Asymmetric Syntheses of Trisubstituted Tetrahydrofuran Lignans, Sesaminone and 4-Epidihydrosesamin

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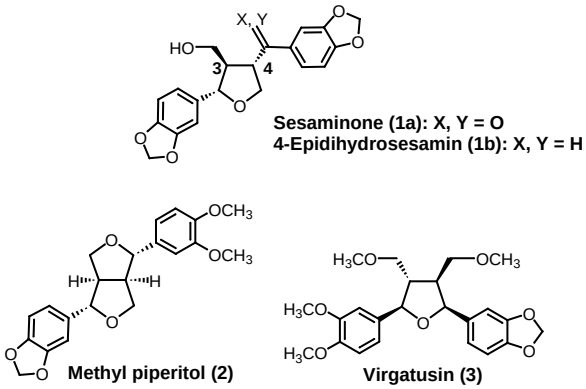
Abstract: An efficient and stereodefined process is described for the preparation of 2,3,4-trisubstituted tetrahydrofuran lignans, sesaminone and 4-epidihydrosesamin. The synthetic strategy is based on the similar chemoselective hydrogenation of functionalized lactol derivatives, elaborated through asymmetric condensation of a 4,5-*trans*-disubstituted lactone.

Key words: sesaminone, dihydrosesamin, lignan, chemoselective deoxygenation, trisubstituted γ-lactone

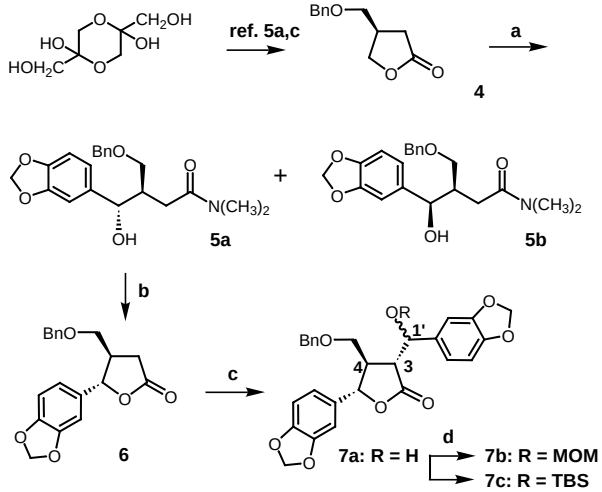
The lignan class of natural products displays a wide variety of constitution based on phenolic and *O*-heterocyclic substructures, and an equally wide range of biological activities such as antitumor activity, platelet-activating factor (PAF) antagonists, and inhibitory effects on microsomal monooxygenases in insects.[1] Due to their interesting activity as well as unique structural characteristics, they have been the subject of an extensive synthetic effort which has culminated in numerous syntheses.[2] Noteworthy members among this class of compounds are optically active tetrahydrofuran derivatives with tri- and tetrasubstituents serving as good templates for the construction of pharmacologically important furanoid groups and exhibiting various degrees of potency and specificity (Figure).[3] Since the synthesis of this type of compounds poses interesting and often unsolved problems of stereocontrol, very few synthetic strategies for the furanolignans have been reported.[4] In this connection we have also recently reported a novel and stereoselective conversion of lactones to polysubstituted cyclic ethers[5a,b] employing nucleophilic addition of Grignard reagents in the presence of $CeCl_3$ followed by the Lewis acid-induced deoxygenation and the first total synthesis of a tetrasubstituted tetrahydrofuran lignan, (-)-virgatusin (**3**).[5c] Herein we wish to communicate the asymmetric syntheses of 2,3,4-trisubstituted tetrahydrofuran lignans, sesaminone (**1a**) and 4-epidihydrosesamin (**1b**) based on chemoselectively requisite hydrogenation starting from dihydroxyacetone dimer. The former, first isolated in 1994 by Nakayama et al., revealed micromolar activity against *Enterococcus faecium*[6] and, to our knowledge, only one approach to the total synthesis has been reported to date.[7]

As shown in Scheme 1, the homochiral benzylated lactone **4** ($[\alpha]_D^{26}$ -32.1° (c 1.05, $CHCl_3$), 99% e.e.), a key compound for the synthesis of these furanoid lignans, was easily prepared in an enantiomerically pure form according to our procedure through diastereomer separation.[5a,c] For the



Figure

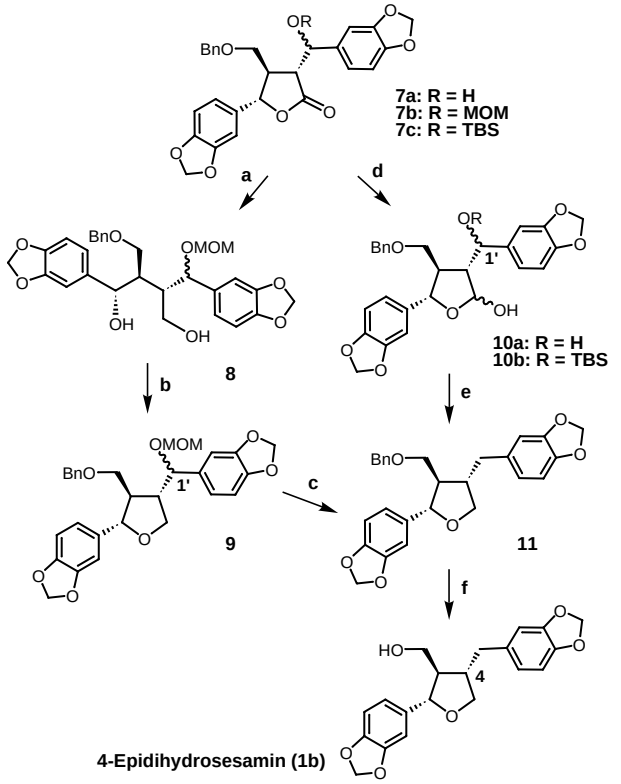
introduction of a new stereogenic center at the C-5 position in **4**, aminolysis with Me_2NH opened the lactone ring to give the amide intermediate. Then, Swern oxidation followed by the nucleophilic addition of Grignard reagent in situ was investigated under various conditions. Finally, the desired amide alcohol **5a**[8] was produced exclusively under the conditions as described in Scheme 1. These results can be explained in terms of the thermodynamically more stable Cram's non-chelation transition model. **5a** thus obtained was cyclized to afford the *trans*-substituted lactone **6** ($[\alpha]_D^{25}$+40.6° (c 1.03, MeOH)). For the purpose



cheme 1 Reagents and conditions: (a) 1. $(CH_3)_2NH$, -20 ~ 0 ºC; 7%; 2, $(COCl)_2$, DMSO, THF, then Et_3N, -78 ~ -45 ºC; 3, 3,4-methylenedioxyphenylmagnesium bromide, THF, 0 ºC; 68% (**5a**) 2 steps); trace (**5b**) (2 steps); (b) *p*-TsOH, benzene, 50 ºC; 69%; c) LiHMDS, piperonal, THF, -78 ºC; 91%; (d) MOMCl, (i-Pr)$_2$NEt, H_2Cl_2; 83% (**7b**); TBSOTf, 2,6-lutidine, CH_2Cl_2; 93% (**7c**).

of creating the third asymmetric center, treatment of **6** with piperonal in the presence of LiHMDS at -78 °C fortunately provided the 3,4-*trans* adduct **7a**[9] as a sole product in 91% yield (the ratio of stereoisomers at C-1', on the contrary, was almost 1:1) and accompanying formation of the *cis*-isomer was not observed in this reaction (determined by ^{13}C NMR and HPLC analysis).

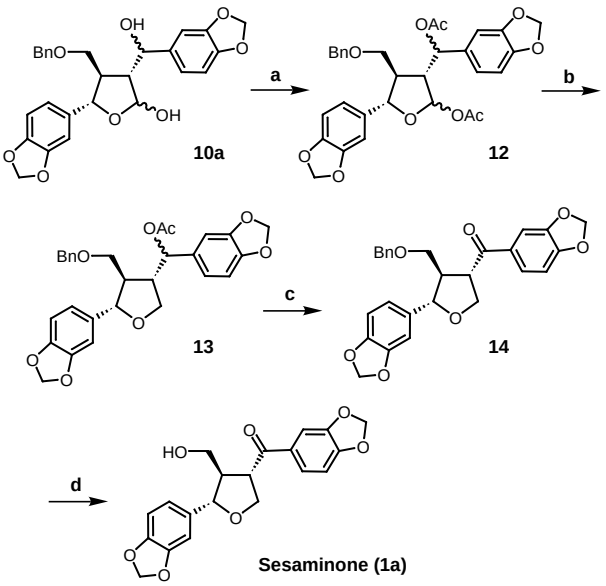
In light of the above outcome, we turned our attention to the synthesis of target compounds. To begin with, we investigated the conversion of a lactone to the tetrahydrofuran skeleton through ring-opening reaction (Scheme 2).



Scheme 2 Reagents and conditions: (a) $LiAlH_4$, THF; 76%; (b) *p*-TsCl, pyridine; 80%; (c) acidic conditions (see text); (d) DIBAL-H, THF, -78 ºC; (e) Et_3SiH, BF_3•OEt_2, CH_2Cl_2, -78 ~ -20 ºC; 64% (2 steps from **7c**); (f) Pd (black), 4.4% HCOOH-MeOH; 60%.

Thus, reduction of MOM-protected **7b** gave the diol **8** which was in turn effected by tosylation followed by simultaneous cyclization to lead to the trisubstituted furan **9** in 61% 2 steps yield. Deprotection of **9** thus obtained, however, did not proceed cleanly under any acidic conditions (aqueous HCl, *p*-TsOH/MeOH, or BF_3•OEt_2/CH_2Cl_2) to give many unknown products together with a small amount of deoxygenated **11** (10~36% yields). Next, we focused the transformation of **7** into the furanoid structure via lactol intermediates. Whereas the direct hydrogenation of **10a** obtained from the reduction of **7a** with Et_3SiH in the presence of BF_3•OEt_2[5,10] yielded the inseparable mixture even at low temperature, use of TBS-protected **10b** prepared from **7c** in analogy with **10a** changed the result and brought about the concomitantly deoxgenated and desilyloxgenated product **11** ($[\alpha]_D^{24}$+38.3° (c 0.22, MeOH)) as a predominant product. These results show that the C-1' position in **9** and **10** is quite reactive under acidic conditions. With the compound **11** in hand, the synthesis of **1b**, (4*S*)-isomer of natural dihydrosesamin isolated from *Daphne tangutica* Maxim., the Chinese drug 'Ai Tuotuo' used in the treatment of rheumatism, etc,[11] was accomplished with Pd (black) in 60% yield as a resinous mass ($[\alpha]_D^{24}$ -12.1° (c 0.92, MeOH)).[12]

On the other hand, when diacetylated **12** obtained from **10a** as shown in Scheme 3 was treated carefully with Et_3SiH in the presence of BF_3•OEt_2 in a similar manner, it reversely provided the desired furan **13** in high yield. The beneficial result on this chemoselectively reductive deoxygenation was applied to the synthesis of a natural type of sesaminone (**1a**). Thus, hydrolysis of **13** with K_2CO_3 in MeOH smoothly afforded the alcohol, which was successively oxidized with tetrapropylammonium perruthenate (TPAP)-NMO reagent,[13] leading to the desired ketone **14** ($[\alpha]_D^{25}$+10.8° (c 0.59, $CHCl_3$)) in 72% yield without racemization. Finally, **14** was subjected to deprotection with Pd (black) to complete the total synthesis of **1a** ($[\alpha]_D^{26}$ -26.3° (c 0.40, $CHCl_3$[14]), lit.[6] $[\alpha]_D^{25}$ -25.0° (c 0.140, MeOH)) in 82% yield as a crystalline solid (mp 132-133 °C, lit.[7] 133-134 °C). The spectral data of synthesized **1a** were completely identical with those of the reported natural[6] and synthetic[7] compound.



Scheme 3 Reagents and conditions: (a) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2; quant.; (b) Et_3SiH, BF_3•OEt_2, CH_2Cl_2, -78 ~ 0 ºC; 54%; (c) 1, K_2CO_3, MeOH; 76%; 2, cat. Pr_4NRuO_4(TPAP), NMO, CH_2Cl_2; 72%; (d) Pd (black), 4.4% HCOOH-MeOH; 82%.

In summary, an efficient and novel synthetic pathway starting from dihydroxyacetone dimer to two furanoid lignans has been established by means of the choice of hydroxy-protecting groups on hydrogenation. This procedure will serve for the synthesis of other lignan natural products.

Acknowledgement

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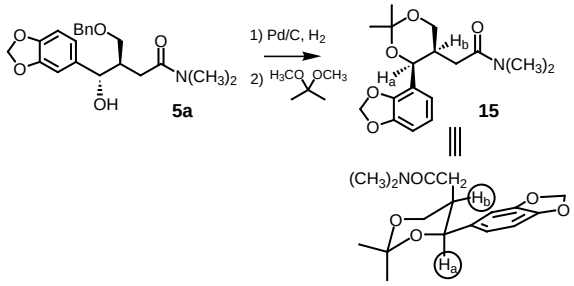
(8) The absolute stereochemistry of the newly created carbon center in **5a** was proved to be *S* by the transformation into the acetonide **15**, since the observed vicinal coupling constant ($J_{a,b}$) in **15** was 2.7 Hz, indicating the axial-equatorial relationship.



(9) The absolute configuration at the C-3 position in **7a** was unambiguously determined to be *R* based on its spectral data of the synthsized **1a**[6,7] and **1b**.[4a]

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(12) IR (cm^{-1}), ^1H and ^{13}C NMR data ($CDCl_3$) for **1b**. IR (thin film) 3220, 2779, 1504, 1245, 1099. ^1H NMR δ 1.65 (1H, bs), 1.78-2.15 (1H, m), 2.30-2.54 (1H, m), 2.65-2.85 (2H, m), 3.60 (2H, d, J = 5.4 Hz), 3.80-4.20 (2H, m), 4.57 (1H, d, J = 8.3 Hz), 5.91 (2H, s), 5.93 (2H, s), 6.55-6.89 (6H, m). ^{13}C NMR δ 39.4, 44.1, 55.6, 62.7, 72.9, 84.0, 100.8, 101.0, 106.6, 108.1, 108.2, 109.0, 119.6, 121.5, 133.9, 136.1, 146.0, 147.0, 147.5, 147.9.

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(14) Since the synthetic **1a** was a crystalline solid in analogy with the product described in the preceding synthetic report[7] and insoluble in MeOH, its specific rotation was measured in $CHCl_3$.

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