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Total Synthesis of (+)-Galbulin and Unnatural Lignans

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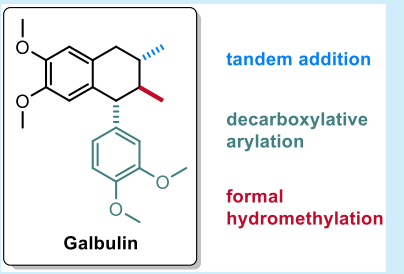
ABSTRACT: The total synthesis of (+)-galbulin was achieved in 15% yield and 99% ee over eight steps from commercially available 4-veratraldehyde. The key steps include Meyer's asymmetric tandem addition to a chiral 2-oxazoline-substituted naphthalene, a Pd-catalyzed stereospecific decarboxylative γ-arylation, and a formal anti-Markovnikov hydromethylation. In addition, five unnatural lignans were synthesized using the same synthetic strategy.



Galbulin (**1**) is a naturally occurring tetrahydronaphthalene lignan (THNL) which was isolated from the trees *Himantandra baccata* Bail., found in north Queensland, and *Himantandra belgraveana* F. Muell. found in New Guinea, at subtropical altitudes (Figure 1).[1] THNL and dihydronaphthalene lignans show broad biological activity including neurotoxic,[2] antifungal,[3] anti-HIV, anticancer,[4] and antiviral,[5] rendering these secondary metabolites highly interesting target compounds. Noteworthy, podophyllotoxin (**2**) and its glycosylated derivative etoposid (**3**) have previously been used for the treatment of external warts[6] and numerous types of cancer including lung cancer, testicular cancer, leukemia, and ovarian cancer.[7,8] The core structure of **2** is related to the backbone of galbulin, and novel strategies for accessing the latter might pave the way to prepare more complex THNL derivatives.

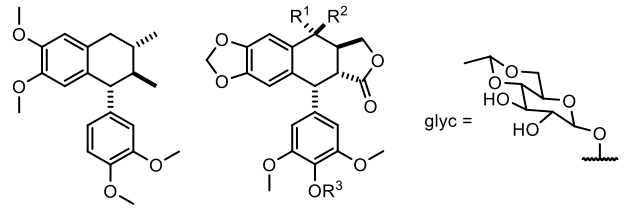
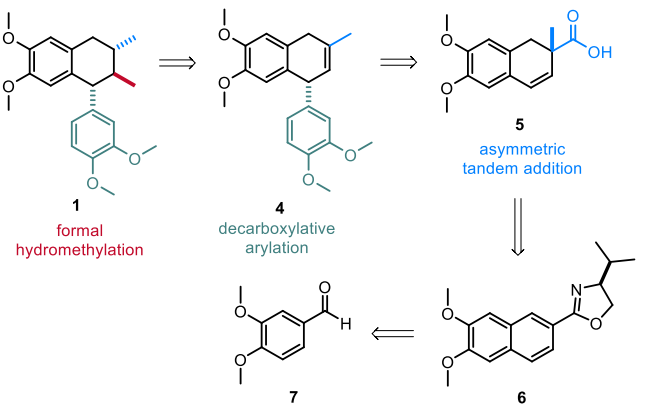


Figure 1. Galbulin (**1**), podophyllotoxin (**2**), and etoposid (**3**) are members of the THNL family and are important secondary metabolites.

To date, a variety of racemic total syntheses of galbulin (**1**) have been reported (Scheme 1).[9−12] However, to the best of our knowledge, only two enantioselective variants have been disclosed. In 2012, Hong et al. investigated an organocatalyzed domino Michael−Michael−aldol condensation in combination with a kinetic resolution as key steps to access the core structure of **1**.[13] More recently, Li et al. described an alternative strategy using an Evans asymmetric alkylation and a Sharpless epoxidation as key steps for the stereoselective construction of galbulin.[14]

Scheme 1. Retrosynthesis of Galbulin (1)



The retrosynthetic analysis of our approach is depicted in Scheme 2. The motivation for the design of the key building block **5** for our galbulin synthesis arouse from the total syntheses of podophyllotoxin[15] (**2**) of Reynolds et al. and epipodophyllotoxin[16] of Engelhardt et al. that use chiral dihydronaphthalenes as intermediates. Guided by their syntheses, we planned to prepare the dihydronaphthalene **5** using Meyers' asymmetric tandem silyl anion addition/

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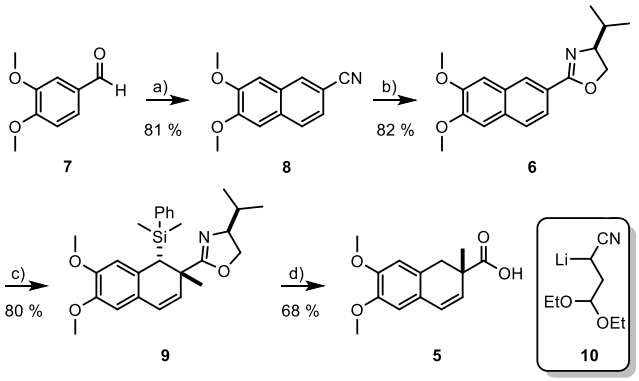
Scheme 2. Synthesis of Building Block 5[a]



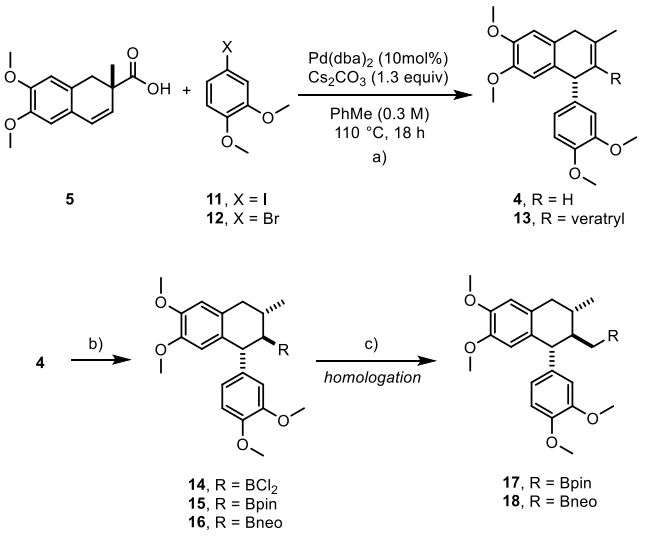
[a]Key: (a) **10** (1.2 equiv), THF, −78 to 0 °C; H_2SO_4 (20%), H_2O/MeOH;[24] (b) $HCl_{(g)}$ (bubbled through solution, 2 h), EtOH, 0 °C; (*S*)-valinol (2.0 equiv), CH_2Cl_2, 40 °C 24 h; (c) $Me_2PhSiLi$ (0.5 M in THF, 3.0 equiv), −20 °C, 24 h; Me_2SO_4 (5.0 equiv); (d) HCl (3 M in H_2O/dioxane, 1 mL/mmol of **9**).

alkylation of the appropriately substituted naphthalene derivative **6**,[17] itself accessible from commercially available 4-veratraldehyde (**7**). The second veratryl moiety should then be installed by applying our stereospecific decarboxylative γ-arylation on acid **5** to give **4**.[18−22] A formal anti-Markovnikov hydromethylation, recently introduced by our group,[23] should finally serve to install the remaining two chirality centers including the methyl group to eventually afford galbulin.

We commenced our investigations by developing a robust protocol for the synthesis of the building block **5** (Scheme 2). In analogy to a literature procedure[24] disclosed by Yamada et al., the commercially available 4-veratraldehyde (**7**) was treated with a slight excess of the alkyllithium compound **10**. The corresponding benzylic alcohol thus generated was heated with diluted aqueous sulfuric acid in methanol under reflux to engage in an intramolecular Friedel−Crafts-type reaction. Subsequent elimination of ethanol and water provided the cyanonaphthaline **8** in 81% yield. Nitrile **8** was reacted with gaseous HCl in ethanol to afford the corresponding ethyl imidate, which was further converted to the oxazoline **6** upon treatment with 2.0 equiv of (*S*)-valinol (82% yield, 99% ee). A variation of Meyers' asymmetric tandem addition strategy[17] allowed to break the aromaticity and to introduce a methyl group α to the oxazoline moiety. Hence, reaction of naphthalene **6** with an excess of dimethylphenylsilyl lithium followed by quenching of the adduct anion with dimethyl sulfate provided the β-silylated α-methylated oxazoline **9** in 80% yield as a single diastereoisomer. Hydrolysis of the oxazoline ring and simultaneous protodesilylation of the dimethylphenylsilyl group using aqueous HCl in dioxane at elevated temperature led to the carboxylic acid **5** in 68% yield and 99% ee. The ee of acid **5** was determined on its methyl ester readily prepared upon treatment of **5** with iodomethane and potassium carbonate in DMF (see the Supporting Information).

With the desired building block **5** in hand, we started to examine the stereospecific decarboxylative γ-arylation for the introduction of the veratryl ring (Scheme 3). Careful experimentation revealed that the reaction works best using 4-veratryl bromide (**12**) as the electrophile with $Pd(dba)_2$ as the catalyst (10 mol %) in toluene at 110 °C using Cs_2CO_3 (1.3 equiv) as the base. However, we found the product **4** to

Scheme 3. Decarboxylative γ-Arylation of 5 and Preparation of Galbulin Precursor 18 via a Hydroboration−Matteson−CH_2 Homologation Sequence[a]



[a]Key: (a) 4-veratryl bromide (**12**) (1.2 equiv), Cs_2CO_3 (1.3 equiv), $Pd(dba)_2$ (10 mol %), PhMe (0.3 M), 110 °C, 18 h; (b) Et_3SiH (3.0 equiv), BCl_3 (1.0 M in CH_2Cl_2, 3.0 equiv), CH_2Cl_2, 0 °C, 3 h; 2,2-dimethyl-1,3-propanediol (3.0 equiv); (c) CH_2BrI (10.0 equiv), *n*-BuLi (1.6 M in hexanes, 8.0 equiv), THF, −78 to rt; $NaOH_{(aq)}$ (0.2 M), pinacol (5.0 equiv).

be highly sensitive toward oxidation and clean isolation without decomposition was not possible. We therefore decided to carry out the planned hydroboration−Matteson−CH_2 homologation sequence on crude **4** without any further purification. Of note, decarboxylative γ-arylation with 4-veratryl iodide (**11**) provided a significant amount of undesired dihydronaphthalene **13**, resulting from Heck-type arylation of targeted **4** (ratio **4**:**13** around 1:1 at 110° and around 3:1 at 90 °C; see the Supporting Information).

Diastereoselective hydroboration of crude **4** was achieved with in situ generated Cl_2BH. To this end, triethylsilane was added to the crude mixture of **4**, and the solution was then filtered directly into a solution of boron trichloride in CH_2Cl_2 at 0 °C to give the hydroboration product **14** (dr around 5:1, see below).[25] Addition of pinacol provided the corresponding boronic ester **15**, which was again highly unstable, forcing us to continue the reaction sequence without any further purification. Unfortunately, under standard Matteson−CH_2 homologation conditions with dibromomethane as the source of the carbenoid after a permutational interconversion, **15** could not be converted to the boronic ester **17**, likely for steric reasons. Substitution of dibromomethane with chloroiodomethane led to the desired homologation, though the conversion as monitored by GC−FID was not satisfactory. We therefore switched to the sterically less bulky neopentyl boronic ester **16**, which is readily obtained from **14** upon treatment with neopentyl glycol. As already noted for the corresponding pinacol ester **15**, **16** turned out to be too labile for purification and was therefore directly used in the next step. Pleasingly, in combination with chloroiodomethane as carbenoid source, the homologation proceeded smoothly to give **18** that, unfortunately, was again very unstable. However, after transesterification with pinacol, the pinacol boronic ester **17** could be

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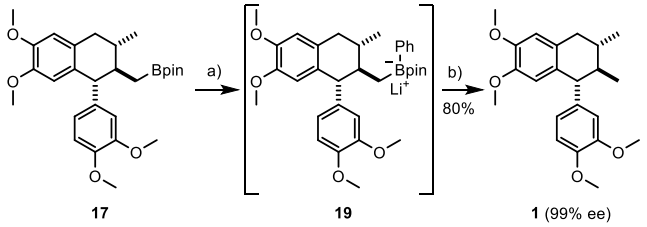
isolated in 51% overall yield with a diastereomeric ratio of 5:1 over three steps (one pot).

Final protodeboronation of **17** leading to galbulin (**1**) turned out to be highly challenging. Several known strategies[26−28] were tested on **17**; however, all these established protocols failed to deliver **1**. To our delight, the protodeboronation protocol recently developed by our group[23] was applicable to this substrate. Hence, treatment of **17** with phenyllithium gave the corresponding phenylboron−"ate" complex **19**. Subsequent oxidation under photoredox conditions and trapping of the generated primary alkyl radical with thiophenol gave (+)-galbulin (**1**) in 80% yield with a diastereomeric ratio of 5:1 and an ee of 99% (Scheme 4).

Scheme 4. Final Transformation to (+)-Galbulin (1)[a]

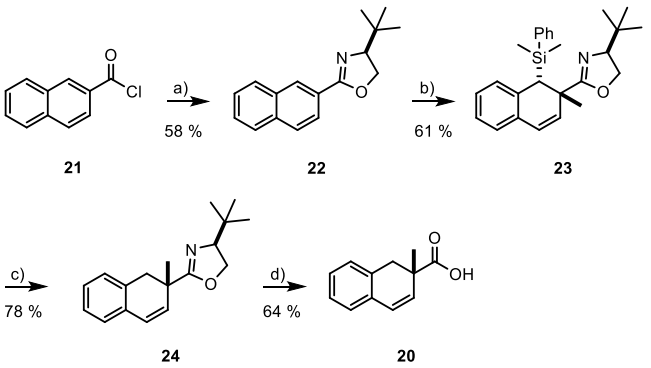


[a]Key: (a) PhLi (1.1 equiv), Et_2O, 0 °C to rt, 1 h; (b) $Ir(dFCF_3ppy)_2$-(dtbbpy)PF_6 (2 mol %), PhSH (1.1 equiv), MeOH/acetone (1:1), blue LED, rt, 18 h.

To further harvest the potential of this newly developed strategy for the synthesis of lignans, galbulin analogues were synthesized starting from the nonmethoxylated precursor **20**.

The carboxylic acid **20** was prepared in four steps, starting from commercially available 2-naphthoyl chloride (**21**) and racemic *tert*-leucinol, to give oxazoline **22** in 58% yield (Scheme 5). Tandem silylation/methylation provided **23** in

Scheme 5. Synthesis of *rac*-Carboxylic Acid (20)[a]

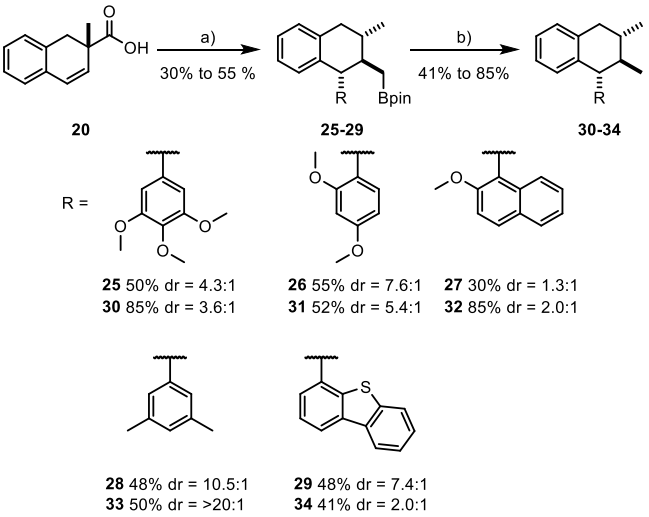


[a]Key: (a) *rac-tert*-leucinol (1.5 equiv), NEt_3 (1.5 equiv), CH_2Cl_2, rt, overnight; $SOCl_2$, 3 h; (b) $Me_2PhSiLi$ (0.9 M in THF, 3.0 equiv), −20 °C, 24 h; MeI (4.0 equiv); (c) TBAF (6.2 equiv), THF, rt, overnight; (d) H_2SO_4, dioxane/H_2O (4:1).

61% yield. Hydrodesilylation with TBAF in THF delivered the oxazoline **24** (78%), which was hydrolyzed under acidic conditions to afford the key carboxylic acid **20** (64%), ready for further diversification toward lignans.

Decarboxylative γ-arylation was achieved using five different aryl iodides (Scheme 6). As for the galbulin synthesis, these intermediates turned out to be sensitive toward air oxidation and the subsequent hydroboration−homologation was there-

Scheme 6. Synthesis of Unnatural Lignans from Acid 20[a]



[a]Key: (a) aryl iodide (1.1 equiv), Cs_2CO_3 (1.2 equiv), $Pd(dba)_2$ (20 mol %), PhMe (0.3 M), 110 °C, 18 h, then Et_3SiH (3.0 equiv), BCl_3 (1.0 M in CH_2Cl_2, 3.0 equiv), CH_2Cl_2, 0 °C, 3 h; 2,2-dimethyl-1,3-propanediol (5.0 equiv). then CH_2ICl (10.0 equiv), *n*-BuLi (1.6 M in hexanes, 8.0 equiv), THF, −78 to rt.; $NaOH_{(aq.)}$ (0.2 M), pinacol (5.0 equiv); (b) PhLi (1.1 equiv), THF, −78 °C to rt, 1 h, then $Ir(dFCF_3ppy)_2$-(dtbbpy)PF_6 (2 mol %), PhSH (1.1 equiv), MeOH/acetone (1:1), blue LED, rt, 18 h.

fore conducted without further purification to give the boronic esters **25**−**29** in 30−55% isolated yields with diastereomeric ratios varying from 1.3:1 to 10.5:1. Our protodeboronation protocol afforded the lignans **30**−**34** in moderate to good overall yields (41%−85%). The protodeboronation is a stereospecific process and the varying diastereoisomeric ratio in **30**−**34** as compared to the starting boronic esters **25**−**29** is caused either by the different reactivity of the two isomeric esters toward the protodeboronation or by isomer enrichment during purification.

In summary, we have reported an enantioselective total synthesis of (+)-galbulin (**1**) starting from commercially available 4-veratraldehyde (**7**). A Meyers' asymmetric tandem addition, a highly stereospecific γ-arylation, and a diastereoselective formal anti-Markovnikov hydromethylation were successfully used as key steps. The same strategy was also applied to the synthesis of a small series of unnatural lignans **30**−**34**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02294.

General experimental procedures and characterization of compounds including NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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