A Concise Asymmetric Synthesis of (–)-Virolin, (–)-Surinamensin, (–)-Raphidecursinol B and (–)-Polysphorin

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Abstract: Highly concise and general asymmetric syntheses of biologically important natural (–)-8,4′-oxyneolignans [(–)-virolin, (–)-surinamensin, (–)-raphidecursinol B, and (–)-polysphorin] are reported. The key step in the synthesis is the Evan's *syn*-aldol reaction to achieve the adducts with the desired stereochemistry. The four biologically important plant metabolites were synthesized using two common intermediates.

Key words: asymmetric synthesis, chiral auxiliary, aldol reaction, natural products, oxyneolignans

Virolin (**I**), surinamensin (**II**), raphidecursinol B (**III**), and polysphorin(**IV**) are members of the 8,4′-oxyneolignan family[1] and exhibit rich and diverse biological properties. These compounds, whose common structural feature is the presence of 1-aryl-2-aryloxypropanol moiety, occur in *Myristicaceae* and other primitive plant families in neotropical regions and are often isolated in racemic forms.[2] While raphidecursinol B (**III**) and polysphorin (**IV**) show antimalarial activity,[2c,3] virolin (**I**) and surinamensin (**II**) exhibit activity against leishmaniasis.[2b,4] They are also reported to possess antifungal,[5] antioxidant,[6] and antischistosomal[7] activities (Figure 1). The pharmaceutically important biological profiles coupled with the scarce availability from natural sources prompted many groups to attempt the laboratory synthesis of this compound class,[2a,b,8–11] often as racemates. Synthetic methods also provide the opportunity to expand the diversity by generating non-natural congeners. Usually the aromatic rings of these compounds are highly oxygenated, containing hydroxyl, methoxy, or methylenedioxy groups. One of the rings also carries an alkenyl – either an (*E*)-propenyl or allyl – pendent group.

The first asymmetric route to (–)-polysphorin and analogues was reported by Prof. Ley's group making use of polymer-supported reagents, catalysts, and scavengers.[9] Subsequently Curti et al. described another asymmetric route employing (*S*)- or (*R*)-methyl lactate as the chiral sources.[10] We have been pursuing antimalarial drug candidates, because of the re-emergence of the disease with strains resistant to traditionally administered quinoline class of drugs, most notably chloroquine. Polysphorin and structurally related compounds emerged attractive as they target the pathogen in the hepatic stages of the infection,

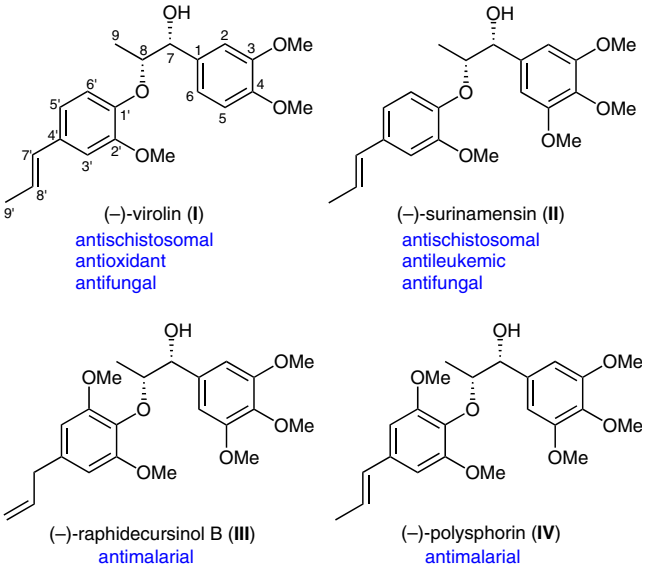

Figure 1 Structures of (–)-virolin (**I**), (–)-surinamensin (**II**), (–)-raphidecursinol B (**III**), and (–)-polysphorin (**IV**)

which is complementary to the drugs targeting the erythrocytic stages.[3] The preliminary results of our research endeavors form the subject matter of the present communication, wherein we report the asymmetric synthesis of (–)-virolin (**I**), (–)-surinamensin (**II**), (–)-raphidecursinol B (**III**), and (–)-polysphorin (**IV**) employing Evans *syn*-aldol reaction as the common strategy.

Our strategy is depicted retrosynthetically in Scheme 1. It was envisaged that the reductive deoxygenation of the primary hydroxyl group resulting from the auxiliary-assisted aldol reaction of suitable substrates would afford the 1-aryl-2-aryloxypropanol moiety in the required stereochemistry. The auxiliary-linked chiral precursor could easily be generated from aryloxyacetic acid, which in turn could be readily prepared from commercially available starting materials. A closer look at the target structures reveals that all the four natural compounds could be arrived at using only two different aryloxyacetic acids as virolin and surinamensin share the same B-ring motif while a simple isomerization of the B-ring double bond in raphidecursinol B would afford polysphorin.

The B-ring precursor for virolin and surinamensin was assembled starting from vanillin (**1**). The alkylation of the phenolic group with ethylbromoacetate afforded the α-aryloxy ester derivative (Scheme 2). The introduction of the propenyl group under Wittig conditions resulted in a

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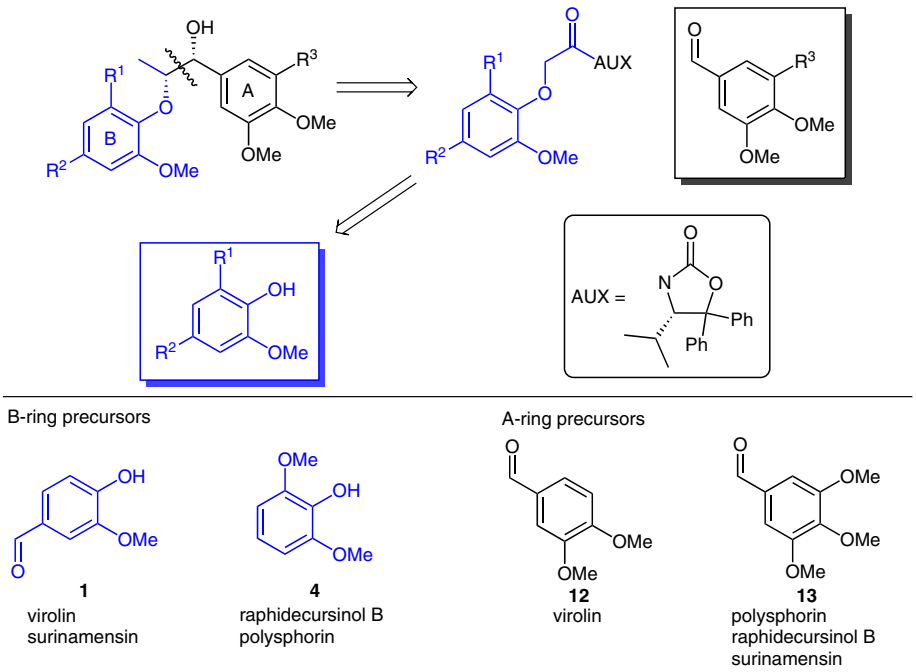
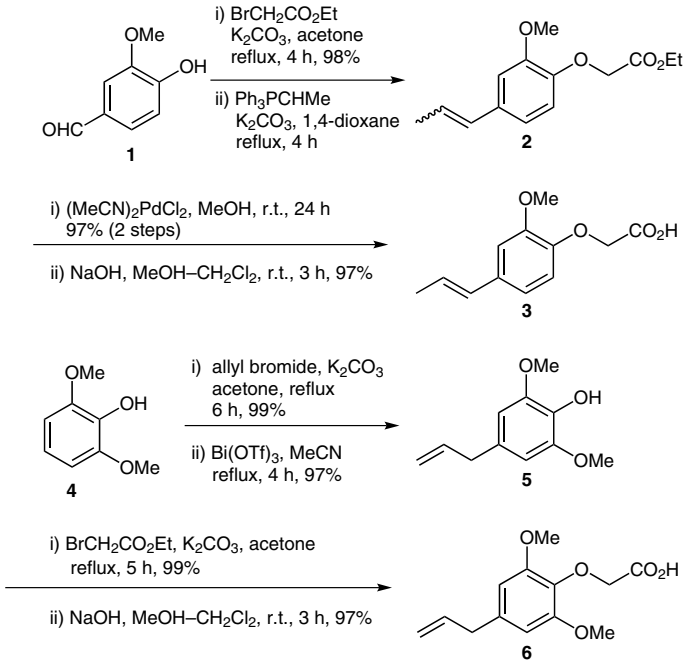


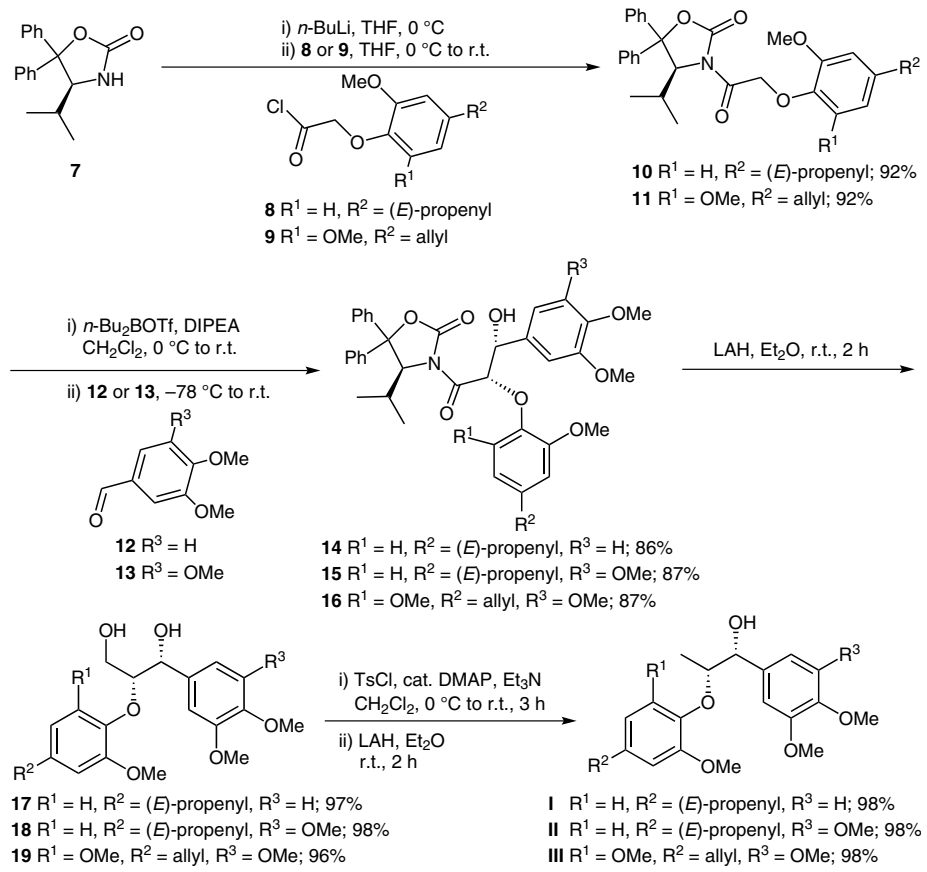
Scheme 1 Retrosynthetic strategy and the building blocks

mixture of *E*- and *Z*-isomers **2**,[12] which was converted into the exclusive *E*-form using $(MeCN)_2PdCl_2$ in methanol at room temperature.[13] Subsequent hydrolysis of the ester moiety yielded the requisite aryloxyacetic acid **3**.[14] The yield of the four-step procedure is 92%. For the generation of B-ring building block of polysphorin and raphidecursinol B, 2,6-dimethoxyphenol (**4**) was initially allylated, and the resultant allylaryl ether was subjected to Claisen rearrangement to afford 4-allylphenol derivative **5** (Scheme 2).[15] Alkylation of the phenol derivative with ethyl bromoacetate followed by the hydrolysis provided the corresponding aryloxyacetic acid derivative **6** (92% for four steps).

With both the A- and B-ring counterparts at our disposal, we proceeded to the crucial auxiliary-assisted aldol reaction. A thorough literature scouting of the prior art convinced us the use of valine-based chiral oxazolidinone **7** as the auxiliary since it affords the aldol adducts in consistently high yields and enantioselection. It could also be readily prepared from inexpensive starting materials.[16]

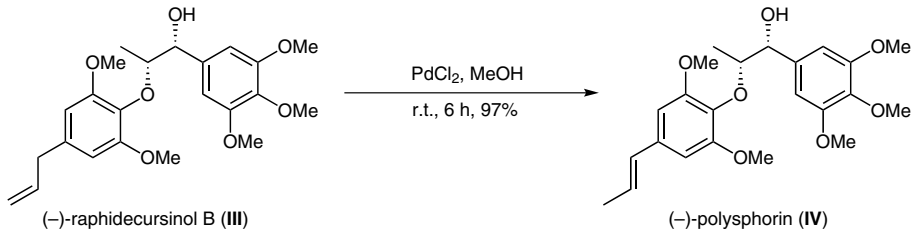


Scheme 2 Preparation of intermediates **3** and **6**



Scheme 3 Synthesis (–)-virolin (**I**), (–)-surinamensin (**II**), and (–)-raphidecursinol B (**III**)

Aryloxyacetic acid derivatives **3** and **6**, prepared as detailed earlier, were attached to the auxiliary following the literature reported procedures.[16] Thus the reaction of lithium salt of the auxiliary with aryloxyacid chlorides, prepared from **3** and **6**, afforded the corresponding *N*-acylimidazolidinone derivatives **10** and **11** in excellent yields (Scheme 3). The aldol reaction of the boron enolates, generated from imidazolinones **10** and **11** by treating with *n*-dibutylborontriflate in the presence of Hünig's base[17] afforded only a single diastereomer (the ^{1}H NMR spectra of the crude reaction samples show signals corresponding to only one diastereomer with a de >99%).[17–19] Further NMR analysis of the isolated, pure sample confirmed the diastereomer to be the *syn*-aldol adduct. The coupling constants ($J_{\alpha,\beta}$ of the methyne protons of the newly formed bond) of the aldol adducts **14**, **15**, and **16** were found to be 3.77, 3.96, and 6.00 Hz, respectively, which falls within the range 2–6 Hz reported for *syn*-aldol adducts.[18,19] The reductive removal of the auxiliary afforded the diols **17**, **18**, and **19** in near quantitative yields.[16] The last step in our synthetic sequence is the deoxygenation of the primary hydroxyl group from the diols **17**, **18**, and **19**. This is achieved by the tosylation of the primary OH group followed by the reductive removal of the tosylate moiety to afford (–)-virolin (**I**), (–)-surinamensin (**II**), and (–)-raphidecursinol B (**III**). The spectral characteristics of the natural products prepared compare favorably with the literature-reported spectral data (see Supporting Information). Structural integrity of **I**, **II**, and **III** was further confirmed by the specific rotation analysis, which matched well with literature-reported values. Employing this protocol, the overall yields achieved for the final compounds (–)-virolin, (–)-surinamensin, and (–)-raphidecursinol B are 70%, 75%, and 67%, respectively, starting from **1** and **4**.



Scheme 4 Synthesis of (–)-polysphorin (**IV**)

Finally, the synthesis of (–)-polysphorin (**IV**) was achieved by the isomerization of the double bond in (–)-raphidecursinol B (**III**, 97%). The double-bond isomerization, carried out in the presence of catalytic $PdCl_2$ in MeOH,[10] afforded only the *E*-isomer as reported in the literature (Scheme 4).

In conclusion, we have achieved an efficient and concise asymmetric total synthesis of biologically important plant metabolites (–)-virolin, (–)-surinamensin, (–)-raphidecursinol B, and (–)-polysphorin using two common intermediates, beginning from readily available starting materials. These structurally very similar compounds differ in their biological properties depending on the degree of oxygenation of phenyl rings as well as the nature of the alkene chain present. This augers well for the development of novel drug candidates employing structure–activity relationship (SAR) studies, especially since these compounds exhibit useful biological properties. Synthesis of non-natural congeners of the compounds with a view to obtaining molecules with better biological profiles, using the synthetic strategy presented in this communication, is currently being pursued.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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