reduced with BH_3·DMS in THF which provided a mixture of alcohol **16** and the lactone **17**. Subsequent treatment of the resulting mixture with a sub-stoichiometric amount of PPTS in benzene at 60 °C afforded the pure lactones **17a,b** in 81% yields over two steps.

To complete the synthesis of C7′-hydroxy lignans alkylation of **17a,b** with corresponding benzyl bromides was studied with different bases. There was no reaction with LDA in THF at different temperatures (−78 to −30 °C). The reaction also failed to provide the desired alkylated products when it was carried out with LiHMDS and KHMDS in THF and also in the presence of DMPU and TMEDA as co-solvent/additive. But the alkylation was successful when HMPA was used as a co-solvent with THF. LiHMDS-mediated alkylation of **17b** in the presence of HMPA afforded the desired product **19b** along with non-separable uncharacterized compounds. Under the same conditions, KHMDS-mediated alkylation of **17** was found to be very promising. Thus in the presence of HMPA (1.4 equiv), alkylation of lactones **17a,b** using KHMDS (1.3 equiv) with 4-silyloxy-3-methoxybenzyl bromide **18** gave the desired alkylated products **19a** and **19b** in 78% and 67% yields, respectively, with high diastereoselectivity (dr: >95:5; Scheme 3). Silyl deprotection of **19a,b** with TBAF at low temperature produced (7′*S*)-hydroxymatairesinol **3** and (7′*S*)-hydroxyarctigenin **9**, respectively, in 80% and 88% yields. Thus the synthesis of (7′*S*)-hydroxymatairesinol **3** with optical rotation **of** $[\alpha]_D^{26}$ −9.6 (*c* 1.6, THF), [lit.[14a] $[\alpha]_D^{25}$ −11.0 (*c* 4.0, THF)] and (7′*S*)-hydroxyarctigenin **9** with optical rotation of $[\alpha]_D^{26}$ −22.8 (*c* 1.1, $CHCl_3$), [lit.[14a] $[\alpha]_D^{21}$ −22.4 (*c* 1.1, $CHCl_3$) were completed in 28.5% and 31.5% overall yields in six steps from *N*-succinyl-2-oxazolidinone **11**. Spectral data and optical rotation values were in good agreement with those in the literature.[14a]

In conclusion, we have described an efficient route for the synthesis of (7′*S*)-hydroxymatairesinol and **(**7′*S*)-hydroxyarctigenin via asymmetric aldol reaction of chiral succinyl substrate followed by chemoselective hydrolysis, reduction and lactonization, and a subsequent stereoselective alkylation. Further application of these

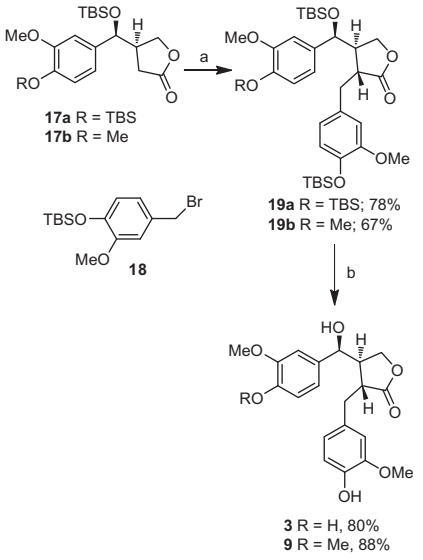


Scheme 1. Retrosynthesis of 7′-hydroxydibenzyl-butyrolactone lignans.



Reagents : (a) (*cy*-Hex)$_2$ BOTf (1.2 equiv), (*i*-Pr)$_2$NEt (1.3 equiv), OTBS-vanilin **12a** or veratraldehyde **12b** (1.4 eq), –45°C, 3 h; (b) TBSOTf (3.0 equiv), lutidine (4.0 equiv), DMAP (0.2 equiv), CH_2Cl_2, 5°C, 16 h; **14a** 68% (for two steps) and **14b** 75% (for two steps); (c) LiOH (1.5 equiv), H_2O_2 (10.0 equiv), THF-H_2O (5:1), 0°C to rt 10 h; **15a** 83% and 5**6b** 88%; (d) BH_3.Me_2S (1.5 equiv), THF,0°C to r.t, 6h; (e) PPTS (0.2 equiv), benzene, 60°C, 6 h; **17a** and **17b** 81% (for two steps).

Scheme 2. Asymmetric aldol reaction for the synthesis of lactone **17**.



Reagent : (a) KHMDS (1.3 equiv), HMPA, **18** (1.5 equiv), THF, –78°C to –54°C, 4 h; (b) *n*-Bu_4NF, THF, 0°C, **19a**, 26 h and **19b**, 12 h.

Scheme 3. Asymmetric synthesis of (7′*S*)-hydroxymatairesinol and (7′*S*)-hydroxyarctigenin.

two lignans to their 7′-deoxy analogues and the synthesis of other natural and unnatural members of this lignan family are in progress.

Acknowledgments

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Supplementary data

Supplementary data (the detailed experimental procedures, characterization data of the compounds and ^1H and ^{13}C NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.044.

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