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Studies toward a synthesis of trilobatin B, a lignan from the liverwort *Bazzania trilobata*: asymmetric construction of the tetrahydrofuran segment

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Abstract—A novel and stereocontrolled process is described for the asymmetric synthesis of the tetrahydrofuran segment of a 2,3-dicarboxy-6,7-dihydroxy-1-(3′,4′-dihydroxyphenyl)-1,2- dihydronaphthalene mono-ester, trilobatin B, a lignan from the liverwort *Bazzania trilobata*. The key *cis*-substituted lactone ring was constructed in a stereoselective manner by Horner–Emmons reaction followed by the subsequent tandem Michael addition and cyclization of two types of lactol intermediates elaborated from natural sources.

Substituted tetrahydrofurans feature in many biologically potent natural products such as annonaceous acetogenins,[1] macrolides,[2] cytotoxic polyethers,[3] marine toxins,[4] pheromones,[5] and epoxylipids.[6] To fully exploit the opportunities offered by these compounds requires access to synthetic methodology capable of targeting chiral substituted tetrahydrofurans. In this connection many strategies have been explored in developing synthetic routes to these compounds and the natural products themselves. However, most methods were concerned with the construction of 2,5-disubstituted furans, while few focused on tri- and tetrasubstituted ones,[7] although the synthesis of this type of compounds poses interesting and often unsolved problems of stereocontrol. We have recently succeeded in the development of novel and stereoselective asymmetric syntheses of biologically active tri-[8a,b] and tetrasubstituted[8c,d] furan-type of natural products through elaboration of commercially available materials based on new routes exploited in this laboratory. On the other hand, new interesting lignans such as trilobatin A (**1**), methyl ester derivative of **1** (**2**), and trilobatin B (**3**) containing a polysubstituted tetrahydropyran or furan skeleton were recently isolated from the liverwort *Bazzania trilobata* in a research for the genus *Bazzania* with its several hundred species distributed in the tropics and subtropics, which represents one of the four European species, that grow in dense, widespread pads on forest ground, boggy soil, and trunks (Fig. 1).[9]

The structural and stereochemical complexity of these secondary metabolites with respect to the heterocyclic moiety coupled with their diverse and potentially useful characteristics would make them hereafter inviting targets for synthesis. In this communication we wish to report the

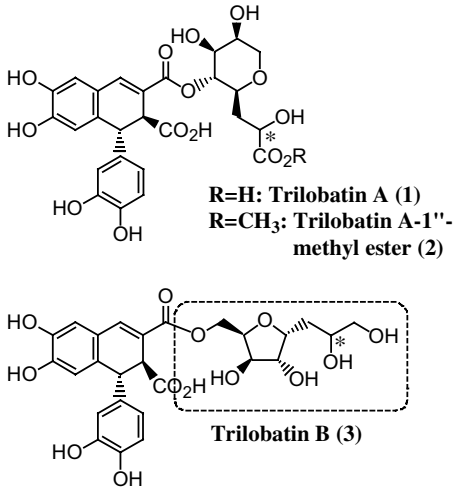

Figure 1. Trilobatins.

Keywords: Trilobatin; Substituted tetrahydrofuran; Horner–Emmons reaction; Xylose; Glucuronolactone.
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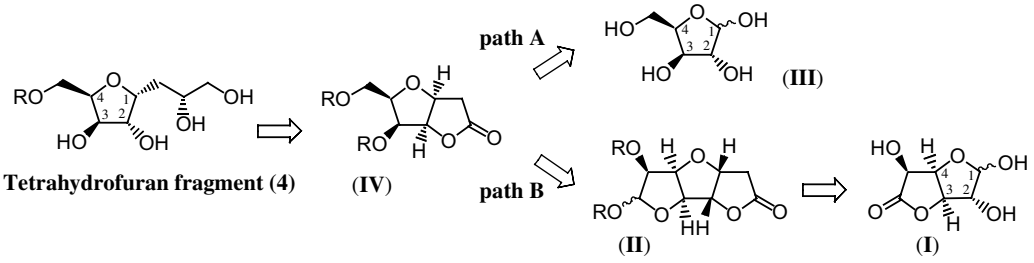


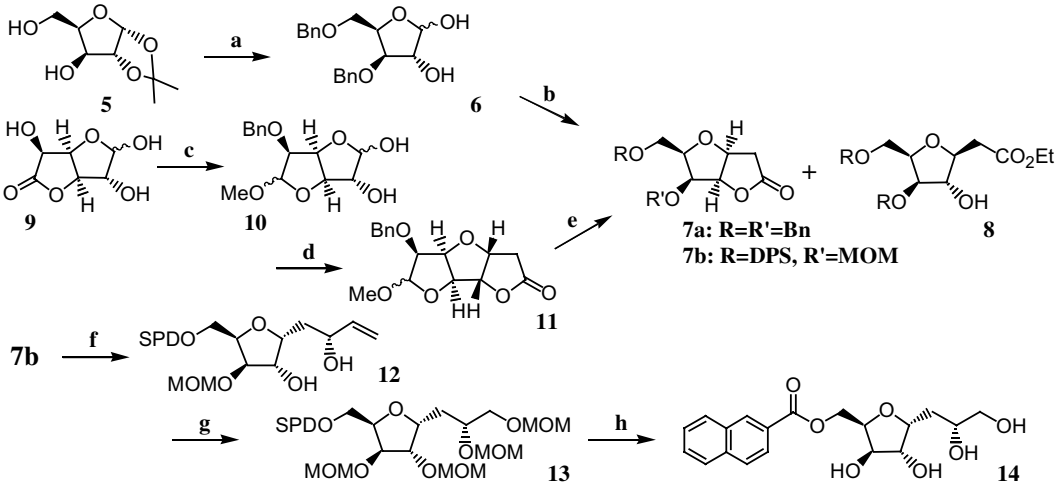
Figure 2. Retrosynthetic pathways.

details of a novel route for the stereoselective construction of the requisite tetrasubstituted tetrahydrofuran segment of trilobatin B (**3**) from two natural sources.

In formulating the synthetic plan for the core segment **4**, we recognized that nucleophilic addition of an organometallic reagent to the lactone (**IV**) followed by its transformation could undergo the desired reaction, allowing the synthesis of the target **4** (Fig. 2). In this case, D-xylofuranose (**III**) would be selected as one of the starting material, since the absolute configurations at C(2), C(3), and C(4) in **4** are the same as the configurations at the corresponding centers C(2), C(3), and C(4) of (**III**) (path A). Meanwhile, the tricyclic lactone (**II**), which would have to be set in an asymmetric transformation of the corresponding commercially available D-glucuronolactone (**I**), could be independently regarded as an another precursor of **4** (path B).

To begin with, an attempt to synthesize the crucial intermediate furanolactone **7a** based on path A is outlined in Scheme 1. Regioselectively benzyl-protected D-xylofuranose **6** obtained from reactions of benzylation and deacetalization of commercially available 1,2-*O*-isopropylidene-D-xylofuranose (**5**) was effected with ethyl diethylphosphonoacetate in the presence of base at low temperature to afford the desired *cis*-fused **7a**, $[\alpha]_D^{24}$ +12.8° (*c* 1.06, MeOH), fortunately in moderate yield through a three-step sequence such as Horner–Emmons reaction, Michael addition, and intramolecular cyclization, but disappointingly accompanied with the *trans*-furanoester **8** (2.8:1, isolated ratio).[10]

In light of the above outcome, we next focused our research on the reaction employing the same type of the bicyclic lactol derivative **10** under these Horner–Emmons reaction conditions (Scheme 1). This compound was easily prepared from readily available and inexpensive D-glucuronolactone (**9**) through a seven-step sequence in 55% overall yield as follows; thus, three hydroxyl groups of **9** were successively protected by the reactions of acetonide formation and benzylation with Ag_2O followed by exchange of the acetonide protecting group to the TBS ethers, giving the corresponding bis-TBS product.[8d] This was then submitted to the following reactions of DIBAL-H reduction, protection of the resulting hydroxyl function with CH_3I and finally desilylation to provide the desired lactol precursor **10**



Scheme 1. Reagents and conditions: (a) **1**, NaH, BnBr, cat. Bu_4N, THF; 98%; **2**, 1.8% HCl, 1,4-dioxane, 80 °C; 85%; (b) **1**, NaH, $(EtO)_2POCH_2CO_2Et$, THF, −78 to −17 °C; **2**, cat. *p*-TsOH, benzene, 50 °C; 39% (two steps) (**7a**); 14% (two steps) (**8**); (c) **1**, acetone, H_2SO_4; **2**, BnBr, Ag_2O, CH_3CO_2Et; **3**, TFA, THF; **4**, TBSCl, imidazole, DMF; **5**, DIBAL-H, THF, −78 to 0 °C; **6**, *t*-BuOK, CH_3I, cat. Bu_4NI, THF, −78 to −40 °C; **7**, Bu_4NF, THF, 0 °C; 55% (seven steps); (d) NaH, $(EtO)_2POCH_2CO_2Et$, THF, −78 to −17 °C; 87%; (e) **1**, 5% HCl, 1,4-dioxane, 80 °C; 94%; **2**, $NaBH_4$, *i*-PrOH, 0 °C; 92%; **3**, TBSCl, Et_3N, CH_2Cl_2; 98%; **4**, $(i\text{-}Pr)_2NEt$, MOMCl, CH_2Cl_2; **5**, 1.8% HCl, MeOH; 97% (two steps); **6**, Pd/C, H_2, CH_3CO_2Et; quant.; **7**, $NaIO_4$, Et_2O–H_2O (1:1), 0 °C; **8**, $NaBH_4$, THF, 0 °C; **9**, DPSCl, imidazole, CH_2Cl_2; 86% (three steps) (**7b**); (f) **1**, vinylmagnesium bromide, $CeCl_3$, THF, −78 °C; **2**, $NaBH_4$, $CeCl_3$, MeOH, −40 °C; 53% (two steps); (g) **1**, $(i\text{-}Pr)_2$ NEt, MOMCl, CH_2Cl_2; 90%; **2**, cat. OsO_4, NMO, acetone; quant.; **3**, $NaIO_4$, Et_2O–H_2O (1:1), 0 °C; **4**, $NaBH_4$, MeOH, 0 °C; **5**, $(i\text{-}Pr)_2NEt$, MOMCl, CH_2Cl_2; 88% (three steps); (h) **1**, Bu_4NF, THF, 0 °C; 91%; **2**, 2-naphthoic acid, EDCI, DMAP, CH_2Cl_2, 0 °C; quant.; **3**, 10% HCl, MeOH; 98%.

smoothly. Whereas treatment of **6** with ethyl diethylphosphonoacetate gave the separable mixture of the two compounds **7a** and **8** as mentioned above, we were delighted to find that the use of **10** brought about, in turn, the desired tricyclic lactone **11** as the single as well as the sole product in 87% isolated yield (as the anomer mixture) under the same reaction conditions. This high stereoselective performance compared with that of the analogous compound **6** would be attributed simply to the steric demand of the tricyclic core.

With these results in hand, **11** was further transformed into the desired bicyclic lactone **7b** by the routine reaction sequence of hydroxylation under acidic conditions, reduction of the corresponding lactol with $NaBH_4$ and regioselective protection of the secondary hydroxyl group with MOMCl via the TBS-ether. This was then subjected to the reactions of oxidative cleavage after hydrogenation, reduction again, and protection of the primary alcohol with DPSCl, providing the *cis*-fused **7b**, $[\alpha]_D^{26}$ +13.8° (*c* 1.03, MeOH). Then, **7b** thus obtained was effected with vinylmagnesium bromide at low temperature to afford the labile hemiketal intermediate, which was readily treated with $NaBH_4$ in the presence of $CeCl_3$ at −40 °C, leading to the corresponding vinyl alcohol **12**, $[\alpha]_D^{27}$ −9.91° (*c* 0.54, MeOH), surprisingly with complete stereoselectivity (determined by ^{13}C NMR analysis). No other stereoisomer was observed in this reaction.[11] After protection with MOMCl of **12**, the olefinic part was then cleavaged via dihydroxylation to give the aldehyde, which was successively subjected to reduction and MOM-protection again, leading to the tetramethoxymethyl ether **13**, $[\alpha]_D^{27}$ −15.9° (*c* 0.55, MeOH). Finally, **13** was effected by deprotection of DPS group with Bu_4NF and esterification with 2-naphthoic acid (the similar framework of the natural product, trilobatin B (**3**)) in the presence of EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) and DMAP,[12] followed by deprotection of the resulting tetramethoxymethyl ether to accomplish the synthesis of trilobatin B derivative **14**, $[\alpha]_D^{26}$ +32.3° (*c* 0.085, MeOH).

In summary, this work constitutes the first asymmetric synthesis of the tetrahydrofuran segment of the natural lignan product, trilobatin B, based on a stereoselectively tandem reaction sequence via Horner–Emmons reaction, stereoselective Michael addition, and intramolecular cyclization and will be widely applicable to the synthesis of other chiral tetrahydrofuran-containing natural products.

Acknowledgements

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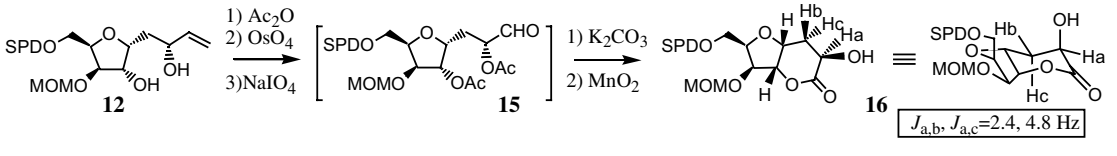
11. The absolute configuration of the newly created stereogenic center of **12** was easily characterized to be *R* after derivatization to the corresponding δ-lactone derivative through a five-step sequence as shown below:
The observed vicinal coupling constants of $J_{a,b}$ and $J_{a,c}$ were



2.4 and 4.8 Hz, respectively, which indicate the hydroxyl group in **16** could occupy the axial position. It is not clear at present, which effect (stereoelectronic or steric effect) would be more predominant on this stereoselectivity.

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