JOC*Article*

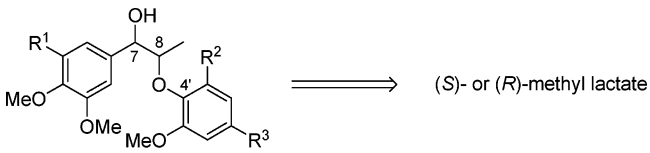
Streamlined, Asymmetric Synthesis of 8,4′-Oxyneolignans

Claudio Curti,[§] Franca Zanardi,*[,§] Lucia Battistini,[§] Andrea Sartori,[§] Gloria Rassu,[‡] Luigi Pinna,[†] and Giovanni Casiraghi*[,§]

Dipartimento Farmaceutico, Università degli Studi di Parma, Viale G.P. Usberti 27A, I-43100 Parma, Italy, Istituto di Chimica Biomolecolare del CNR, Traversa La Crucca 3, I-07040 Li Punti, Sassari, Italy, and Dipartimento di Chimica, Università degli Studi di Sassari, Via Vienna 2, I-07100 Sassari, Italy

franca.zanardi@unipr.it

Received July 21, 2006



R^1, R^2 = OMe, H; R^3 = (*E*)-propenyl, allyl

Highly direct, modular syntheses of several natural 8,4′-oxyneolignans [(−)-**1**, (+)-**1**, (−)-**2**, and (−)-**3**] and some related variants [(−)-**26**, (+)-**26**, (+)-**27**, and (−)-**28**] are reported. Utilizing (*S*)- or (*R*)-methyl lactate as the chiral sources, two complementary *syn*- or *anti*-oriented routes were designed, encompassing nine and five steps, which were carried out to deliver the targets in an enantiomerically pure form. The embodiment of the two independent aryl and aryloxy moieties onto the lactate frame was performed according to a diversity-oriented protocol from the common precursors, aldehydes **6** and *ent*-**6** for the *syn*-oriented routes and mesyl esters **19** and *ent*-**19** for the *anti*-oriented routes. These syntheses set the stage for the generation of a wide and diverse repertoire of 8,4′-oxyneolignan compounds and the broad biological interrogation of its members.

Introduction

Lignans and neolignans comprise a large group of secondary plant metabolites which are biochemically related to the shikimic acid pathway.[1] These products are formed in nature by oxidative coupling of two phenylpropanoid units (e.g., eugenol, coniferyl alcohol, isoeugenol), whose site of connection determines their classification into lignans (8,8′-linkage), neolignans (all other C,C′-linkages), and oxyneolignans (C−O−C′-linkages).[2] Among the 8,4′-oxyneolignan subgroup, various naturally occurring members, such as polysphorin (**1**),[3] raphidecursinol B (**2**),[3b] virolin (**3**),[4] and surinamensin (**4**)[4,5] (Figure 1), were isolated from the Myristicaceae and other primitive plant families in neotropical regions, which displayed interesting and varied biological properties spanning from anti-malarial[3b,6] to anti-fungal,[7] anti-leishmanial,[5,8] anti-oxidant,[9] and anti-schistosomial[10] activities.

The chemical characteristics of these oxyneolignans, featuring a propane diol backbone equipped with aryl and aryloxy components, offer the possibility of achieving a high level of

[§] Università degli Studi di Parma.
[‡] Istituto di Chimica Biomolecolare.
[†] Università degli Studi di Sassari.

(1) (a) Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75−96. (b) Saleem, M.; Kim, H. J.; Ali, M. S.; Lee, Y. S. *Nat. Prod. Rep.* **2005**, *22*, 696−716. (c) Ma, C.; Zhang, H. J.; Tan, G. T.; Hung, N. V.; Cuong, N. M.; Soejarto, D. D.; Fong, H. H. S. *J. Nat. Prod.* **2006**, *69*, 346−350. (d) Apers, S.; Vlietinck, A.; Pieters, L. *Phytochem. Rev.* **2004**, *2*, 201−207.

(2) Moss, G. P. *Pure Appl. Chem.* **2000**, *72*, 1493−1523.

(3) (a) Ma, Y.; Han, G. Q.; Li, C. L.; Arison, B. H.; Hwang, S. B. *Acta Pharm. Sin.* **1991**, *26*, 345−350. (b) Zhang, H.-J.; Tamez, P. A.; Hoang, V. D.; Tan, G. T.; Van Hung, N.; Xuan, L. T.; Huong, L. M.; Cuong, N. M.; Thao, D. T.; Soejarto, D. D.; Fong, H. H. S.; Pezzuto, J. M. *J. Nat. Prod.* **2001**, *64*, 772−777.

(4) Barata, L. E. S.; Baker, P. M.; Gottlieb, O. R.; Ruveda, E. A. *Phytochemistry* **1978**, *17*, 783−786.

(5) Barata, L. E. S.; Santos, L. S.; Ferri, P. H.; Phillipson, J. D.; Paine, A.; Croft, S. L. *Phytochemistry* **2000**, *55*, 589−595.

(6) (a) Ridley, R. G. *Nature* **2002**, *415*, 686−693. (b) Miller, L. H.; Baruch, D. I.; Marsh, K.; Doumbo, O. K. *Nature* **2002**, *415*, 673−679.

(7) (a) Zacchino, S.; Rodríguez, G.; Pezzenati, G.; Orellana, G. *J. Nat. Prod.* **1997**, *60*, 659−662. (b) Zacchino, S.; Rodríguez, G.; Santocchia, C.; Pezzenati, G.; Giannini, F.; Enriz, R. *J. Ethnopharmacology* **1998**, *62*, 35−41. (c) Pinheiro, A. A. C.; Borges, R. S.; Santos, L. S.; Alves, C. N. *J. Mol. Struct. (THEOCHEM)* **2004**, *672*, 215−219.

(8) (a) Andreazza Costa, M. C.; Takahata, Y. *J. Mol. Struct. (THEOCHEM)* **2003**, *625*, 257−263. (b) Aveniente, M.; Barata, L. E. S.; Santos, E. C. T.; Pinto, E. F.; Rossi-Bergmann, B. *24ª Reuniñao Anual da SBQ*; Abstract Book, MD 051, 2001. (c) Andreazza Costa, M. C.; Takahata, Y. *J. Mol. Struct. (THEOCHEM)* **2003**, *638*, 21−25.

10.1021/jo061521t CCC: $33.50
Published on Web 10/06/2006

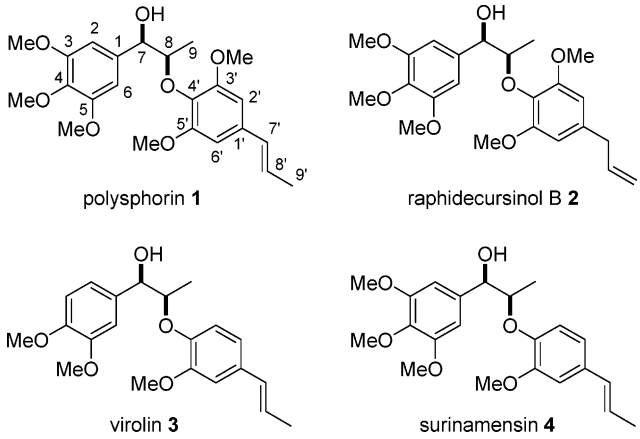


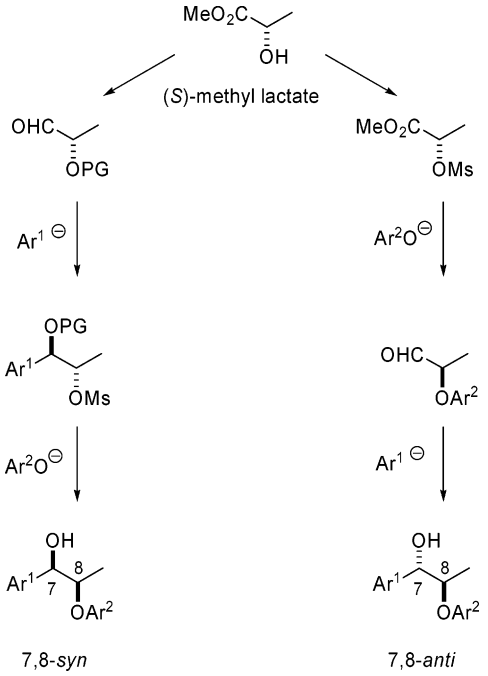
FIGURE 1. Representative members of the 8,4′-oxyneolignan family and conventional atom numbering.[2]

structural diversity, as both the aromatic rings may possess varying numbers and types of substituents (e.g., OH, OMe, O−CH_2−O, (*E*)-propenyl, allyl) and the molecule may sustain four different stereodispositions.

Nature itself offers an extensive library of representatives of this compound class, which the organic synthesis practitioner may faithfully reproduce or, even, expand upon by adding a huge number of non-natural variants. However, obtaining supplies from Nature is an arduous task due to the scarce quantity of isolable compounds and the fact that most of the isolated neolignans reported present themselves as racemic mixtures.[3,11,12] On the other hand, the alternative of obtaining useful quantities of enantiopure materials via synthesis has not been carefully pursued. Most of the pioneering synthetic studies have given rise to racemic mixtures of *syn*- and *anti*-configured products,[4,5,7a,9a,13,14] while existing enantioselective routes appear limited by scarce overall efficiency, poor diastereo- and enantioselective processes,[14] and somewhat confusing stereochemical assignments.[15] More recently, a noteworthy enantioselective synthesis of both enantiomers of polysphorin and analogues was reported,[16] shedding light on the true absolute configuration of these compounds.

Herein, the design and development of a new, truly general and modular asymmetric route to all four possible stereoisomers of the 8,4′-oxyneolignan compound class is outlined and exemplified by the nine-step synthesis of *syn*-configured (7*R*,8*R*)-polysphorin (−)-**1**, (7*S*,8*S*)-polysphorin (+)-**1**, (7*R*,8*R*)-raphidecursinol B (−)-**2**, (7*R*,8*R*)-virolin (−)-**3**, and the five-step synthesis of the corresponding *anti*-configured counterparts (−)-**26**, (+)-**26**, (+)-**27**, and (−)-**28**.

SCHEME 1. Synthesis Plan to the 7,8-*syn* and 7,8-*anti*-Configured Targeted 8,4′-Oxyneolignans



Results and Discussion

Synthesis Planning. Arrival at the targeted oxyneolignan compounds was planned from two directions that are stereochemically complementary. In the first approach (Scheme 1), the aryl module Ar^1 is embodied first into the lactate frame (nucleophilic carbonyl addition), followed by aryloxylation with a second aryloxy module Ar^2O (nucleophilic displacement). In the event, the nature of the two operations, as well as their sequence, should dictate the stereochemical outcome of the reaction, possibly resulting in production of 7,8-*syn*-configured compounds (*R*,*R* absolute configuration from *S*-lactate, and vice versa).

In the alternative route, the aryloxylation (Ar^2O) precedes arylation (Ar^1) so as to generate the product with a 7,8-*anti* configuration (*S*,*R* absolute configuration from *S*-lactate, and vice versa). Of course, for this issue to be realized, the stereochemical bias of the two critical reactions has to be equally operative in both approaches, that is, a Felkin-type mode for the carbonyl aryl addition and a configuration reversal for the aryloxy displacement.

Should this tactical move prove truly feasible, access to all four stereoisomers of a given oxyneolignan target should be close at hand by simply employing cheap and commercially available (*S*)- and (*R*)-methyl lactate as starting materials. We wish to put forward our evidence for this school of thought.

Synthesis of *syn*- and *anti*-Configured 8,4′-Oxyneolignans. The *syn*-oriented route to (−)-polysphorin (−)-**1**, (−)-raphidecursinol B (−)-**2**, and (−)-virolin (−)-**3** (Scheme 2) commenced with (*S*)-methyl lactate (−)-**5**, which was quickly transformed into protected lactaldehyde **6** by three highly productive and

(9) (a) Kónya, K.; Varga, Zs.; Antus, S. *Phytomedicine* **2001**, *8*, 454−459. (b) Ahn, B.-T.; Lee, S.; Lee, S.-B.; Lee, E.-S.; Kim, J.-G.; Bok, S.-H.; Jeong, T.-S. *J. Nat. Prod.* **2001**, *64*, 1562−1564.

(10) Alves, C. N.; Pereira Barroso, L.; Santos, L. S.; Jardim, I. N. *J. Braz. Chem. Soc.* **1998**, *9*, 577−582 and references therein.

(11) Hada, S.; Hattori, M.; Tezuka, Y.; Kikuchi, T.; Namba, T. *Phytochemistry* **1988**, *27*, 563−568.

(12) In effect, most of the in vitro and in vivo biological evaluations reported so far were effected on racemic mixtures.

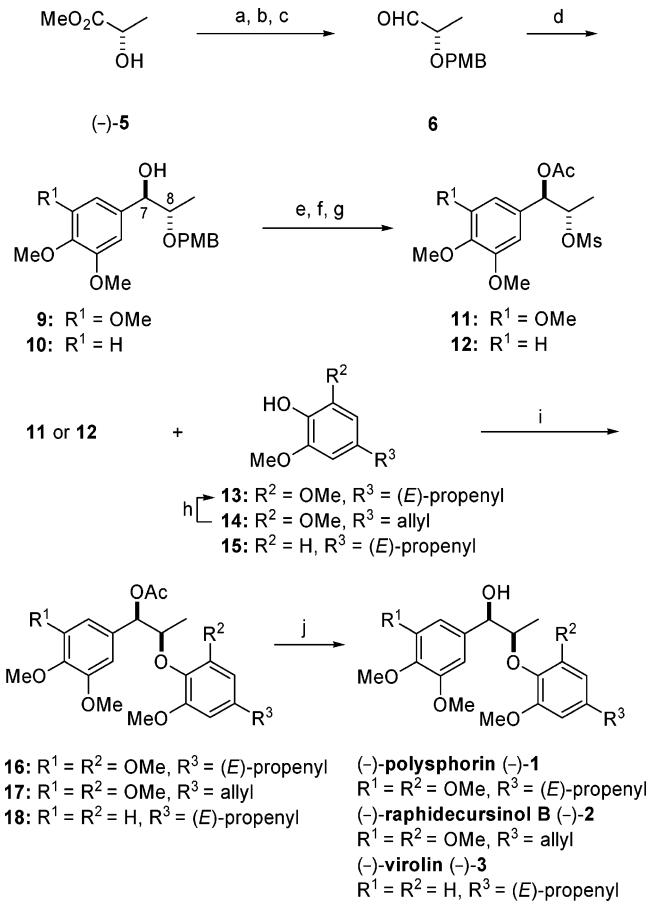
(13) Zacchino, S. A.; Badano, H. *J. Nat. Prod.* **1985**, *48*, 830−832.

(14) (a) Sefkow, M. *Synthesis* **2003**, 2595−2625. (b) Zacchino, S.; Badano, H. *J. Nat. Prod.* **1988**, *51*, 1261−1265. (c) Zacchino, S.; Badano, H. *J. Nat. Prod.* **1991**, *54*, 155−160. (d) Li, K.; Helm, R. F. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2425−2526. (e) Chen, X.; Ren, X.; Peng, K.; Pan, X.; Chan, A. S. C.; Yang, T.-K. *Tetrahedron: Asymmetry* **2003**, *14*, 701−704.

(15) (a) Zacchino, S. *J. Nat. Prod.* **1994**, *57*, 446−451. (b) Shimomura, H.; Sashida, Y.; Oohara, M. *Phytochemistry* **1987**, *26*, 1513−1515.

(16) (a) Lee, A.-L.; Ley, S. V. *Org. Biomol. Chem.* **2003**, *1*, 3957−3966. (b) Zanardi, F.; Appendino, G.; Casiraghi, G. *Chemtracts Org. Chem.* **2004**, *17*, 587−592.

SCHEME 2. Synthesis of 7,8-*syn*-Configured 8,4′-Oxyneolignans[a]



[a] Reagents and conditions: (a) $PMBOC(CCl_3)$═NH, $Sc(OTf)_3$, toluene; (b) $LiAlH_4$, THF; (c) $(COCl)_2$, DMSO, CH_2Cl_2, −80 °C, then Et_3N (91%, three steps); (d) 5-bromo-1,2,3-trimethoxybenzene (**7**) or 4-bromo-1,2-dimethoxybenzene (**8**), ^{t}BuLi, THF, −85 °C (**9**: 80%, dr = 83:17, **10**: 80%, dr = 82:18); (e) Ac_2O, Et_3N, DMAP, MeCN; (f) DDQ, wet CH_2Cl_2; (g) MsCl, Et_3N, toluene (**11**: 80%, **12**: 83%, three steps); (h) cat. $PdCl_2$ (90%), MeOH; (i) Cs_2CO_3, 18-crown-6, DMF, sonication, then MW (200 W, 2 bar, 120 °C, 10 min) (**16**: 70%, **17**: 72%, **18**: 75%); (j) NaOMe, MeOH (**1**: 98%, **2**: 99%, **3**: 99%).

enantioconservative maneuvers[17] consisting of hydroxyl protection with the PMB−acetimidate/scandium triflate system,[18] ester reduction ($LiAlH_4$), and Swern oxidation (91% yield for the three steps). To target (−)-polysphorin (−)-**1**, arylation of **6** was carried out using the lithium derivative of 5-bromo-1,2,3-trimethoxybenzene (**7**) (^{t}BuLi, THF, −85 °C), affording the *anti*-configured compound **9** as the predominant isomer (80% isolated yield), accompanied by minor amounts of the *syn* counterpart (dr = 83:17, as determined by ^{1}H NMR analysis of the crude product mixture). Compound **9** (as well as **10**) emerges from the nucleophilic attack of aryl lithium onto the carbonyl *re* face of the α-alkoxyaldehyde **6**, according to a Felkin dipolar model (Figure 2).[19] It would seem plausible that, even in the presence of a highly coordinating α-alkoxy group, which typically would favor a "Cram-chelate" addition mode leading to *syn*-configured products, in this case, the nature of the aryl lithium reagent and the overall conditions seem to strongly

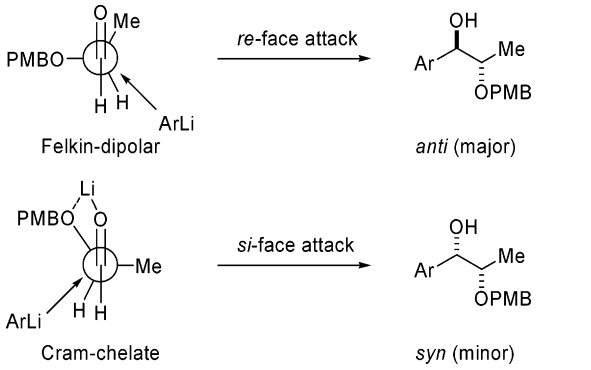


FIGURE 2. Models for stereoselective aryl lithium additions to *p*-methoxybenzyl-substituted (*S*)-lactaldehyde **6**.

influence the stereochemical behavior of the nucleophilic addition process, imparting a good *anti*-favoring stereocontrol.[20]

Advancement to the penultimate polysphorin precursor **16** needed an aryloxy substitution reaction. Drawing from previous discouraging results obtained through applying the Mitsunobu displacement with these substrates,[16a] we envisaged to follow the stepwise C-8 activation/S_N2 displacement procedure. Thus, the free C-7 hydroxyl within **9** was first protected (acetylation), the *p*-methoxybenzyl ether was successively dismantled (DDQ in wet CH_2Cl_2), and the C-8 hydroxyl mesylated (MsCl, Et_3N, toluene). Compound **11** was obtained in 80% yield in three steps.[21]

Subsequent, non-routine nucleophilic substitution was effected by exposure of **11** to the cesium phenoxylate derived from **13**[22] in the presence of 18-crown-6 under microwave irradiation (200 W, 2 bar, 120 °C, 10 min). This procedure[23] gratifyingly led to the 7,8-*syn*-disposed protected polysphorin precursor **16** as the sole stereoisomer (70% isolated yield), which was quickly and almost quantitatively converted to natural (−)-polysphorin (−)-**1** by sodium methoxide deacetylation (40% overall yield for the nine-step sequence; ≥97% ee as determined by chiral HPLC measurements). The physical and NMR spectral characteristics of (−)-**1** matched the value for the (7*R*,8*R*)-enantiomer as reported by Ley and co-workers in the literature ($J_{7,8}$ = 8.4 Hz, $[\alpha]_D^{25}$ −100.4° (*c* 1.0, $CHCl_3$); [lit.[16a] $J_{7,8}$ = 8.4 Hz, $[\alpha]_D^{25}$ −87° (*c* 0.34, $CHCl_3$)]) (see also Table S1 in the Supporting Information).

The same protocol was successfully applied to (−)-raphidecursinol B (−)-**2** and (−)-virolin (−)-**3** utilizing the competent couples of aryl/aryloxy components, namely, aryl bromide **7** and phenol **14** for (−)-**2** and aryl bromide **8** and phenol **15** for

(17) Evidence of the full preservation of the enantiopurity of compound **6** was given by optical activity data which were comparable to those reported in the literature (see experimental section in the Supporting Information).

(18) Rai, A. N.; Basu, A. *Tetrahedron Lett.* **2003**, *44*, 2267−2269.

(19) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199−2204. (b) Anh, N. T.; Eisenstein, O. *New J. Chem.* **1977**, *1*, 61−70. (c) Gawley, R. E.; Aubé, J. *Principles of Asymmetric Synthesis*; Tetrahedron Organic Chemistry Series, Vol. 14; Pergamon Press: Elsevier: Oxford, 1996; pp 121−160. (d) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556−569.

(20) (a) Luanphaisarnnont, T.; Ndubaku, C. O.; Jamison, T. F. *Org. Lett.* **2005**, *7*, 2937−2940. (b) Banfi, L.; Bernardi, A.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Org. Chem.* **1984**, *49*, 3784−3790.

(21) It is worth noting that the acetyl protection in **11** was critical since installation of electron-donating groups at C-7 hydroxyl causes **11** to collapse into stable epoxide derivatives.

(22) Conveniently, propenyl-substituted phenol **13** was obtained from commercially available allyl phenol **14** by clean and efficient $PdCl_2$-catalyzed isomerization. Jing, X.; Gu, W.; Bic, P.; Ren, X.; Pan, X. *Synth. Commun.* **2001**, *31*, 861−867.

(23) The experimental conditions capitalized on the findings previously reported by Helm and Li (excess cesium 2-methoxyphenolate, 18-crown-6, benzene, reflux, 24 h; ref 14d).

(−)-**3**. There, the key non-routine arylation and aryloxylation reactions occurred with the same chemical efficiency and stereocontrol as that observed during the synthesis of (−)-**1**, as shown in Scheme 2. Overall, the nine-step sequence provided (−)-raphidecursinol B (−)-**2** in a 42% yield, which displayed the same characteristics as those reported in the literature for the pure (*R*,*R*)-enantiomer ($J_{7,8}$ = 8.4 Hz, $[\alpha]_D^{25}$ −77.0° (*c* 1.0, $CHCl_3$); [lit.[16a] $J_{7,8}$ = 8.1 Hz, $[\alpha]_D^{25}$ −58.2° (*c* 5.26, $CHCl_3$), lit.[7a] $J_{7,8}$ = 8.0 Hz]) (Table S1, Supporting Information).

For (−)-virolin (−)-**3**, obtained here in a 45% overall yield, a (7*R*,8*R*)-absolute configuration was assigned, based on the configuration of the starting lactate ester as well as the faithful stereochemical behavior of the chemistry experienced. Disappointingly enough, while the NMR spectral characteristics of our synthetic (−)-virolin ($J_{7,8}$ = 8.4 Hz) wholly matched the reported data for both the natural and synthetic racemic substances,[13] as well as for an enantioenriched sample previously obtained via synthesis (Table S1, Supporting Information),[15a] the optical rotation of our (7*R*,8*R*)-configured sample ($[\alpha]_D^{25}$ −99.6° (*c* 1.0, $CHCl_3$)) strongly deviates both in sign and value from that reported in the literature for a 78% ee synthetic virolin sample ($[\alpha]_D^{25}$ −29° (*c* 1.0, $CHCl_3$)) to which a (7*S*,8*S*)-configuration was allegedly attributed.[15a,24]

The reaction platform of Scheme 2 proved to be also utilitarian in paving the way to stereoisomeric (+)-**1**, provided that (*R*)-methyl lactate (+)-**5** was employed as the starting chirality source. Thus, the (7*S*,8*S*)-configured polysphorin (+)-**1** was obtained in a 38% overall yield for the sequence of nine steps, thus confirming the reliability and predictability of our synthesis protocol ($[\alpha]_D^{25}$ +99.3° (*c* 1.0, $CHCl_3$); lit.[16a] $[\alpha]_D^{25}$ +95° (*c* 0.8, $CHCl_3$)).

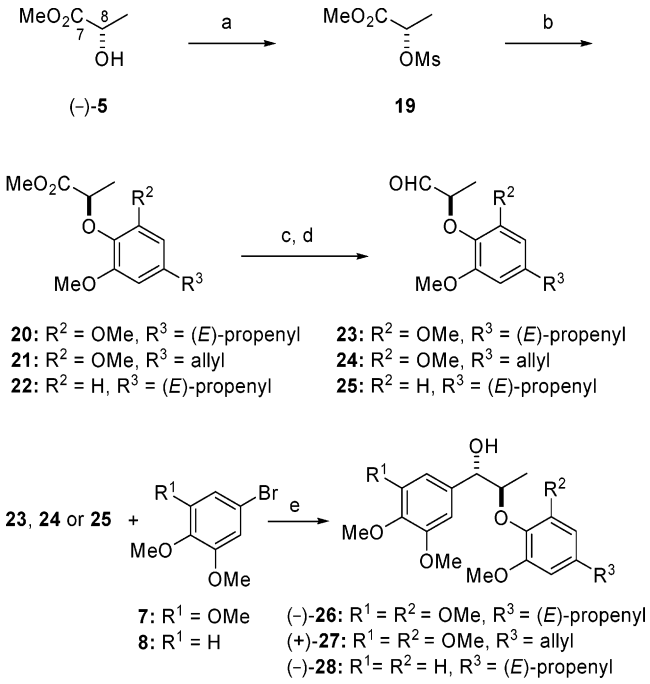
Having a solid, modular protocol to create 7,8-*syn*-configured 8,4′-oxyneolignan compounds, we next challenged the same systems in the 7,8-*anti* stereoisomeric series. Thus, as depicted in Scheme 3, (*S*)-lactate (−)-**5** was quickly transformed into mesyl derivative **19** (98% yield),[25] which was directly and parallely subjected to nucleophilic displacement by means of the suitable phenols **13**,[22] **14**, or **15**.[26] Three aryloxy lactate esters **20**, **21**, and **22** were produced in yields ranging from 87 to 90%. Next, a two-step ester-to-aldehyde conversion was carried out, consisting of an ester-to-alcohol reduction ($LiAlH_4$) followed by Swern oxidation. The three aldehyde intermediates **23**, **24**, and **25** eventually were formed in excellent isolated yields (95−96%), ready for the subsequent arylation maneuvers.

To access *anti*-configured oxyneolignans (−)-**26** and (+)-**27**, intermediates **23** and **24** had to be coupled to **7**, while to arrive at (−)-**28**, coupling of **25** to **8** was needed. All the planned nucleophilic additions occurred smoothly and, even in this case, a Felkin-type addition mode nicely applied, producing the *anti*-configured targets (−)-**26**, (+)-**27**, and (−)-**28** with high efficiency (81−90% yields) and high level of diastereocontrol (dr ≥ 85:15).

Noteworthily, implementation of the aryloxy moiety onto the lactate frame prior to arylation allowed us to speed up the synthesis, avoiding lengthy protection/deprotection maneuvers, with the aryloxy moiety itself serving as a protecting element for the target C-8 hydroxyl. Overall, the C-7 epimers of polysphorin, raphidecursinol B, and virolin, (−)-**26**, (+)-**27**, and (−)-**28**, were synthesized on a gram-scale and in an enantiomerically pure form from (*S*)-methyl lactate in only five steps and good 74, 66, and 69% overall yields, respectively. The spectral data for 7,8-*erythro*-configured compounds (+)-**27**, and (−)-**28** matched the published data for the respective previously reported substances (Table S1, Supporting Information),[7a,14b,27] while (−)-**26** ($J_{7,8}$ = 3.0 Hz) represents a new compound. To further confirm the (7*S*,8*R*)-configurational assignment to (−)-**26**, (+)-**27**, and (−)-**28**, circular dichroism analysis was performed, based on the established empirical relationship[28] between the characteristic CD transitions and the absolute configuration of the stereocenters in *anti*-disposed 8,4′-oxyneolignans (positive Cotton effects in the range of 230−290 nm correspond to 7*R*,8*S* configurations, and vice versa).[29]

As for the *syn*-oriented (*R*,*R*)-series, the dextrorotatory (7*R*,8*S*)-configured enantiomer of 8-*epi*-polysphorin (+)-**26** was assembled, by starting with (*R*)-methyl lactate (+)-**5** and faithfully paralleling the chemistry just disclosed. Thus, in this special case, the polysphorin family was fully represented by all four diastereoisomers.

SCHEME 3. Synthesis of 7,8-*anti*-Configured 8,4′-Oxyneolignans[a]



[a] Reagents and conditions: (a) MsCl, Et_3N, toluene (98%); (b) **13**, **14**, or **15**, Cs_2CO_3, 18-crown-6, DMF, sonication (**20**: 88%, **21**: 87%, **22**: 90%); (c) $LiAlH_4$, THF; (d) $(COCl)_2$, DMSO, CH_2Cl_2, −80 °C, then Et_3N (**23**: 95%, **24**: 95%, **25**: 96%, two steps); (e) ^{t}BuLi, $Ti(O^iPr)_3Cl$, THF, −85 °C (**26**: 90%, dr = 90:10, **27**: 81%, dr = 85:15, **28**: 82%, dr = 85:15).

(24) On the basis of our results, the absolute configuration of levorotatory virolin in ref 15a should be reverted (7*R*,8*R*).

(25) Hillis, L. R.; Ronald, R. C. *J. Org. Chem.* **1981**, *46*, 3348−3349.

(26) Here, milder conditions were found (Cs_2CO_3, 18-crown-6 in DMF, sonication) as compared to the previous microwave-assisted substitution procedure (see text) since it is known that the presence of a carboxylate or a carbonyl group adjacent to the alcohol (or bromine) function strongly activates the substrate for nucleophilic displacement. See, for example, ref 16a.

(27) Herrera Braga, A. C.; Zacchino, S.; Badano, H.; Sierra, M. G.; Rúveda, E. A. *Phytochemistry* **1984**, *23*, 2025−2028.

(28) Kónya, K.; Kiss-Szikszai, A.; Kurtán, T.; Antus, S. *J. Chromatogr. Sci.* **2004**, *42*, 478−483.

(29) Overall, these findings indirectly confirmed a (7*R*,8*R*)-configuration for the minor *syn*-configured products, whose structures coincide with those of compounds (−)-**1**, (−)-**2**, and (−)-**3**.

Conclusions

To recapitulate, two complementary and large-scale adaptable syntheses of enantiomerically pure (>95% ee) 7,8-*syn*- and 7,8-*anti*-configured oxyneolignans are reported, which employ (*S*)- or (*R*)-lactate esters as convenient sources of chirality. Apart from a few run-of-the mill transformations, both routes are centered upon two highly stereoselective and predictable operations of grafting the aromatic modules onto the lactate frame which are sequenced in opposite directions. In the longest *syn*-oriented route (nine steps), a Felkin-type carbonyl addition precedes a bimolecular nucleophilic substitution reaction, while in the shortest *anti*-oriented path (five steps) these two operations are reversed.

In principle, as well as in practice, the overall plan ensures that all four possible stereoisomers of a given target skeleton are accessible in high yields. Bearing in mind the uncertainty which has accompanied several structural attributions of compounds in this class, the intent of this work is to provide a sure means of establishing the relationship between molecular structure and both spectral and chiro-optical properties.

A definitive biological interrogation of the eight 8,4′-oxyneolignans in this study and structurally modified congeners in the anti-malarial compound area will be the subject of future investigations.

Experimental Section

(1*R*,2*S*)-2-(4-Methoxybenzyloxy)-1-(3,4,5-trimethoxyphenyl)-propan-1-ol (9). Typical Procedure. A 1 L three-neck round-bottom flask equipped with a dropping funnel and an argon inlet/outlet was charged with anhydrous THF (200 mL). 5-Bromo-1,2,3-trimethoxybenzene (**7**) (7.63 g, 30.88 mmol) was then added in one portion, and the resulting solution was cooled to −85 °C. ^{t}BuLi (1.7 M in pentane, 18.16 mL, 30.88 mmol) was added during a 25 min period. After 15 min at −85 °C, a solution of aldehyde **6** (3.00 g, 15.44 mmol) dissolved in anhydrous THF (50 mL) was added in a 15 min period, and the resulting mixture was allowed to stir for 1 h at −85 °C. The reaction mixture was quenched by the addition of citrate−sodium hydroxide buffer (65 mL) at −85 °C, allowed to warm to 25 °C, and extracted with hexanes (3 × 50 mL). The organic layers were dried ($MgSO_4$), filtered, and concentrated to give a crude residue which was purified by silica gel flash chromatography (hexanes/EtOAc 1:1). Protected compound **9** (4.48 g, 80%) was obtained, along with minor amounts of the *syn*-configured diastereoisomer 7-*epi*-**9** (not shown) (dr = 83:17). Compound **9**: a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 2H), 6.88 (m, 2H), 6.58 (m, 2H), 4.79 (m, 1H), 4.58 (1/2 ABq, J = 11.3 Hz, 1H), 4.44 (1/2 ABq, J = 11.3 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 6H), 3.82 (s, 3H), 3.70 (qd, J = 6.2, 4.3 Hz, 1H), 2.60 (br s, 1H), 1.09 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3 (C), 153.1 (2C, C), 137.1 (C), 136.6 (C), 129.5 (C), 129.3 (2C, CH), 113.8 (2C, CH), 103.3 (2C, CH), 78.4 (CH), 75.3 (CH), 70.7 (CH_2), 60.8 (CH_3), 56.1 (2C, CH_3), 55.3 (CH_3), 13.8 (CH_3). Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.39; H, 7.05.

Compound 7-*epi*-**9**: a colorless oil; $[\alpha]_D^{25}$ +11.9° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 2H), 6.90 (m, 2H), 6.58 (m, 2H), 4.63 (1/2 ABq, J = 11.0 Hz, 1H), 4.41 (1/2 ABq, J = 11.1 Hz, 1H), 4.38 (dd, J = 7.5, 1.8 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 6H), 3.80 (s, 3H), 3.61 (dq, J = 7.6, 6.1 Hz, 1H), 3.24 (d, J = 2.1 Hz, 1H), 1.11 (d, J = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0 (C), 152.8 (2C, C), 132.1 (C), 129.1 (C), 129.0 (C), 128.3 (2C, CH), 113.6 (2C, CH), 103.8 (2C, CH), 79.2 (CH), 73.6 (CH), 70.6 (CH_2), 60.6 (CH_3), 55.9 (CH_3), 55.8 (CH_3), 55.0 (CH_3), 14.4 (CH_3).

(1*R*,2*S*)-1-Acetoxy-1-(3,4,5-trimethoxyphenyl)-2-propyl methanesulfonate (11). Typical Procedure. To a stirring solution of compound **9** (4.20 g, 11.58 mmol) in dry acetonitrile (150 mL) under argon were sequentially added acetic anhydride (5.46 mL, 57.90 mmol), Et_3N (3.23 mL, 23.17 mmol), and 4-dimethylaminopyridine (DMAP, 707 mg, 5.79 mmol) at room temperature. The reaction mixture was allowed to stir for 1 h, after which time it was quenched with brine and saturated aqueous NH_4Cl, until neutral pH was achieved. The reaction mixture was extracted with hexanes (3 × 20 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to give a colorless oily residue (4.66 g, 100% yield) which was used as such in the subsequent reaction: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (m, 2H), 6.81 (m, 2H), 6.54 (m, 2H), 5.71 (d, J = 5.4 Hz, 1H), 4.46 (1/2 ABq, J = 11.3 Hz, 1H), 4.36 (1/2 ABq, J = 11.3 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 6H), 3.77 (s, 3H), 3.74 (m, 1H), 2.12 (s, 3H), 1.19 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 159.2, 153.2 (2C), 135.9, 132.2, 130.2, 128.5 (2C), 113.9 (2C), 104.2 (2C), 77.3, 76.6, 71.0, 60.7, 56.0 (2C), 55.2, 21.2, 15.9.

To a solution of the previous acetyl intermediate (4.66 g, 11.58 mmol) in CH_2Cl_2 (200 mL) at 0 °C were added water (25 mL) and DDQ (2.63 mg, 11.58 mmol). The reaction mixture was stirred for 3 h at room temperature, and then brine (100 mL) and saturated $NaHCO_3$ (50 mL) were added. After separation of the organic layer, the aqueous phase was washed with dichloromethane (2 × 30 mL), and the collected organic layers were dried over magnesium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by silica gel flash chromatography (Et_2O/hexanes 90:10) to afford a partially deprotected intermediate (2.63 g, 80% yield) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52 (m, 2H), 5.46 (d, J = 5.6 Hz, 1H), 3.98 (quint, J = 6.0 Hz, 1H), 3.78 (s, 6H), 3.75 (s, 3H), 2.33 (br s, 1H), 2.05 (s, 3H), 1.12 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 153.1 (2C), 137.7, 132.8, 104.4 (2C), 79.4, 69.7, 60.7, 56.0 (2C), 21.1, 18.5.

To a stirring solution of the previously obtained intermediate (2.63 g, 9.26 mmol) in toluene (100 mL) at 0 °C was added triethylamine (Et_3N, 1.68 mL, 12.04 mmol). After 10 min, methanesulfonyl chloride (MsCl, 0.79 mL, 10.19 mmol) was added over a 15 min period. The light orange suspension was kept an additional hour in the ice bath and then was allowed to warm to room temperature. The mixture was filtered through Celite and concentrated under vacuum to give a light brown oil. Silica gel flash chromatographic purification (hexanes/EtOAc 60:40) afforded pure mesyl derivative **11** (3.36 g) in a 100% yield as a colorless oil: $[\alpha]_D^{25}$ −41.6° (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (m, 2H), 5.73 (d, J = 4.3 Hz, 1H), 4.94 (qd, J = 6.2, 4.8 Hz, 1H), 3.80 (s, 6H), 3.76 (s, 3H), 2.80 (s, 3H), 2.10 (s, 3H), 1.31 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5 (C), 153.2 (2C, C), 138.3 (C), 130.9 (C), 104.7 (2C, CH), 79.3 (CH), 76.1 (CH), 60.7 (CH_3), 56.2 (2C, CH_3), 38.4 (CH_3), 20.9 (CH_3), 16.7 (CH_3). Anal. Calcd for $C_{15}H_{22}O_8S$: C, 49.71; H, 6.12. Found: C, 49.66; H, 6.25.

2,6-Dimethoxy-4-[(*E*)-prop-1-enyl]phenol (13). Typical Procedure. To a stirring solution of commercially available 4-allyl-2,6-dimethoxyphenol (**14**) (1.0 g, 5.15 mmol) in anhydrous and previously degassed methanol (40 mL) was added a catalytic amount of $PdCl_2$ (46 mg, 0.26 mmol) at room temperature. After 24 h, the brown reaction mixture was filtered and concentrated under vacuum to leave an oily crude residue which was purified by silica gel flash chromatography under argon flow (petroleum ether/EtOAc 85:15). Pure phenol **13** was obtained (900 mg, 90%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (s, 2H), 6.33 (dq, J = 15.6, 1.5 Hz, 1H), 6.11 (dq, J = 15.6, 6.5 Hz, 1H), 5.48 (s, 1H), 3.91 (s, 6H), 1.88 (dd, J = 6.5, 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1 (2C, C), 134.0 (C), 131.0 (CH), 129.6 (C), 123.8 (CH), 102.7 (2C, CH), 56.2 (2C, CH_3), 18.3 (CH_3).

(1*R*,2*R*)-2-[2,6-Dimethoxy-4-((*E*)-prop-1-enyl)phenoxy]-1-(3,4,5-trimethoxyphenyl)propyl acetate (16). Typical Procedure. To a flame-dried round-bottom flask were sequentially added anhydrous

Cs_2CO_3 (228 mg, 0.70 mmol) and anhydrous DMF (5 mL) under argon atmosphere at room temperature. The suspension was kept under ultrasonic irradiation for 5 min, then phenol **13** (0.124 mL, 0.7 mmol) was added. The resulting dark green suspension was allowed to stir under ultrasonic irradiation for an additional 30 min period, after which time the supernatant solution was transferred to a 10 mL glass vessel containing a solution of mesyl derivative **11** (100 mg, 0.28 mmol) in DMF (1 mL). To the resulting green mixture was added 18-crown-6 ether (209 mg, 0.56 mmol), and the vessel was sealed with a septum, placed in the microwave cavity, and locked with the pressure device. The microwave source was then turned on. Constant microwave irradiation (200 W, 2 bar, 120 °C) as well as simultaneous air-cooling (2 bar) was used during the entire reaction time (10 min). After cooling to room temperature, the brown mixture was quenched with citrate−sodium hydroxide buffer (3 mL) and brine (3 mL) and extracted with hexanes (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by silica gel flash chromatography (hexanes/Et_2O 50:50) to give compound **16** (90 mg, 70%) as a colorless oil: $[\alpha]_D^{25}$ −10.9° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (s, 2H), 6.58 (s, 2H), 6.35 (dq, J = 15.6, 1.2 Hz, 1H), 6.16 (dq, J = 15.6, 6.5 Hz, 1H), 5.87 (d, J = 7.2 Hz, 1H), 4.47 (quint, J = 6.8 Hz, 1H), 3.87 (s, 6H), 3.84 (s, 9H), 1.94 (s, 3H), 1.89 (dd, J = 6.4, 1.2 Hz, 3H), 1.15 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0 (C), 153.1 (4C, C), 136.5 (2C, C), 133.8 (2C, C), 130.9 (CH), 125.1 (CH), 104.6 (2C, CH), 103.1 (2C, CH), 80.2 (CH), 79.8 (CH), 60.8 (CH_3), 56.2 (2C, CH_3), 56.1 (2C, CH_3), 21.1 (CH_3), 18.3 (CH_3), 17.3 (CH_3). Anal. Calcd for $C_{25}H_{32}O_8$: C, 65.20; H, 7.00. Found: C, 65.11; H, 7.18.

(1*R*,2*R*)-2-[2,6-Dimethoxy-4-((*E*)-prop-1-enyl)phenoxy]-1-(3,4,5-trimethoxyphenyl)propan-1-ol [(−)-Polysphorin] (−)-1. Typical Procedure.[30] To a stirring solution of protected polysphorin (**16**) (90 mg, 0.19 mmol) in methanol (5 mL) was slowly added a 1% methanolic NaOMe solution (2 mL). After 1 h at room temperature, methanol was removed under vacuum, affording an oily colorless residue which was purified by silica gel flash chromatography (hexanes/EtOAc 55:45) providing pure polysphorin (−)-**1** (78 mg, 98% yield, corresponding to a 40% overall yield for nine steps from (−)-**5**) as a white resin. The enantiomeric excess was 97% as determined by chiral HPLC analysis (Chiralcel OD-H; hexane/2-propanol, 90:10, 1.0 mL/min, λ = 254 nm; 25 °C; major isomer, $t_{R,R}$ = 20.30 min; minor isomer, $t_{S,S}$ = 15.98 min): $[\alpha]_D^{25}$ −100.4° (*c* 1.0, $CHCl_3$); [lit.[16a] $[\alpha]_D^{25}$ −87° (*c* 0.34, $CHCl_3$)]; CD (hexane/2-propanol, 90:10) 266 nm ($\Delta\epsilon$ = −2.56), 221 nm ($\Delta\epsilon$ = −3.32); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.56 (s, 2H, Ar), 6.54 (s, 2H, Ar), 6.31 (dq, J = 15.6, 1.2 Hz, 1H, H7′), 6.15 (dq, J = 15.6, 6.6 Hz, 1H, H8′), 4.93 (br s, 1H, OH), 4.57 (d, J = 8.4 Hz, 1H, H7), 3.92 (dq, J = 7.8, 6.0 Hz, 1H, H8), 3.86 (s, 6H, OMe), 3.82 (s, 6H, OMe), 3.78 (s, 3H, OMe), 1.85 (dd, J = 6.6, 1.2 Hz, 3H, H9′), 1.19 (d, J = 6.6 Hz, 3H, H9); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.3 (2C, C Ar), 153.0 (2C, C Ar), 136.6 (2C, C Ar), 134.1 (2C, C Ar), 130.9 (C7′), 125.9 (C8′), 104.4 (2C, CH Ar), 103.0 (2C, CH Ar), 86.7 (C8), 79.6 (C7), 61.0 (OMe), 56.3 (2C, OMe), 56.2 (2C, OMe), 18.6 (C9′), 17.9 (C9). Anal. Calcd for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 65.89; H, 7.30. HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{30}O_7Na$ 441.1889. Found 441.1875.

(1*S*,2*S*)-2-[2,6-Dimethoxy-4-((*E*)-prop-1-enyl)phenoxy)-1-(3,4,5-trimethoxyphenyl]propan-1-ol [(+)-Polysphorin] (+)-1. The title compound was prepared from (*R*)-methyl lactate (+)-**5** (20 μL, 0.20 mmol) following exactly the nine-step sequence described for its enantiomer (−)-**1**.

In the last deprotective step, after silica gel flash chromatographic purification (hexane/EtOAc 55:45), (+)-polysphorin (+)-**1** was obtained (40 mg, 97% yield, corresponding to a 38% overall yield for nine steps from (+)-**5**) as a white resin. The enantiomeric excess was 97% as determined by chiral HPLC analysis (Chiralcel OD-H; hexane/2-propanol, 90:10, 1.0 mL/min, λ = 254 nm; 25 °C; major isomer, $t_{S,S}$ = 15.98 min; minor isomer, $t_{R,R}$ = 20.30 min): $[\alpha]_D^{25}$ +99.3° (*c* 1.0, $CHCl_3$); [lit.[16a] mp 107−108 °C; $[\alpha]_D^{25}$ +95° (*c* 0.8, $CHCl_3$)]; ^{1}H and ^{13}C NMR data identical to those reported for its enantiomer (−)-**1**. Anal. Calcd for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 66.20; H, 7.16. HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{30}O_7Na$ 441.1889. Found 441.1902.

(1*R*,2*R*)-2-[4-Allyl-2,6-dimethoxyphenoxy)-1-(3,4,5-trimethoxyphenyl]propan-1-ol [(−)-Raphidecursinol B] (−)-2.[30] The title compound was prepared from protected raphidecursinol B **17** (93 mg, 0.20 mmol) following the procedure described for (−)-**1**. After silica gel flash chromatographic purification (Et_2O/petroleum ether 70:30), (−)-raphidecursinol B (−)-**2** was obtained (84 mg, 99% yield, corresponding to a 42% overall yield for the nine-step sequence from (−)-**5**) as a white resin: $[\alpha]_D^{25}$ −77.0° (*c* 1.0, $CHCl_3$); [lit.[16a] white solid; mp 81−82 °C; $[\alpha]_D^{25}$ −58.2° (*c* 5.26, $CHCl_3$)]; CD (hexane/2-propanol, 90:10) 278 nm ($\Delta\epsilon$ = +0.40), 243 nm ($\Delta\epsilon$ = −5.28); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.55 (s, 2H, Ar), 6.42 (s, 2H, Ar), 5.93 (ddt, J = 17.4, 10.2, 6.6 Hz, 1H, H8′), 5.10 (dq, J = 16.8, 1.8 Hz, 1H, H9′), 5.07 (dq, J = 10.8, 1.2 Hz, 1H, H9′), 4.96 (d, J = 1.2 Hz, 1H, OH), 4.56 (br d, J = 8.4 Hz, 1H, H7), 3.91 (dq, J = 8.4, 6.0 Hz, 1H, H8), 3.84 (s, 6H, OMe), 3.82 (s, 6H, OMe), 3.79 (s, 3H, OMe), 3.32 (bd, J = 6.6 Hz, 2H, H7′), 1.18 (d, J = 6.6 Hz, 3H, H9); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.3 (2C, C Ar), 152.8 (2C, C Ar), 137.2 (C8′), 136.6 (C Ar), 136.2 (2C, C Ar), 135.4 (C Ar), 116.4 (C9′), 105.6 (2C, CH Ar), 104.5 (2C, CH Ar), 86.6 (C8), 79.6 (C7), 61.0 (OMe), 56.3 (2C, OMe), 56.2 (2C, OMe), 40.7 (C7′), 17.9 (C9). Anal. Calcd for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 66.16; H, 7.11. HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{30}O_7Na$ 441.1889. Found 441.1899.

(1*R*,2*R*)-2-[2-Methoxy-4-((*E*)-prop-1-enyl)phenoxy]-1-(3,4-dimethoxyphenyl)propan-1-ol [(−)-Virolin] (−)-3.[30] The title compound was prepared from protected virolin **18** (90 mg, 0.22 mmol) following the procedure described for (−)-**1**. After silica gel flash chromatographic purification (hexanes/EtOAc 55:45), (−)-virolin (−)-**3** was obtained (79 mg, 99% yield, corresponding to a 45% overall yield for the nine-step sequence from (−)-**5**) as a white resin: $[\alpha]_D^{25}$ −99.6° (*c* 1.0, $CHCl_3$); [lit.[15a] for the (1*S*,2*S*)-enantiomer $[\alpha]_D^{25}$ −29.0° (*c* 1.0, $CHCl_3$)]; CD (hexane/2-propanol, 90:10) 298 nm ($\Delta\epsilon$ = −1.57), 290 nm ($\Delta\epsilon$ = −1.41), 249 nm ($\Delta\epsilon$ = −4.98); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.7−7.0 (m, 6H, Ar), 6.32 (dq, J = 15.6, 1.8 Hz, 1H, H7′), 6.12 (dq, J = 16.2, 6.6 Hz, 1H, H8′), 4.60 (br d, J = 7.8 Hz, 1H, H7), 4.14 (br s, 1H, OH), 4.07 (dq, J = 8.4, 6.0 Hz, 1H, H8), 3.89 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.84 (s, 3H, OMe), 1.85 (dd, J = 6.6, 1.8 Hz, 3H, H9′), 1.13 (dd, J = 6.6, 1.2 Hz, 3H, H9); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.0 (C Ar), 149.2 (C Ar), 149.0 (C Ar), 146.9 (C Ar), 133.7 (C Ar), 132.7 (C Ar), 130.6 (C7′), 125.1 (C8′), 120.2 (CH Ar), 119.2 (CH Ar), 119.0 (CH Ar), 111.0 (CH Ar), 110.1 (CH Ar), 109.3 (CH Ar), 84.4 (C8), 78.6 (C7), 56.1 (2C, OMe), 55.9 (OMe), 18.6 (C9′), 17.3 (C9). Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.21; H, 7.39. HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{26}O_5Na$ 381.1678. Found 381.1666.

(*R*)-Methyl 2-[2,6-dimethoxy-4-((*E*)-prop-1-enyl)phenoxy)propanoate (20). The title compound was prepared from methyl ester **19** (3.0 g, 16.46 mmol) and phenol **13** (8.0 g, 41.15 mmol) following the procedure described for **16**. The use of microwave apparatus was here replaced by sonication for 1 h. After silica gel flash chromatographic purification (hexanes/EtOAc 80:20), methyl ester **20** was obtained (4.06 g, 88% yield) as a white solid: mp 43−45 °C; $[\alpha]_D^{25}$ +42.9° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.51 (s, 2H), 6.29 (br d, J = 16.0 Hz, 1H), 6.12 (dq, J = 15.6, 6.5 Hz, 1H), 4.62 (q, J = 6.8 Hz, 1H), 3.80 (s, 6H), 3.74 (s, 3H), 1.84 (br d, J = 6.4 Hz, 3H), 1.51 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6 (C), 153.1 (2C, C), 135.0 (C), 134.0 (C), 130.9 (CH), 125.3 (CH), 102.9 (2C, CH), 77.3 (CH), 56.0 (2C,

(30) For direct comparison with NMR data reported in the literature, ^{1}H and ^{13}C chemical shift assignments follow the conventional 8,4′-oxyneolignan numbering. See ref 2.

CH_3), 51.9 (CH_3), 18.3 (2C, CH_3). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.13; H, 7.11.

(1*S*,2*R*)-2-[2,6-Dimethoxy-4-((*E*)-prop-1-enyl)phenoxy]-1-(3,4,5-trimethoxyphenyl)propan-1-ol (−)-26. Typical Procedure.[30] A solution of aldehyde **23** (800 mg, 3.20 mmol) was dissolved in THF (8 mL) at room temperature and treated with $Ti(O^iPr)_3Cl$ (0.76 mL, 3.20 mmol). The resulting yellow mixture was transferred via cannula dropwise over 30 min to a solution cooled at −85 °C previously obtained by treatment of 5-bromo-1,2,3-trimethoxybenzene (**7**) (1.97 g, 8.0 mmol) in anhydrous THF (30 mL) with ^{t}BuLi (1.7 M in pentane, 4.7 mL, 8.0 mmol) at −85 °C for 15 min. The resulting brownish mixture was allowed to stir for 2 h at this temperature, turning colorless. The reaction mixture was quenched by the addition of citrate−sodium hydroxide buffer (20 mL) at −85 °C. The reaction mixture was allowed to warm to 25 °C, diluted with brine (20 mL), and extracted with hexane (3 × 20 mL). The organic layer was dried ($MgSO_4$), concentrated, and the yellow oily residue was purified by silica gel flash chromatography (hexanes/Et_2O 50:50) to afford 8,4′-oxyneolignan (−)-**26** as a white resin (1.27 g, 90%, corresponding to a 74% overall yield for five steps from (−)-**5**) along with minor amounts of the *syn*-configured diastereoisomer (corresponding to (−)-polysphorin (−)-**1**) (dr = 90:10). The enantiomeric excess of 96% was determined by chiral HPLC analysis (Chiralcel OD-H; hexane/2-propanol, 95:5, 1.0 mL/min, λ = 254 nm; 25 °C; major isomer, $t_{S,R}$ = 27.19 min; minor isomer, $t_{R,S}$ = 30.40 min): $[\alpha]_D^{25}$ −3.06° (*c* 0.9, $CHCl_3$); CD (hexane/2-propanol, 90:10) 267 nm ($\Delta\epsilon$ = −5.74), 233 nm ($\Delta\epsilon$ = +7.45); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.56 (s, 2H, Ar), 6.49 (s, 2H, Ar), 6.31 (dq, *J* = 15.6, 1.8 Hz, 1H, H7′), 6.16 (dq, *J* = 15.6, 6.6 Hz, 1H, H8′), 4.75 (d, *J* = 3.0 Hz, 1H, H7), 4.30 (qd, *J* = 6.6, 3.0 Hz, 1H, H8), 4.07 (br s, 1H, OH), 3.85 (s, 6H, OMe), 3.80 (s, 6H, OMe), 3.77 (s, 3H, OMe), 1.85 (dd, *J* = 6.6, 1.8 Hz, 3H, H9′), 1.09 (d, *J* = 6.6 Hz, 3H, H9); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.8 (2C, C Ar), 153.3 (2C, C Ar), 135.8 (2C, C Ar), 134.3 (2C, C Ar), 130.9 (C7′), 125.1 (C8′), 103.1 (2C, CH Ar), 103.0 (2C, CH Ar), 82.6 (C8), 73.3 (C7), 61.0 (OMe), 56.3 (2C, OMe), 56.2 (2C, OMe), 18.6 (C9′), 13.0 (C9). Anal. Calcd for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 65.88; H, 7.12. HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{30}O_7Na$ 441.1889. Found 441.1894.

(1*R*,2*S*)-2-[2,6-Dimethoxy-4-((*E*)-prop-1-enyl)phenoxy]-1-(3,4,5-trimethoxyphenyl)propan-1-ol (+)-26. The title compound was prepared from (*R*)-methyl lactate (+)-**5** (20 μL, 0.21 mmol) following exactly the five-step sequence described for its enantiomer (−)-**26**. In the last aryl addition step, after silica gel flash chromatographic purification (hexanes/Et_2O 50:50), 8,4′-oxyneolignan (+)-**26** was obtained (62 mg, 88% yield, corresponding to a 70% overall yield for five steps from (+)-**5**) as a white resin. The enantiomeric excess of 97% was determined by chiral HPLC analysis (Chiralcel OD-H; hexane/2-propanol, 95:5, 1.0 mL/min, λ = 254 nm; 25 °C; major isomer, $t_{R,S}$ = 30.45 min; minor isomer, $t_{S,R}$ = 27.22 min): $[\alpha]_D^{25}$ +3.6° (*c* 1.0, $CHCl_3$); ^{1}H and ^{13}C NMR data are identical to those reported for its enantiomer (−)-**26**. Anal. Calcd for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 65.98; H, 7.15. HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{30}O_7Na$ 441.1889. Found 441.1901.

(1*S*,2*R*)-2-(4-Allyl-2,6-dimethoxyphenoxy)-1-(3,4,5-trimethoxyphenyl)propan-1-ol (+)-27.[30] The title compound was prepared from aldehyde **24** (1.12 g, 4.47 mmol) and bromide **7** (2.76 g, 11.17 mmol) following the procedure described for (−)-**26**. After silica gel flash chromatographic purification (Et_2O/petroleum ether 70:30), 8,4′-oxyneolignan (+)-**27** was obtained (1.51 g, 81% yield, corresponding to a 66% overall yield for five steps from (−)-**5**) along with minor amounts of the *syn*-configured diastereoisomer (corresponding to (−)-raphidecursinol B (−)-**2**) (dr = 85:15). Compound (+)-**27**: a white resin; $[\alpha]_D^{25}$ +13.5° (*c* 0.9, $CHCl_3$); [lit.[14b] $[\alpha]_D^{25}$ +7.2° (*c* 1.0, $CHCl_3$)]; CD (hexane/2-propanol, 90:10) 275 nm ($\Delta\epsilon$ = −1.77), 244 nm ($\Delta\epsilon$ = −12.40), 230 nm ($\Delta\epsilon$ = +1.86); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.49 (s, 2H, Ar), 6.42 (s, 2H, Ar), 5.93 (ddt, *J* = 16.8, 9.6, 6.6 Hz, 1H, H8′), 5.09 (dq, *J* = 17.2, 1.8 Hz, 1H, H9′), 5.06 (dq, *J* = 9.6, 1.8 Hz, 1H, H9′), 4.74 (d, *J* = 1.8 Hz, 1H, H7), 4.29 (qd, *J* = 6.0, 2.4 Hz, 1H, H8), 4.12 (br s, 1H, OH), 3.82 (s, 6H, OMe), 3.79 (s, 6H, OMe), 3.76 (s, 3H, OMe), 3.31 (d, *J* = 6.6 Hz, 2H, H7′), 1.07 (d, *J* = 6.6 Hz, 3H, H9); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.7 (2C, C Ar), 153.2 (2C, C Ar), 137.2 (C8′), 136.4 (2C, C Ar), 135.9 (2C, C Ar), 116.4 (C9′), 105.6 (2C, CH Ar), 103.1 (2C, CH Ar), 82.4 (C8), 73.3 (C7), 61.0 (OMe), 56.3 (4C, OMe), 40.8 (C7′), 13.1 (C9). Anal. Calcd for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 66.10; H, 7.30. HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{30}O_7Na$ 441.1889. Found 441.1904.

(1*S*,2*R*)-2-[2-Methoxy-4-((*E*)-prop-1-enyl)phenoxy]-1-(3,4-dimethoxyphenyl)propan-1-ol (−)-28.[30] The title compound was prepared from aldehyde **25** (1.04 g, 4.72 mmol) and bromide **8** (2.56 g, 11.80 mmol) following the procedure described for (−)-**26**. After silica gel flash chromatographic purification (Et_2O/petroleum ether 55:45), 8,4′-oxyneolignan (−)-**28** was obtained (1.39 g, 82% yield, corresponding to a 69% overall yield for five steps from (−)-**5**) along with minor amounts of the *syn*-configured diastereoisomer (corresponding to (−)-virolin (−)-**3**) (dr = 85:15). Compound (−)-**28**: a white resin; $[\alpha]_D^{25}$ −44.8° (*c* 0.9, $CHCl_3$); CD (hexane/2-propanol, 90:10) 289 nm ($\Delta\epsilon$ = −1.96), 255 nm ($\Delta\epsilon$ = −4.95), 234 nm ($\Delta\epsilon$ = +4.89); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.8−7.0 (m, 4H, Ar), 6.79 (M, 2H, Ar), 6.32 (dq, *J* = 15.6, 1.2 Hz, 1H, H7′), 6.12 (dq, *J* = 16.0, 6.6 Hz, 1H, H8′), 4.81 (d, *J* = 2.4 Hz, 1H, H7), 4.31 (qd, *J* = 6.0, 3.0 Hz, 1H, H8), 3.85 (s, 6H, OMe), 3.82 (s, 3H, OMe), 3.51 (br s, 1H, OH), 1.84 (dd, *J* = 6.6, 1.2 Hz, 3H, H9′), 1.14 (d, *J* = 6.0 Hz, 3H, H9); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.6 (C Ar), 149.0 (C Ar), 148.3 (C Ar), 145.8 (C Ar), 133.8 (C Ar), 132.7 (C Ar), 130.7 (C7′), 125.2 (C8′), 120.0 (CH Ar), 119.2 (CH Ar), 118.6 (CH Ar), 111.0 (CH Ar), 109.6 (CH Ar), 109.5 (CH Ar), 82.6 (C8), 73.7 (C7), 56.1 (2C, OMe), 56.0 (OMe), 18.6 (C9′), 13.6 (C9). Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.42; H, 7.39. HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{26}O_5Na$ 381.1678. Found 381.1687.

Acknowledgment. We thank the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR, COFIN 2004 and FIRB 2001) for financial support. We also thank the Centro Interfacoltà Misure "G. Casnati" (Università di Parma) for instrumental facilities.

Supporting Information Available: Experimental procedures and spectral data for compounds **6**, **10**, **12**, **15**, **17**−**19**, **21**−**25**, NMR data (Table S1), and copies of ^{1}H and ^{13}C NMR spectra for compounds (−)-**1**, (−)-**2**, (−)-**3**, (−)-**26**, (+)-**27**, and (−)-**28**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO061521T