OL | Organic Letters

pubs.acs.org/OrgLett Letter

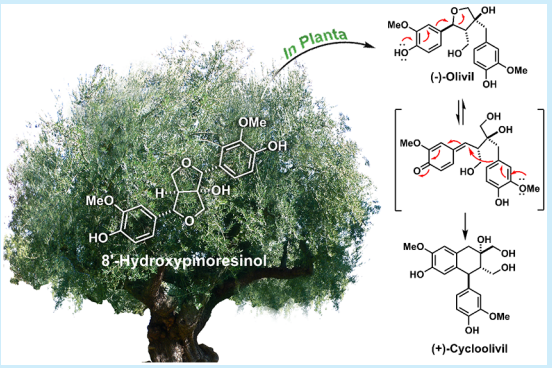
Total Synthesis and Stereochemical Confirmation of (−)-Olivil, (+)-Cycloolivil, (−)-Alashinols F and G, (+)-Cephafortin A, and Their Congeners: Filling in Biosynthetic Gaps

Jithender Reddy Vakiti and Stephen Hanessian*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c00773 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: For the first time, we describe the stereocontrolled total syntheses of olivil, cephafortin A, 4-des-*O*-methyl-4-*O*-rhamnosyl cephafortin A, and alashinol F from a common precursor using a combination of chemoenzymatic and biomimetic methods for the systematic introduction of functional groups on three vicinal stereogenic carbon atoms. We revised the previously assigned stereochemistry of (+)-cephafortin A, which was reported as the enantiomer. Natural and unnatural congeners provide insights into the biogenetic interrelations of members of this family.



The lignan family of natural products is among the most abundant in the plant world and is historically relevant[1] and frequently utilized in traditional Chinese medicines.[2] Their antioxidant, antidiabetic, antiangiogenesis, and antitumor activities, among others, have been known for some time.[3] A unique subgroup of lignans consists of 4-hydroxymethyl tetrahydrofuran or 4-hydroxymethyl dihydrofuran-2-(5*H*)-one (butyrolactone) cores with appended aryl and benzyl moieties as well as a tertiary hydroxyl group varying in its position and spatial disposition (Figure 1).

(−)-Olivil (**1**), first reported by Pelletier in 1816,[4] was originally obtained from extracts of olive tree bark. Since then, it has been frequently isolated from a variety of plant sources and is still considered to be a "reference" compound for new isolates[5] (Figure 1). The constitutional structure of olivil was reported by Freudenberg and Weinges in 1962,[6] subsequent to an initial assignment by Vanzetti.[7] These findings were questioned by Ayres and Mhasalkar, and alternatives were suggested.[8] The first ^{13}C NMR spectral data for olivil were reported by Roux and coworkers in 1979.[9] Complete spectroscopic data for olivil were provided by Ghogomu-Tih and coworkers in 1985.[10] These initial studies were followed by the isolation and characterization of (−)-olivil from various sources by Nishibe and coworkers[11] as well as by other groups.[12] The currently accepted structure and relative stereochemistry of (−)-olivil are shown in Figure 1. Despite the plethora of reports describing the isolation of (−)-olivil, there is considerable variation in the physical data, especially with regard to optical rotation values and melting points depending on the original plant source.[13] The structures and stereochemistries of the related tetrahydrofuran lignans (−)-diepiolivil (**4**),[14] (−)-massinoresinol (**2**),[15] and (−)-berchemol (**3**)[16] having different patterns of hydroxylation at C-8 and C-8′ have been proposed based on comparisons of NMR and circular dichroism data. To the best of our knowledge,

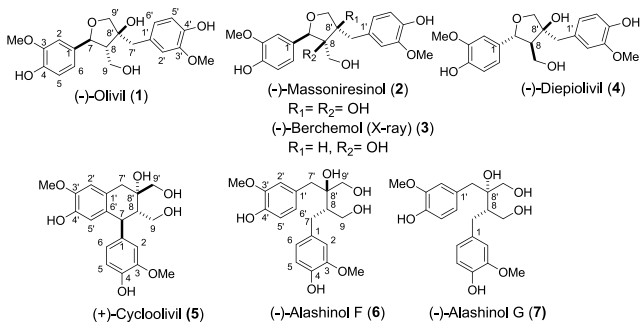


Figure 1. Structures of (−)-olivil (**1**) and related naturally occurring tetrahydrofuran lignan congeners. Structures of (+)-cycloolivil (**5**) and the acyclic metabolites (−)-alashinol F and (−)-alashinol G (**6** and **7**).

Received: February 28, 2020

https://dx.doi.org/10.1021/acs.orglett.0c00773
Org. Lett. XXXX, XXX, XXX−XXX

(−)-berchemol (**3**) is the only congener whose structure and stereochemistry have been definitively confirmed by X-ray crystallographic analysis.[16] Another frequently found compound from extracts of plants producing (−)-olivil is (+)-cycloolivil (**5**).[8,10,11,17] Very recently, two acyclic lignans named (−)-alashinol F (**6**) and (−)-alashinol G (**7**) were reported to exhibit antimyocardial ischemic activity.[18,19] Alashinol G has been previously isolated from the roots of *Carissa carandas* and designated as carinol.[20] A total synthesis of (−)-carinol was reported by Brown and coworkers in 1990.[21]

The structure and stereochemistry of an unnamed butyrolactone flavonoid glycoside isolated from the sugar maple family of *Aceracea* was proposed to be the rhamnoside **8** based on detailed NMR data (Figure 2).[22] The aglycone **9** was

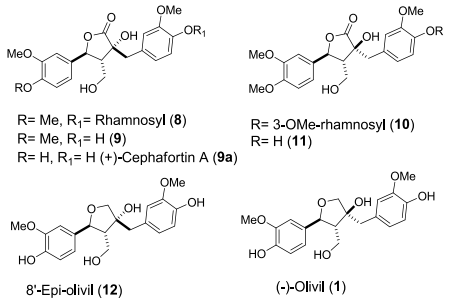


Figure 2. Structures of unnamed natural butyrolactone-type lignans **8** and **10**, their respective epimeric aglycones **9** and **11**, as well as (+)-cephafortin A (**9a**). Stereochemical correlation with corresponding tetrahydrofuran counterparts, (−)-olivil (**1**) and (−)-8′-epi-olivil (**12**).

independently isolated and arbitrarily designated as the enantiomer.[23] Recently, the bis-phenolic variant (+)-cephafortin A (**9a**) was isolated from the twigs and leaves of *Cephalotaxus fortunei* and assumed to be the enantiomer.[24] It follows that the lactone **8** can now be named 4-des-*O*-methyl-4-*O*-rhamnosyl cephafortin A. Exceptionally, lactone **8** harbors an α-oriented tertiary hydroxyl group (butyrolactone numbering). An otherwise identical compound, except for the presence of an inverted tertiary hydroxyl group isolated from *Cephalotaxus koreana*, was designated as the 3-*O*-methyl rhamnoside **10**.[25] However, the corresponding aglycone (**11**) is yet to be found and isolated.

The biosynthesis of lignans is believed to initiate with coniferyl alcohol, leading to a pivotal central intermediate (+)-pinoresinol (**13**), which undergoes a series of biosynthetic oxido-reductive transformations to (+)-lariciresinol (**14**) and (−)-secoisolariciresinol (**15**).[13] Pioneering studies primarily by Davin and Lewis have enriched our understanding of these complex processes.[1,26−28] Another minor subclass of oxidized lignans consists of 8′-hydroxy and 8,8′-dihydroxy pinoresinols, which exhibit antioxidant activity.[29] Despite the rich history of lignans, the discrete biosynthetic steps leading to tertiary hydroxylated lignans, such as the ones shown in Figures 1 and 2, are scantly documented. (−)-Alashinol G (**7**) (carinol) with an 8′*S*/8*S* trans junction is the hydroxylated version of the pivotal acyclic lignan (−)-secoisolariciresinol **15** (Figure 3). Similarly, olivil is the 8′-hydroxylated form of (+)-lariciresinol (**14**). It is tempting to speculate that as in the case of pinoresinol, a bioreductive pathway starting with 8′-hydroxy pinoresinol (**16**) involving sequential NAPDH-mediated

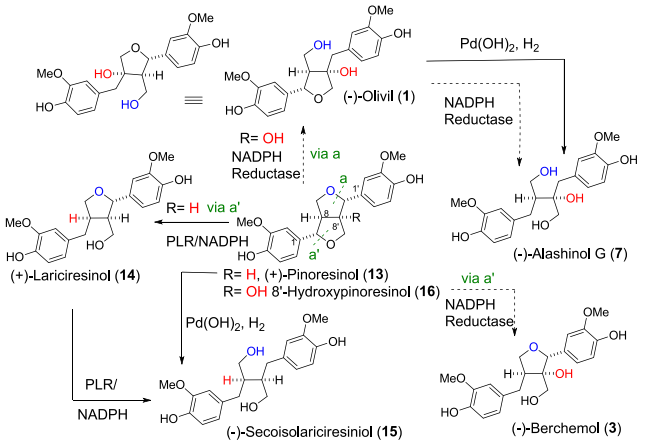


Figure 3. Established biosynthetic pathway from (+)-pinoresinol (**13**) to (+)-lariciresinol (**14**) and (−)-secoisolariciresinol (**15**) according to Lewis et al. (→).[1d] Proposed possible pathway from 8′-hydroxypinoresinol (**16**) (dotted arrow). Conversion of synthetic (−)-olivil (**1**) to (−)-alashinol G (**7**) and (+)-pinoresinol to (−)-secoisolariciresinol (→) by catalytic hydrogenation $Pd(OH)_2/H_2$.[13] PLR = pinoresinol−lariciresinol−secoisolariciresinol reductase, NADPH = reduced nicotinamide adenine dinucleotide phosphate.

benzylic ether cleavages[27] can, in principle, lead to the hydroxylated lignans alashinol G, olivil, and berchemol depending on which benzylic ether bond is cleaved (Figure 3). Although there may be alternative biosynthetic pathways,[13] sequential bioreductive benzylic ether cleavage is a plausible proposal because pinoresinol, 8′-hydroxypinoresinol, olivil, and berchemol have all been isolated from the same plant.[30]

It is noteworthy to draw attention to a common biosynthetic progenitor that links the tetrahydrofuran and butyrolactone lignans harboring identical substituents via well-established oxido-reductive processes.[27] Collectively, the two pairs of lignans **1**/**11** and **9a**/**12** constitute a biogenetically related quartet.

In numerous instances, the isolation of olivil is accompanied by other biosynthetic intermediates, such as cycloolivil.[8] We propose that once activated *in planta*, olivil can lead to cycloolivil by an intramolecular Friedel−Crafts type cyclization, on the one hand, and to the acyclic metabolite alashinol G, on the other hand, by the action of a reductase (Figure 4). We have successfully reproduced these transformations by chemical means.[13]

To the best of our knowledge, and with the exception of (±)-cycloolivil[31] and (−)-alashinol G (carinol),[21] there are no reported total chemical syntheses of any of the lignans shown in Figures 1 and 2, including the venerable (−)-olivil.[32] Some

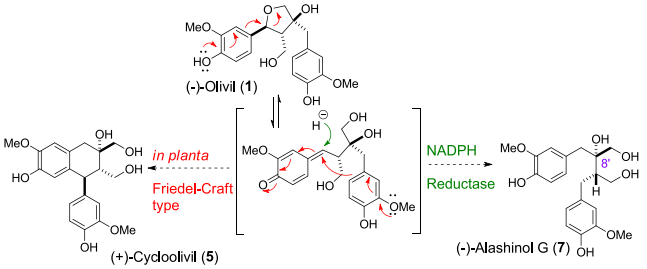


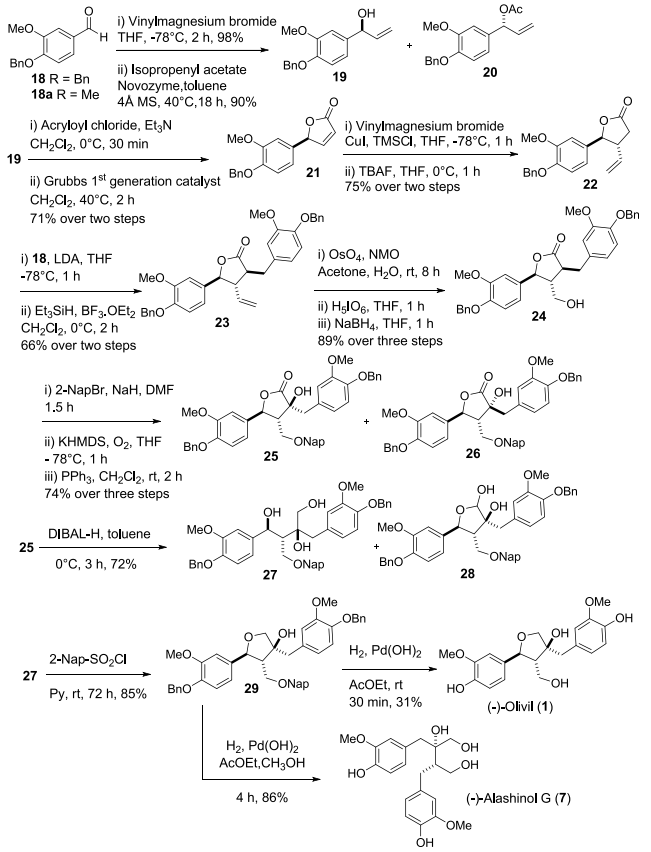
Figure 4. Proposed rearrangement of (−)-olivil to (+)-cycloolivil and bioreductive opening of (−)-olivil to (−)-alashinol G.

https://dx.doi.org/10.1021/acs.orglett.0c00773
Org. Lett. XXXX, XXX, XXX−XXX

efforts toward the synthesis of olivil-like compounds as diastereomers derived from D-xylose[33] and D-arabinose[34] as chirons have been described. A report addressing the total synthesis of (±)-cycloolivil alludes to a crystal structure with no further detail.[31]

Herein we report on the first total synthesis of (−)-olivil (**1**), (+)-cycloolivil (**5**), the *Acer* rhamnoside (**8**), (+)-cephafortin A (**9a**), unnamed lignan (**9**) (*O*-methyl cephafortin A), (−)-alashinols F and G (**6** and **7**), as well as (−)-8′-epi-olivil (**12**) and (+)-8′-epi-cycloolivil (**17**) from a common precursor (Scheme 1).

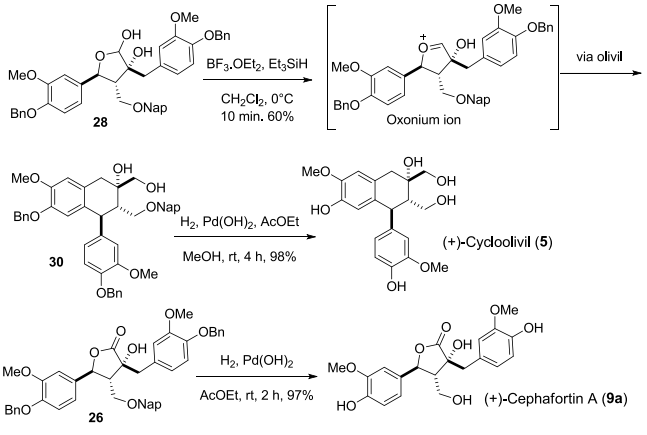
Scheme 1. Synthetic Route to (−)-Olivil (1) and (−)-Alashinol G (7)



In considering a synthetic strategy toward the target lignans, we sought to arrive at a common intermediate that would lead to the naturally occurring products as well as to their respective, yet-to-be-isolated congeners. The linear sequence started with the addition of vinylmagnesium bromide to 3-methoxy-4-benzyloxy benzaldehyde **18** to give the corresponding allylic alcohol (Scheme 1). Novozyme-mediated acetylation with 2-acetoxypropene[35] led to the *S*-alcohol **19** and the *R*-acetate **20**. Esterification of **19** with acryloyl chloride followed by ring-closing metathesis with the Grubbs first-generation catalyst[36] gave the butenolide **21** in 71% yield. 1,4 Conjugate addition with vinylmagnesium/CuI followed by treatment with TBAF led to the vinyl lactone **22**, which was converted to the aldol product with aldehyde **18**. Deoxygenation of the benzylic alcohol group mediated by $Et_3SiH/BF_3{\cdot}OEt_2$ afforded lactone **23** as a single isomer (Scheme 1). A Lemieux−Johnson oxidation of **23** followed by sodium borohydride reduction gave alcohol **24** in high overall yield, which was protected as the naphthylmethyl (Nap) ether. The stereoselective introduction of the tertiary hydroxyl group at C-4 was the next challenge. Direct hydroxylation of the K-enolate with MoOPh[37] or the Davis oxaziridine reagent[38] gave mediocre yields favoring the "unnatural" R configuration. However, hydroxylation of the Li or K-enolate with molecular oxygen, as reported by Belletire,[39] Brown,[40] and Mäkelä[41] for (−)-nortrachelogenin related butyrolactones, led to a 1:1.4 mixture of hydroperoxides (not shown),[13] which were chromatographically separated and treated with triphenylphosphine to give the *β*-hydroxy lactones **25** and **26**, respectively, in 74% overall yield for three steps. Alternatively, hydroxylation in the presence of trimethylphosphite led to **25** and **26** in 85% combined yield and with a ratio of 1:1.5. An X-ray crystal structure of an intermediate hydroperoxide resulting from **26** confirmed the stereochemical assignment.[13] The reduction of **25** with DIBAL-H led to the triol **27** and the hemiacetal **28** in 72% yield with a ratio of 1:1, respectively. Treatment of the triol **27** with 2-naphthylsulfonyl chloride ensured a selective reaction at the primary hydroxyl group, which underwent a slow but selective intramolecular displacement by the benzylic hydroxyl group to give the corresponding tetrahydrofuran **29**. Hydrogenation with Pearlman's catalyst in EtOAc led to olivil (**1**) and alashinol G (**7**) in a ratio of 1.1:1. However, hydrogenation in the presence of EtOAc and MeOH led to alashinol G (**7**).

Treatment of the hemiacetal **28** with $Et_3SiH/BF_3{\cdot}OEt_2$ led directly to the cycloolivil precursor **30** via the oxonium ion and *in situ* reduction to olivil, which underwent an intramolecular rearrangement. Catalytic hydrogenation of **30** afforded (+)-cycloolivil (**5**).[13] Catalytic hydrogenation of **26** afforded cephafortin A (**9a**), the newest member of the butyrolactone lignans[13,24] (Scheme 2).

Scheme 2. Synthesis of (+)-Cycloolivil (5) and (+)-Cephafortin A (9a)

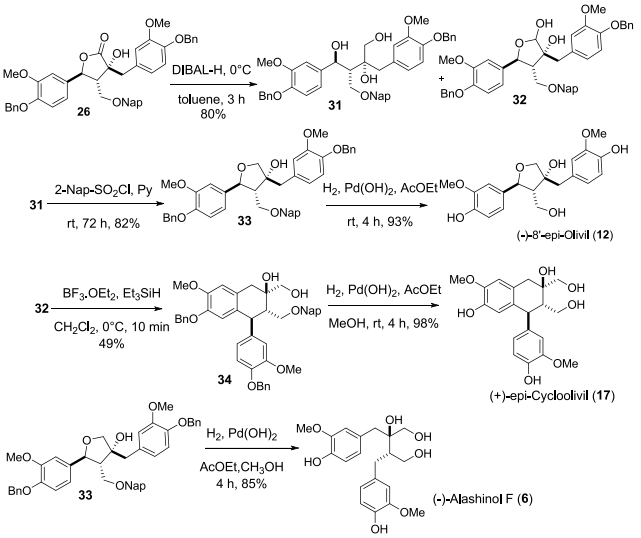


Following the same protocol shown in Scheme 1 led to the synthesis of the unnatural (−)-8′-epi-olivil (**12**) and (+)-8′-epi-cycloolivil (**17**). Catalytic hydrogenation of **33** in AcOEt/MeOH afforded (−)-alashinol F (**6**) (Scheme 3).

The lactone rhamnoside **8**, its aglycone **9**, and the recently reported[24] bis-phenolic congener (+)-cephafortin A **9a** appear to be the exception among the tetrahydrofuran and butyrolactone lignans, in that they possess an *α*-configured tertiary hydroxyl group (Figure 2).[22−24] The reported spectroscopic data for **8** encouraged us to initiate a total

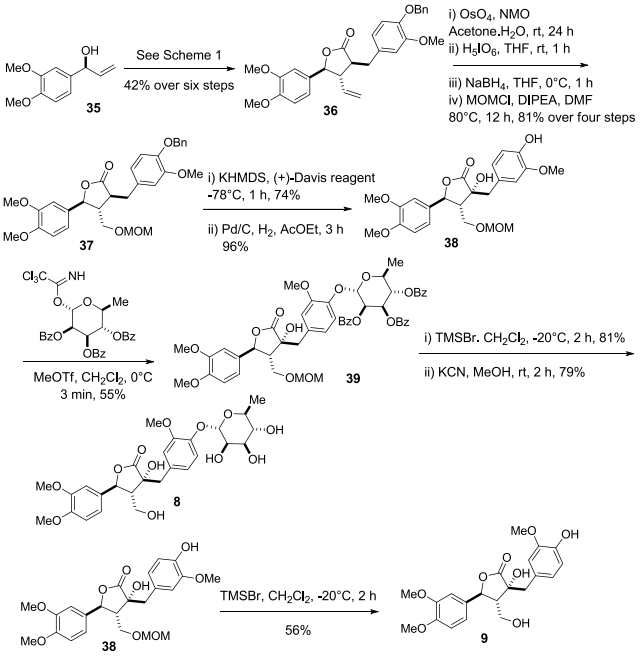
https://dx.doi.org/10.1021/acs.orglett.0c00773
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Synthesis of (−)-8′-Epi-olivil (12), (+)-8′-Epi-cycloolivil (17), and (−)-Alashinol F (6)



synthesis of this apparently unique lignan lactone congener. Following the sequence in Scheme 1 and starting with the aldehyde **18a** (Scheme 1) led to intermediate **35**, which was elaborated to the vinyl lactone **36** (Scheme 4). Lemieux–

Scheme 4. Synthesis of Unnamed Natural Lignans 8 and 9



Johnson oxidation followed by reduction of the resulting aldehyde and protection as the MOM ether gave **37** in good overall yield. Treatment of the K enolate with the Davis oxaziridine reagent led to the C-4′ α-hydroxylated lactone, which was de-O-benzylated to expose the phenolic hydroxyl group. Glycoside formation adopting the Schmidt protocol[42] using methyl triflate as an activator gave **39**, which was treated with TMSBr and then KCN to cleave the benzoate esters[43] and gave the intended lactone rhamnoside **8**.[13] Cleavage of the MOM ether of **38** with TMSBr gave unnamed lignan **9**, which was incorrectly assumed to be the enantiomer.[23]

In conclusion, we have reported the total synthesis of (−)-olivil, (+)-cycloolivil, (−)-alashinols F, the *Acer saccarrum* lactone **8**, and its aglycone **9** as well as the stereochemical revision of **9** and (+)-cephafortin A **9a** (previously reported as the enantiomers) for the first time from a common precursor. The synthetic route also allowed us to obtain the known (−)-alashinol G as well as (−)-8′-epi-olivil and (+)-8′-epi-cycloolivil, which are plausible new metabolites. Their availability as authentic samples will help their detection and eventual isolation from extracts from diverse plant sources. The structural and stereochemical confirmation of the downstream oxido-reduction metabolites (−)-alashinols F and G (carinol) by total synthesis consolidates a decades-old biochemical paradigm initiated with (+)-pinoresinol (or its 8′-hydroxy congener). Lignans in the (−)-olivil family and related butyrolactone congeners can now be biosynthetically interrelated with existing members of this century-old and seemingly unchallenged family of plant natural products.[44,45]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00773.

General information, biosynthetic pathways and references, experimental procedures and characterization, physical data comparison for (−)-olivil **1** and (+)-cycloolivil **5**, TLC of synthetic (−)-olivil **1** and (−)-8′-epi-olivil **12**, X-ray crystallography data, and spectra (PDF)

Accession Codes

CCDC 1973819−1973820 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Stephen Hanessian − *Department of Chemistry, Université de Montreal, Montreal, Quebec H3C 3J7, Canada;* orcid.org/0000-0003-3582-6972; Email: stephen.hanessian@umontreal.ca

Author

Jithender Reddy Vakiti − *Department of Chemistry, Université de Montreal, Montreal, Quebec H3C 3J7, Canada*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00773

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank NSERC and the NSERC/Servier Senior Industrial Research Chair program for generous financial assistance. We thank Dr. Daniel Simard of the X-ray facility at the Universite de Montreal. We also thank Mattia Fredditori for technical assistance during the first phase of this project

https://dx.doi.org/10.1021/acs.orglett.0c00773
Org. Lett. XXXX, XXX, XXX−XXX

REFERENCES

(1) For selected reviews, see: (a) Teponno, R. B.; Kusari, S.; Spiteller, M. Recent advances in research on lignans and neolignans. *Nat. Prod. Rep.* **2016**, *33*, 1044−1092. (b) Topcu, G.; Demirkiran, O. Lignans from *Taxus* Species. *Top.Heterocycl.Chem.* **2007**, *11*, 103−144. (c) Lewis, N. G.; Davin, L. B.; Sarkanen, S. In *Comprehensive Natural Products Chemistry*; Barton, D. H. R., Nakanishi, K., Meth-Cohn, O., Eds.; Elsevier: Oxford, U.K., 1999; Vol. 3, pp 617−745. (d) Ayres, D. C.; Loike, J. D. *Chemistry and Pharmacology of Natural Products. Lignans: Chemistry, Biology and Clinical Properties*; Cambridge University Press: Cambridge, U.K., 1990. (e) Ward, R. S. *Tetrahedron* **1990**, *46*, 5029−5041. (f) Hearon, W.; MacGregor, W. The naturally occurring lignans. *Chem. Rev.* **1955**, *55*, 957−1068.

(2) See, for example: Zhu, C.; Jing, L.; Yu, N.; Yang, X.; Zhao, Y. *Acta Pharm. Sin. B* **2013**, *3*, 109−112 and references cited therein.

(3) (a) Xu, J.-P. In *Cancer Inhibitors from Chinese Natural Medicine*; CRC Press, 2017. (b) Satake, H.; Koyama, T.; Bahabadi, S.; Matsumoto, E.; Ono, E.; Murata, J. Essences of Metabolic Engineering of Lignan Biosynthesis. *Metabolites* **2015**, *5*, 270−290 and references cited therein. (c) Zhu, C.; Jing, L.; Yu, N.; Yang, X.; Zhao, Y. *Acta Pharm. Sin. B* **2013**, *3*, 109−112 and references cited therein. (d) MaCrae, W. D.; Towers, G. H. N. Biological activities of lignans. *Phytochemistry* **1984**, *23*, 1207−1220.

(4) As cited in: Gmelin, L. *Handbook of Organic Chemistry*; London, U.K., 1862; Vol. *10*, pp 197−199. See also: Pelletier. *Ann. Chim. Phys.*, *51*, 196. Pelletier. *Ann. Pharm.*, *6*, 31. Pelletier. *Ann. Chim. Phys.* **1816**, *3*, 105. Pelletier. *J. Pharm.*, *2*, 336.

(5) See, for example: Jang, S. W.; Suh, W. S.; Kim, C. S.; Kim, K. H.; Lee, K. R. *Arch. Pharmacal Res.* **2015**, *38*, 1943−1951.

(6) (a) Freudenberg, K.; Weinges, K. *Tetrahedron Lett.* **1962**, *3*, 1077−1079. (b) Smith, M. *Tetrahedron Lett.* **1963**, *4*, 991−992.

(7) Vanzetti, B. L. *Acad. d'Italia, Mem. Classe Sci.* **1937**, *13*, 411.

(8) Ayres, D.; Mhasalkar, S. *Tetrahedron Lett.* **1964**, *5*, 335−339.

(9) Viviers, P. M.; Ferreira, D.; Roux, D. G. *Tetrahedron Lett.* **1979**, *20*, 3773−3776.

(10) Ghogomu-Tih, R.; Bodo, B.; Nyasse, B.; Sondengam, B. *Planta Med.* **1985**, *51*, 464−464.

(11) (a) Deyama, T.; Ikawa, T.; Kitagawa, S.; Nishibe, S. *Chem. Pharm. Bull.* **1986**, *34*, 523−527. (b) Tsukamoto, H.; Hisada, S.; Nishibe, S. *Chem. Pharm. Bull.* **1984**, *32*, 4482−4489. (c) Deyama, T.; Ikawa, T.; Nishibe, S. *Chem. Pharm. Bull.* **1985**, *33*, 3651−3657. (d) Tsukamoto, H.; Hisada, S.; Nishibe, S. *Chem. Pharm. Bull.* **1984**, *32*, 2730−2735.

(12) (a) Abe, F.; Yamauchi, T.; Wan, A. S. *Chem. Pharm. Bull.* **1988**, *36*, 795−799. (b) Chang, M.-J.; Hung, T. M.; Min, B.-S.; Kim, J.-C.; Woo, M. H.; Choi, J. S.; Lee, H. K.; Bae, K. *Biosci., Biotechnol., Biochem.* **2008**, *72*, 2750−2755. (c) Kadowaki, E.; Yoshida, Y.; Nitoda, T.; Baba, N.; Nakajima, S. *Biosci., Biotechnol., Biochem.* **2003**, *67*, 415−419.

(13) See the Supporting Information.

(14) Ren, Y.; Chai, H.; Goetz, M.; Kinghorn, A. D. *Tetrahedron Lett.* **2013**, *54*, 4854−4858.

(15) Shen, Z.; Theander, O. *Phytochemistry* **1985**, *24*, 364−365.

(16) Sakurai, N.; Nagashima, S.-i.; Kawai, K.-i.; Inoue, T. *Chem. Pharm. Bull.* **1989**, *37*, 3311−3315.

(17) (a) Wahab Sab, B. A.; Jacob, J.; Manjunath, G. G.; Singh, V. K.; Mundkinajeedu, D.; Shankarappa, S. *Pharmacogn. Res.* **2015**, *7*, 45. (b) Yue, Z.; Qin, H.; Li, Y.; Sun, Y.; Wang, Z.; Yang, T.; Liu, L.; Wang, M.; Feng, F.; Mei, Q. *Molecules* **2013**, *18*, 4766−4775.

(18) (a) Venkateswarlu, R.; Kamakshi, C.; Moinuddin, S. G.; Subhash, P. V.; Ward, R. S.; Pelter, A.; Hursthouse, M. B.; Light, M. E. *Tetrahedron* **1999**, *55*, 13087−13108. (b) Ward, R. S.; Pelter, A.; Venkateswarlu, R.; Kamakshi, C.; Subhash, P. V.; Moinuddin, S. G.; Hursthouse, M. B.; Coles, S. J.; Hibbs, D. E. *Tetrahedron* **1999**, *55*, 13071−13086. (c) Korner, G.; Vanzetti, L. *Atti R. Accad. Lincei, Rend.* **1903**, *12* (1), 122−125 (as cited in ref 9).

(19) Feng, X.; Su, G.; Ye, Y.; Zhang, R.; Yang, X.; Du, B.; Peng, B.; Tu, P.; Chai, X. *Nat. Prod. Res.* **2017**, *31*, 1555−1560.

(20) See, for example: (a) Achenbach, H.; Waibel, R.; Addae-Mensah, I. *Phytochemistry* **1983**, *22*, 749−753. (b) Pal, R.; Kulshreshtha, D. K.; Rastogi, R. P. *Phytochemistry* **1975**, *14*, 2302−2303.

(21) Khamlach, K.; Dhal, R.; Brown, E. *Heterocycles* **1990**, *31*, 2195−2199.

(22) Yoshikawa, K.; Kawahara, Y.; Arihara, S.; Hashimoto, T. *J. Nat. Med.* **2011**, *65*, 191−193.

(23) (a) Li, L.; Seeram, N. P. *J. Agric. Food Chem.* **2011**, *59*, 7708−7716. (b) Li, L.; Seeram, N. P. J. *J. Agric. Food Chem.* **2010**, *58*, 11673−11679.

(24) Zhao, J.-X.; Fan, Y.-Y.; Xu, J.-B; Gan, L.-S; Xu, C.-H.; Ding, J.; Yue, J.-M. *J. Nat. Prod.* **2017**, *80*, 356−362.

(25) Yoon, K. D.; Jeong, D. G.; Hwang, Y. H.; Ryu, J. M.; Kim, J. *J. Nat. Prod.* **2007**, *70*, 2029−2032.

(26) For selected reviews, see: (a) Davin, B. L.; Lewis, N. G. *Phytochem. Rev.* **2003**, *2*, 257−288. (b) Suzuki, S.; Umezawa, T. *J. Wood Sci.* **2007**, *53*, 273−284. (c) Umezawa, T. *Phytochem. Rev.* **2003**, *2*, 371−390. (d) Kato, A.; Hashimoto, Y.; Kidokor, M. *J. Nat. Prod.* **1979**, *42*, 159−162. (e) Umezawa, T.; Okunishi, T.; Shimada, M. *Wood Res.* **1997**, *84*, 62−75. (f) Nishibe, S.; Hisada, S.; Inagaki, I. *Phytochemistry* **1971**, *10*, 2231−2232.

(27) Chu, A.; Dinkova, A.; Davin, L. B.; Bedgar, D. L.; Lewis, N. G. *J. Biol. Chem.* **1993**, *268*, 27026−27033.

(28) (a) Sainvitu, P.; Nott, K.; Richard, G.; Blecker, C.; Jerome, C.; Wathelet, J.-P.; Paquot Deleu, M. *Biotechnol. Agron. Soc. Environ.* **2012**, *16*, 115−124. (b) Niemeyer, H. B.; Honig, D. M.; Kulling, S. E.; Metzler, M. *J. Agric. Food Chem.* **2003**, *51*, 6317−6325. (c) Ford, J. D.; Huang, K.-S.; Wang, H.-B.; Davin, L. B.; Lewis, N. G. *J. Nat. Prod.* **2001**, *64*, 1388. (d) Kuhlmann, S.; Kranz, K.; Lucking, B.; Alfermann, A. W.; Petersen, M. *Phytochem. Rev.* **2002**, *1*, 37−431. (e) Katayama, T.; Davin, L. B.; Lewis, N. G. *Phytochemistry* **1992**, *31*, 3875−3881.

(29) See, for example: (a) Piccinelli, A. L.; Arana, S.; Caceres, A.; Sorrentino, R.; Rastrelli, L. *J. Nat. Prod.* **2004**, *67*, 1135. (b) Luecha, P.; Umehara, K.; Miyase, T.; Noguchi, H. *J. Nat. Prod.* **2009**, *72*, 1954−1959. (c) Chang, M.; Hung, T. M.; Min, B.-S.; Kim, J.-C.; Woo, M. H.; Choi, J. S.; Lee, H. K.; Bae, K. *Biosci., Biotechnol., Biochem.* **2008**, *72*, 2750−2755.

(30) Schumacher, B.; Scholle, S.; Holzl, J.; Khudeir, N.; Hess, S.; Muller, C. E. *J. Nat. Prod.* **2002**, *65*, 1479−1485.

(31) Moritani, Y.; Ukita, T.; Ohmizu, H.; Iwasaki, T. *J. Chem. Soc., Chem. Commun.* **1995**, 671−672.

(32) For selected reviews, see: (a) Peng, Y. In *From Biosynthesis to Total Synthesis: Strategies and Tactics for Natural Products*; Zografos, A L., Ed.; J. Wiley & Sons: Hoboken, NJ, 2016; pp 331−379. (b) Del Signore, G.; Berner, O. M. *Stud. Nat. Prod. Chem.* **2006**, *33*, 541−600.

(33) (a) Yamauchi, S.; Kinoshita, Y. *Biosci., Biotechnol., Biochem.* **2000**, *64*, 1563−1571. (b) Yamauchi, S.; Hayashi, Y.; Kirikihira, T.; Masuda, T. *Biosci., Biotechnol., Biochem.* **2005**, *69*, 113−122.

(34) Yamauchi, S.; Kinoshita, Y. *Biosci., Biotechnol., Biochem.* **2000**, *64*, 2320−2327.

(35) Stambasky, J.; Malkov, A. V.; Kocovsky, P. *J. Org. Chem.* **2008**, *73*, 9148−9150.

(36) (a) Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651−4654. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.

(37) (a) Moritani, Y.; Fukushima, C.; Ukita, T.; Miyagishima, T.; Ohmizu, H.; Iwasaki, T. *J. Org. Chem.* **1996**, *61*, 6922−6930. (b) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944−5946. (c) Vedejs, E.; Larsen, S. *Org. Synth.* **2003**, *64*, 127−127.

(38) (a) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. G.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241−3243. (b) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919−934.

(39) (a) Belletire, J. L.; Fry, D. F. *J. Org. Chem.* **1988**, *53*, 4724−4729. (b) Belletire, J. L.; Ho, D. M.; Fry, D. F. *J. Nat. Prod.* **1990**, *53*, 1587−1592.

(40) Khamlach, K.; Dhal, R.; Brown, E. *Tetrahedron Lett.* **1989**, *30*, 2221−2224.

https://dx.doi.org/10.1021/acs.orglett.0c00773
Org. Lett. XXXX, XXX, XXX−XXX

(41) Mäkelä, T. H.; Kaltia, S. A.; Wähälä, K. T.; Hase, T. A. *Steroids* **2001**, *66*, 777−784.
(42) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212−235.
(43) (a) Corey, E. J.; Kim, S.; Yoo, S. E.; Nicolaou, K. C.; Melvin, L. S., Jr.; Brunelle, D. J.; Falck, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4620−4622. (b) Herzig, J.; Nudelman, A.; Gottlieb, H. E.; Fischer, B. *J. Org. Chem.* **1986**, *51*, 727−730. (c) Hanessian, S.; Kagotani, M. *Carbohydr. Res.* **1990**, *202*, 67−79.
(44) For the importance of lignans to human health, see: Adlercreutz, H. *Crit. Rev. Clin. Lab. Sci.* **2007**, *44*, 483.
(45) In the course of our work, we realized that the structure of diepiolivil, as reported by Kinghorn and coworkers,[14] corresponds to the enantiomer of 8′-epi-olivil. However, the reported ^{1}H and ^{13}C NMR data in the same solvent and the optical rotation did not match with our 8′-epi-olivil. Rather, there was a strong correlation with the data for olivil, although the question remains open at this time. (See the SI.)

https://dx.doi.org/10.1021/acs.orglett.0c00773
Org. Lett. XXXX, XXX, XXX−XXX