Sustainable Chemistry

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Xylochemistry—Making Natural Products Entirely from Wood

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Dedicated to Prof. Dr. Horst Kunz on the occasion of his 75th birthday

***Abstract:** The first total synthesis of the dimeric berberine alkaloid ilicifoline (ilicifoline B) is reported. Its carbon skeleton is constructed from ferulic acid, veratrole, and methanol. The synthesis reported herein employs starting materials solely derived from wood. The natural product is thus constructed entirely from renewable resources. The same strategy is applied to a formal total synthesis of morphinan alkaloids. The use of wood-derived building blocks (xylochemicals) instead of the conventional petrochemicals represents a sustainable alternative to classical synthetic approaches.*

Our current chemical infrastructure relies heavily on petroleum starting materials that required millions of years to produce under conditions that are not easily accessible in laboratory or industrial settings. Additionally, these materials must be extracted from underground deposits, and their use creates a carbon imbalance in our ecosystem. For these and other reasons, an alternative, sustainable chemical infrastructure must be developed that obviates the need to rely on non-renewable resources and prevents imbalances in the biosphere while remaining cost effective. Attention is increasingly turning to the use of biomass as a raw material for energy and chemical production.[1] Many of these sustainability concepts have their origins in the principles set forth in the Rio Declaration on Environment and Development from The United Nations Conference on Environment and Development in 1992.[2] Implementation of these sustainability concepts requires several key chemical issues to be addressed. First, renewable raw materials must provide sources of chemical building blocks, intermediates, and reagents. Second, to the greatest extent possible, chemical functionality found in naturally occurring renewable chemical building blocks (functional groups, chirality,[3] heteroatoms, etc.) should be employed and maintained rather than destroyed and rebuilt. Third, chemical reagents and catalysts need to be designed to take advantage of the chemistry and functionality in renewable biomass. Fourth, and finally, chemical transformations, modifications, solvents, and syntheses should be designed such that they can be operated and utilized in an efficient continuous production mode rather than as batch processes. These four tasks represent “grand challenges” in chemistry as we seek to move towards a sustainable chemical infrastructure. We propose to do this by relying directly on wood as a starting resource.[4] Herein, we report results that demonstrate the first stages of this approach (xylochemistry): a sequence in which a natural product is produced, the carbon atoms of which are entirely derived from wood-based chemicals.

The target of the synthesis reported herein is ilicifoline, a dimeric berberine-type alkaloid first isolated from *Berberis ilicifolia*, a Patagonian shrub, by Fajardo et al. in 1996.[5] This name was proposed earlier by Itokawa et al. for a triterpene isolated from *Maytenus ilicifolia*, a shrubby tree endemic to southern Brazil and environs.[6] The subject of this report will therefore be referred to as ilicifoline B (**1**).[7] Its monomer, 8-oxopseudopalmatine (**2**), is also a natural product and was isolated from *Guatteria hispida* by Costa et al.[8] Isoquinolone **2** exhibits stronger cytotoxic activity towards MDA-MB-231 cells than its direct biosynthetic precursor, pseudopalmatine (**3**), which can be isolated from *Stephania suberosa*.[9] Scheme 1 depicts the first total synthesis of ilicifoline B.

Ferulic acid (**4**) can be isolated from numerous types of biomass, including rice bran,[10] wheat leaves,[11] vines,[12] or the wood of various trees.[13] O-Methylation at the phenolic hydroxy group with dimethyl sulfate (available by reacting wood alcohol with oleum)[14] produces 3,4-dimethoxycinnamic acid (**5**), which is hydrogenated to acid **6** and transformed into an intermediate isocyanate by Curtius rearrangement of the azide (generated in situ). Subsequent reduction to *N*-formylhomoveratrylamine (**7**) by sodium borohydride is accomplished in the same reaction vessel as part of a one-pot reaction.[15]

Bischler–Napieralski cyclization to 6,7-dimethoxy-3,4-dihydroisoquinoline (**8**) and addition of HCN[16] furnishes α-aminonitrile **9**.[17] Veratrole (**10**), a pyrolysis product of wood,[18] undergoes double bromomethylation with formaldehyde (also derived from wood)[19] and HBr to produce the dibromide, **11**. Compounds **9** and **11** directly produce the berberine alkaloid pseudopalmatine (**3**) in a cascade involving spirocyclization, α-deprotonation, Stevens rearrangement, dehydrocyanation, and oxidation.[20] Aerial oxidation in alkaline solution, possibly through the carbene, produces lactam **2**, which is subsequently dimerized with PIFA/$BF_3 \cdot OEt_2$[21] to ilicifoline B.

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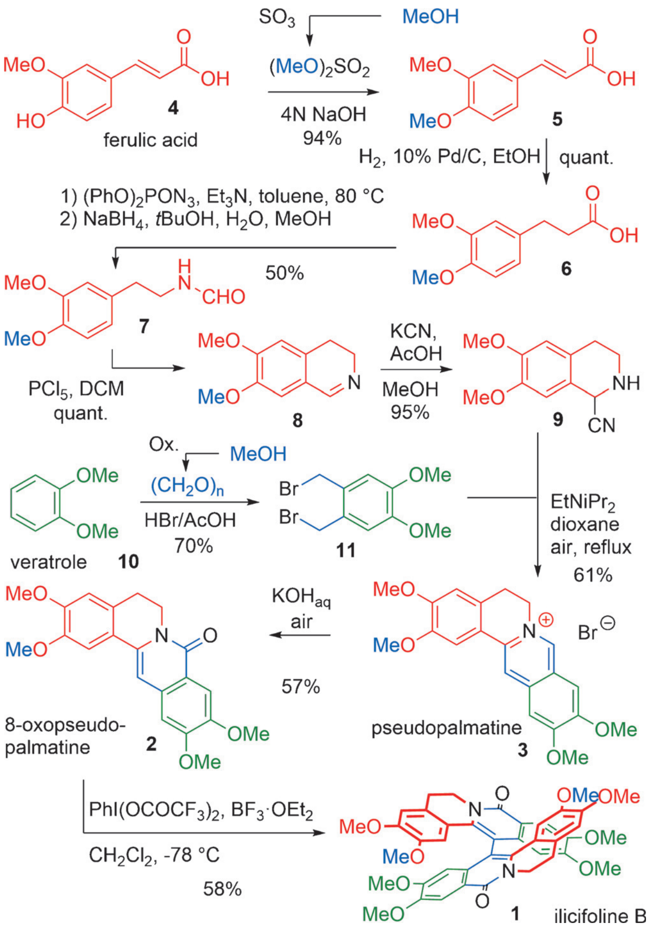

Scheme 1. Synthesis of ilicifoline B from wood-based carbon sources. The color codes trace the origin of the respective atoms.

With regard to the intermediacy of an N-heterocyclic carbene in the transformation **3**→**2**, deprotonation of the sp^2 center in **3** alpha to the iminium group would produce a carbene/carbeneoid intermediate. Preliminary kinetic acidity studies show that this position is indeed the most acidic.

We previously reported an enantioselective synthesis of morphine alkaloids,[22] which can be updated by using the xylochemical principles herein to afford a short and efficient wood-based alternate approach to the synthesis. Starting from methyl ferulate, which is found in the bark of pine trees[23] or obtained by methanolysis of wood, a two-step, one-pot reduction gives methyl 3-(3-methoxyphenyl)propanoate. Subsequently, saponification, Curtius rearrangement, and reduction produces a formamide that can be cyclized to 6-methoxy-3,4-dihydroisoquinoline (see page S51 of the Supporting Information).

From this stage on, the synthesis proceeds as reported earlier, with methyl gallate, another well-known wood component,[24] as the precursor of the morphine A-ring. In the xylochemical version of the synthesis, the required methyl chloroformate can be prepared from carbon monoxide (abundantly available through the pyrolysis of wood, in the form of wood gas), chlorine, and methanol, while iodomethane can be obtained from wood alcohol and HI. The most efficient classical asymmetric synthesis of the morphinans are Trost's synthesis of codeine[25] (14 linear steps, 3.7% overall yield, 94% *ee* by asymmetric catalysis) and Fukuyama's synthesis of morphine[26] (18 linear steps, 4.8% overall yield, 99% *ee* by enzymatic resolution).[27] By comparison, our xylochemical approach provides dihydrocodeine in an overall yield of 11.2%, with 95% *ee* over 15 linear steps starting from methyl ferulate, thus demonstrating that avoiding petrochemical building blocks is not necessarily associated with reduced efficiency.

The implementation of a wood-based chemical economy represents a formidable challenge for the 21st century. New chemistry needs to be developed for the transformation and manipulation of wood-based intermediates. These challenges present opportunities in the areas of catalysis, functional-group transformations, synthesis, and atom origin. In this report, we have demonstrated a first step towards this last area. In these syntheses, all of the carbon atoms (and the vast majority of other atoms) are directly derived from a sustainable chemical source, wood. The oxygen functionality and substitution patterns on the starting aromatic residues have been preserved. The early implementation of the xylochemical approach illustrated herein relies on transformations, reagents, and procedures designed for use with petrochemical starting resources. A considerable opportunity exists to adjust retrosynthetic analysis and synthetic methods to fit a sustainable xylochemical approach and to eventually replace all petrochemicals involved in transformations and purifications with wood-based resources.

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[1] a) M.-M. Titirici, M. Antonietti, *Chem. Soc. Rev.* **2010**, *39*, 103–116; b) A. Behr, L. Johnen, *ChemSusChem* **2009**, *2*, 1072–1095; c) J. O. Metzger, A. Hüttermann, *Naturwissenschaften* **2009**, *96*, 279–288; d) J. H. Clark, V. Budarin, F. E. I. Deswarte, J. J. E. Hardy, F. M. Kerton, A. J. Hunt, R. Luque, D. J. Macquarrie, K. Milkowski, A. Rodriguez, O. Samuel, S. J. Tavener, R. J. White, A. J. Wilson, *Green Chem.* **2006**, *8*, 853–860; e) F. W. Lichtenthaler, S. Peters, *C. R. Chim.* **2004**, *7*, 65–90; f) P. T. Anastas, M. M. Kirchhoff, *Acc. Chem. Res.* **2002**, *35*, 686–694; g) U. Biermann, U. Bornscheuer, M. A. R. Meier, J. O. Metzger, H. J. Schäfer, *Angew. Chem. Int. Ed.* **2000**, *39*, 2206–2224; *Angew. Chem.* **2000**, *112*, 2292–2310.

[2] M. Eissen, J. O. Metzger, E. Schmidt, U. Schneidewind, *Angew. Chem. Int. Ed.* **2002**, *41*, 414–436; *Angew. Chem.* **2002**, *114*, 402–425.

[3] The use of chiral renewable resources: a) P. H. van der Schaft in *Flavours and Fragrances*, Springer, Heidelberg, **2007**, p. 285–301; b) R. I. Hollingsworth, *Chem. Eng.* **2001**, *108*, 66–69; c) H.-U. Blaser, *Chem. Rev.* **1992**, *92*, 935–952; d) S. Hanessian, *Total Synthesis of Natural Products: The "Chiron" Approach, Vol. 3.*, Oxford, Pergamon Press, **1983**.

[4] It is noteworthy that the annual global production of wood and that of petroleum are similar. The current annual wood production is roughly 5×10^9 m^3/year according to the Food and Agriculture Organization of the United Nations: http://www.fao.org/forestry/35445-0e287e9c252335f2936d3-cdc5b6bbd5ff.pdf. The petroleum production is roughly 3.3×10^9 m^3/year according to the U.S. Energy Information Administration/Monthly Energy Review June 2015, see: http://www.eia.gov/totalenergy/data/monthly/pdf/sec11_5.pdf.

[5] V. Fajardo, C. Carcamo, B. Moreno, *Heterocycles* **1996**, *43*, 949–952.

[6] H. Itokawa, O. Shirota, H. Ikuta, H. Morita, K. Takeya, Y. Iitaka, *Phytochemistry* **1991**, *30*, 3713–3716.

[7] The B captures the second suggestion of the name ilicifoline, as well as the source (*Berberis*).

[8] E. V. Costa, M. L. B. Pinheiro, A. Barison, F. R. Campos, M. J. Salvador, B. H. L. N. S. Maia, E. C. Cabral, M. N. Eberlin, *J. Nat. Prod.* **2010**, *73*, 1180–1183.

[9] A. Patra, C. T. Montgomery, A. J. Freyer, H. Guinaudeau, M. Shamma, B. Tantisewie, K. Pharadai, *Phytochemistry* **1987**, *26*, 547–549.

[10] a) W. Wang, J. Guo, J. Zhang, J. Peng, T. Liu, Z. Xin, *Food Chem.* **2015**, *171*, 40–49; b) H.-I. Jun, J.-W. Shin, G.-S. Song, Y.-S. Kim, *J. Food Sci.* **2015**, *80*, C262–C268.

[11] H. K. Lichtenthaler, J. Schweiger, *J. Plant Physiol.* **1998**, *152*, 272–282.

[12] B. Max, A. M. Torrado, A. B. Moldes, A. Converti, J. M. Domínguez, *Biochem. Eng. J.* **2009**, *43*, 129–134.

[13] a) Z. Abe, K. Minami, *Tokyo Daigaku Nogakubu Enshurin Hokoku* **1975**, *67*, 16–19; b) A. S. Gromova, V. I. Lutskii, N. A. Tyukavkina, *Khim. Drev.* **1978**, 99–102; c) K. Y. Jae, B. K. Lim, S. W. Han, G. W. Cheong, Korean patent KR 668260 B1, Jan 16, **2007**; d) J. W. Rowe, A. H. Conner, General Technical Report FPL - United States, Forest Product Laboratory, Madison, Wisconsin **1979**, *18*.

[14] J. Guyot, L. J. Simon, *C. R. Hebd. Seances Acad. Sci.* **1919**, *169*, 795–797.

[15] a) K. Aksu, M. Nar, M. Tanc, D. Vullo, İ. Gülçin, S. Göksu, F. Tümer, C. T. Supuran, *Bioorg. Med. Chem.* **2013**, *21*, 2925–2931; b) D. F. Taber, H. Yu, C. D. Incarvito, A. L. Rheingold, *J. Am. Chem. Soc.* **1998**, *120*, 13285–13290.

[16] It should be noted that cyanide is also available through pyrolysis of wood in the presence of NO$_x$, but in this synthesis, it is eliminated again in the next step and could potentially be recycled.

[17] a) D. Imbri, J. Tauber, T. Opatz, *Chem. Eur. J.* **2013**, *19*, 15080–15083; b) J. Kobor, K. Koczka, *Szegedi Tanarkepzo Foiskola Tud. Kozl.* **1969**, 179–183.

[18] a) M. Polk, M. Phingbodhipakkiya, *Nucl. Chem. Waste Manage.* **1980**, *1*, 111–118; b) M. a. D. Guillén, M. a. J. Manzanos, *Food Chem.* **2002**, *79*, 283–292.

[19] a) T. R. Nunn, J. B. Howard, J. P. Longwell, W. A. Peters, *Ind. Eng. Chem. Process Des. Dev.* **1985**, *24*, 844–852; b) M. Z. M. Salem, M. Böhm, *BioResources* **2013**, *8*, 4775–4790.

[20] G. Lahm, J.-G. Deichmann, A. L. Rauen, T. Opatz, *J. Org. Chem.* **2015**, *80*, 2010–2016.

[21] H. Tohma, M. Iwata, T. Maegawa, Y. Kita, *Tetrahedron Lett.* **2002**, *43*, 9241–9244.

[22] M. Geffe, T. Opatz, *Org. Lett.* **2014**, *16*, 5282–5285.

[23] T. Suga, S. Ohta, K. Munesada, N. Ide, M. Kurokawa, M. Shimizu, E. Ohta, *Phytochemistry* **1993**, *33*, 1395–1401.

[24] S. A. O. Santos, C. Vilela, C. S. R. Freire, C. P. Neto, A. J. D. Silvestre, *J. Chromatogr. B* **2013**, *938*, 65–74.

[25] B. M. Trost, W. Tang, *J. Am. Chem. Soc.* **2002**, *124*, 14542–14543.

[26] H. Koizumi, S. Yokoshima, T. Fukuyama, *Chem. Asian J.* **2010**, *5*, 2192–2198.

[27] U. Rinner, T. Hudlicky, *Top. Curr. Chem.* **2012**, *309*, 33–66.

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