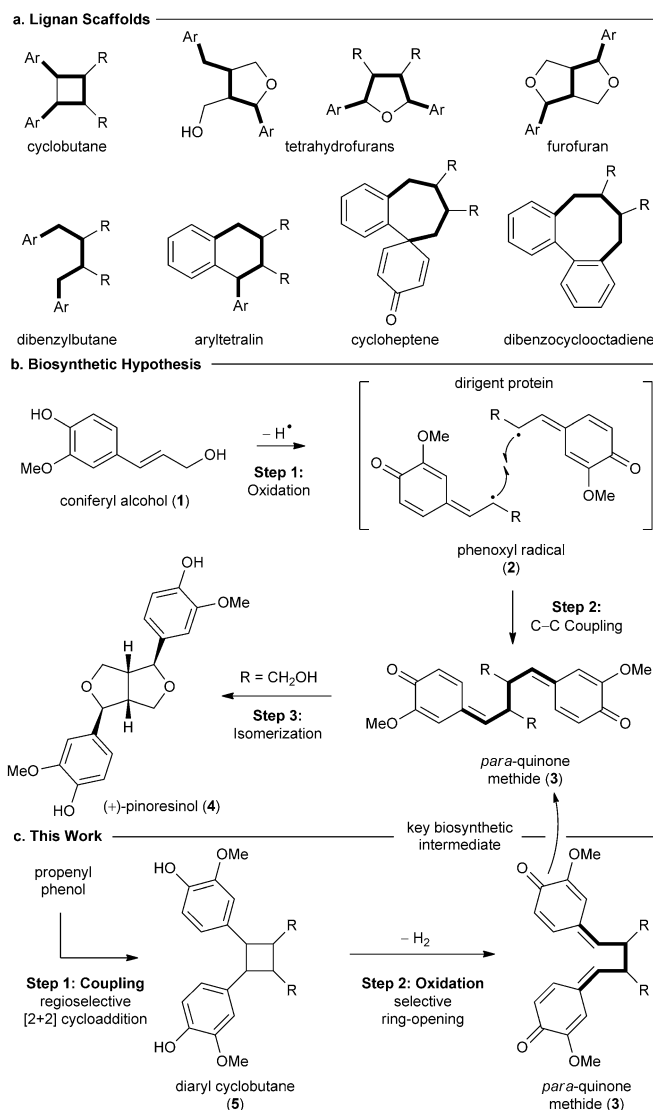


A Bio-Inspired Total Synthesis of Tetrahydrofuran Lignans**

Anna K. F. Albertson and Jean-Philip Lumb*

Abstract: Lignan natural products comprise a broad spectrum of biologically active secondary metabolites. Their structural diversity belies a common biosynthesis, which involves regio- and chemoselective oxidative coupling of propenyl phenols. Attempts to replicate this oxidative coupling have revealed significant challenges for controlling selectivity, and these challenges have thus far prevented the development of a unified biomimetic route to compounds of the lignan family. A practical solution is presented that hinges on oxidative ring opening of a diarylcyclobutane to intercept a putative biosynthetic intermediate. The effectiveness of this approach is demonstrated by the first total synthesis of tanegool in 4 steps starting from ferulic acid, as well as a concise synthesis of the prototypical furanolignan pinosresinol.

The biosynthesis of lignan natural products is characterized by an exceptionally efficient increase in molecular complexity. From only a handful of relatively simple propenyl phenols, plants derive a complex array of secondary metabolites that include 4-, 6-, 7-, and 8-membered carbocycles, linear dibenzylbutanes, and diversely substituted tetrahydrofurans (Scheme 1a).^[1–3] In plants, lignans are a front-line chemical defense against pathogens, while their anticancer, antimutagenic, antiangiogenesis, and antiviral activities have made them the focal point of traditional and pharmaceutical medicine.^[4] Despite their structural diversity, lignan biosynthesis is believed to occur through a common oxidative coupling of propenyl phenols to afford a key bis-*para*-quinone methide (**3**; Scheme 1b). Hydration, reduction, or cyclization of **3** gives rise to parent lignan scaffolds that are further tailored through a range of transformations.^[1d] Given the uniformity of lignan biosynthesis, the direct oxidative coupling of propenyl phenols has been the subject of extensive biomimetic studies, dating to the early work of Haworth and co-workers in the 1940s.^[5] These, and many subsequent examples,^[6] have underscored the difficulties of controlling regio- and stereoselectivity during C–C coupling, and chemoselectivity between oxidation of the starting phenol and over-oxidation of the product. In 1997, Lewis and co-workers elegantly demonstrated that selectivity during biosynthesis



Scheme 1. a) Structural diversity of the lignan family of natural products. b) Proposed biosynthesis through oxidative coupling. c) Bio-inspired synthesis through oxidative ring opening of a diarylcyclobutane.

could be controlled by a rather unique dirigent protein, in the presence of which the one-electron oxidation of coniferyl alcohol (**1**) afforded (+)-pinosresinol (**4**).^[7,8] While of fundamental importance to understanding their biosynthesis, the discovery of dirigent proteins has not yet had a practical impact on the laboratory synthesis of lignans, for which a robust and unified bio-inspired approach has not been reported.

The challenges of controlling selectivity in the oxidative coupling of **1** prompted us to consider an alternative approach

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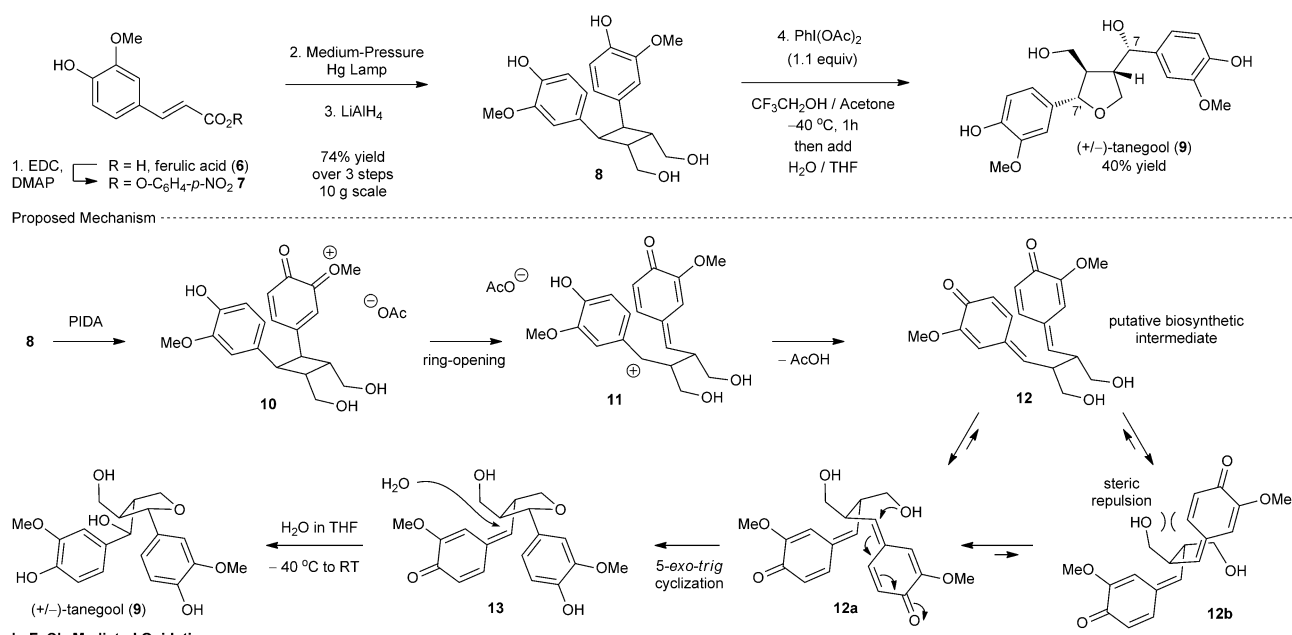
to quinone methide **3** that hinges on the oxidative ring opening of diaryl cyclobutane **5** (Scheme 1c). Strategically, this reverses the steps of coupling and oxidation, such that issues of regio- and stereoselectivity are first addressed in a [2+2]-cycloaddition. The involvement of diaryl cyclobutanes in the biosynthesis of aryltetralin lignans was initially discussed by Kikuchi^[9] and Wilson^[10] and their co-workers, who showed that a one-electron oxidation initiated a 4- to 6-membered-ring expansion, albeit with poor efficiency owing to competitive cycloreversion.^[11–13] The key intermediate in this rearrangement, a delocalized radical cation, has been the topic of extensive investigations, which have helped to shape our understanding of radical-ion reactivity.^[14–16] In the very different context of aminoimidazole alkaloid biosynthesis, Molinski^[17] and Baran^[18] and their co-workers have discussed and implemented a related ring expansion of the cyclobutane sceptorin, thus highlighting close similarities in the potential biosynthetic strategies of two very different organisms. In the current work, we demonstrate that the selective oxidation of diarylcyclobutanes with free phenols leads to an efficient, divergent, and robust bio-inspired synthesis of furanolignans.

Whereas the oxidative coupling of propenyl phenols remains nonselective, significant progress has been made in the corresponding photochemical [2+2] cycloaddition of cinamic acids and esters.^[19–21] In the solution phase, their

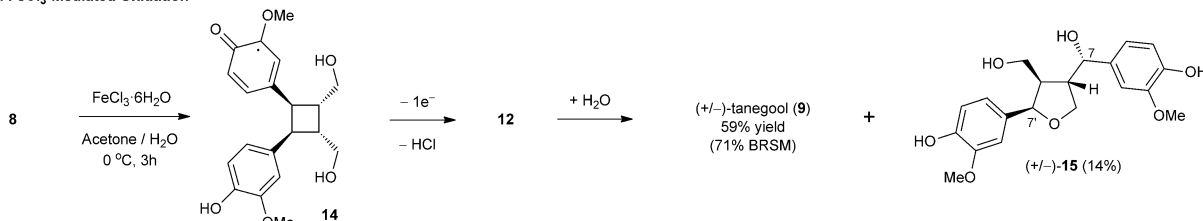
photochemistry is dominated by olefin isomerization, but irradiation of the appropriate polymorph in the solid state leads to selective cycloaddition.^[22] The rules governing the selectivity and efficiency of head-to-head versus head-to-tail coupling have been extensively studied by Schmidt and co-workers^[22,23] and were recently exploited by Kibayashi and co-workers in the total synthesis of incarvilleine.^[24] We began by optimizing the [2+2] photodimerization of *para*-nitro-ferulate ester **7** through irradiation of a suspension in hexanes with a medium-pressure mercury lamp (Scheme 2a). Reduction of the crude material with lithium aluminum hydride completed a 3-step synthesis of diarylcyclobutane diol **8**, which proceeded in an overall yield of 74% on a 10 g scale (see the Supporting Information for details).

We began our investigation into the oxidative ring opening of **8** with phenyliodo diacetate (PIDA) and were encouraged to isolate the natural product (±)-tanegool^[25] as a single diastereomer in yields of up to 40% (Scheme 2a). Under optimized conditions, a homogeneous solution of PIDA in trifluoroethanol was added dropwise to a solution of **8** in acetone at –40 °C. Presumably, this leads to oxonium ion **10** following two-electron oxidation,^[26] which triggers scission of the cyclobutane to provide benzylic carbocation **11**. Loss of acetic acid then generates bis-*para*-quinone methide **12**, which is a presumed biosynthetic intermediate. To obtain

a. PIDA-Mediated Oxidation



b. FeCl₃-Mediated Oxidation

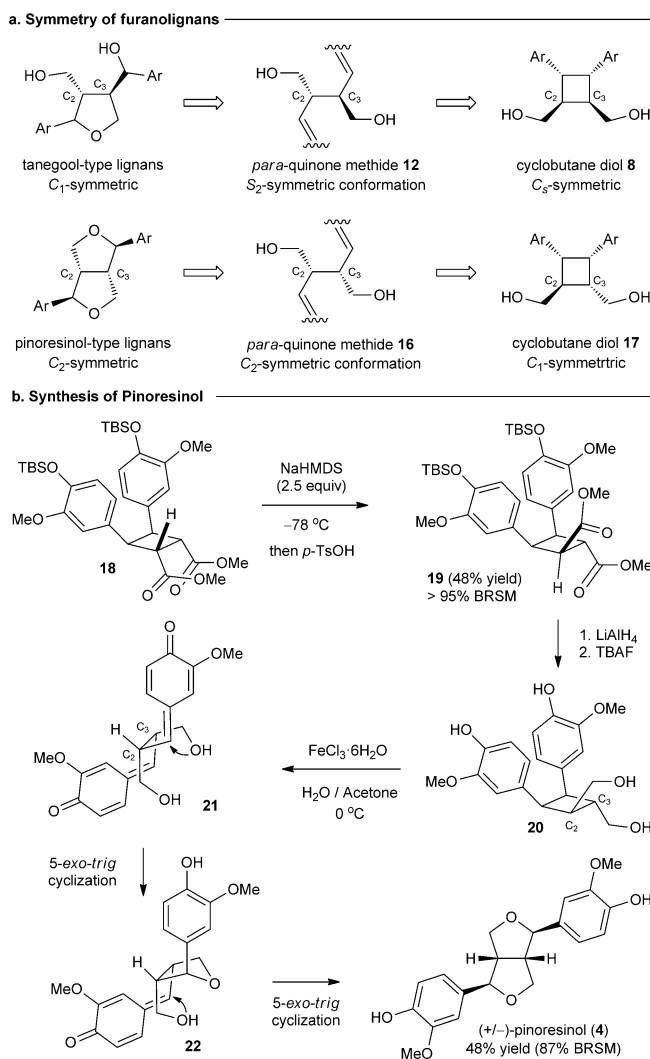


Scheme 2. 4-Step synthesis of (±)-tanegool from ferulic acid. a) Oxidation mediated by phenyliodo diacetate (PIDA) at –40 °C. b) Oxidation mediated by iron trichloride hexahydrate (FeCl₃·6H₂O) at 0 °C.

our highest yields of **9**, we delayed the addition of H₂O as a 1:1 mixture in THF until the consumption of PIDA was complete. We believe that this sequential addition of H₂O prevents the over-oxidation of **9** by keeping the reaction at the stage of *para*-quinone methide **12** until complete consumption of the oxidant. Subsequent 5-*exo*-trig cyclization of the 1° alcohol leads to (±)-tanegool (**9**) after hydration of **13**. The anti relationship between the aromatic ring and the hydroxymethyl substituent in **13** reflects a kinetic bias for the cyclization of rotamer **12a** over **12b**, in which the *para*-quinone methide adopts a conformation that minimizes allylic strain.

Since the yield of **9** could not be improved beyond 40 % with I^{III}-based oxidants, we investigated iron trichloride hexahydrate (FeCl₃·6H₂O) as an alternative one-electron oxidant (Scheme 2b). Whereas PIDA likely proceeds through the ring opening of oxonium ion **10**,^[26] FeCl₃ has the potential to promote a radical-based mechanism for ring opening via **14** or the corresponding arene radical cation.^[10,12] Gratifyingly, the addition of an aqueous solution of FeCl₃·6H₂O to a solution of **8** in acetone at 0 °C dramatically improved the mass balance of the reaction and afforded a 59 % yield of (±)-tanegool (**9**) along with its C7' epimer **15** in 14 % yield at 83 % conversion.^[27] Selectivity for (±)-tanegool could be restored if the oxidation was buffered with an amine base, and exposure of pure **9** to aqueous hydrochloric acid (HCl) led to a 2:1 mixture with **15** after 20 h at RT. These results, along with the complete absence of **15** when **8** is oxidized with PIDA, suggest a kinetic bias for the formation of **9** during the cyclization/hydration of quinone methide **12**, which then isomerizes to **15** in the presence of acid. Among the four possible diastereomers that can form from quinone methide **12**, (±)-tanegool (**9**) and diastereomer **15** are the only two that have been reported as natural products.^[25,28] Interestingly, both are isolated in enantioenriched form, thus suggesting that enantioselective cyclization of **12** may occur during biosynthesis. Whether dirigent proteins can fulfill this function is an intriguing question, since they have traditionally been associated with the oxidative coupling of propenyl phenols^[7,8] but not with the subsequent cyclization of the *para*-quinone methides.

While the tanegool diastereomers originate from the desymmetrization of the S₂-symmetric conformation of *para*-quinone methide **12**, pinoresinol (**4**) and many related lignans possess a syn configuration at C₂ and C₃ of the THF ring (Scheme 3a), which requires cyclization of a C₂-symmetric *para*-quinone methide **16**. The distinction between isomeric *para*-quinone methides **12** and **16** has been discussed in the context of the direct oxidative coupling of coniferyl alcohol (**1**), which favors **16** in the presence of a dirigent protein, but is nonselective otherwise.^[29] In principal, **16** should be accessible from the oxidative opening of C₁-symmetric cyclobutane diol **17** by following our approach. Thus, desymmetrization of a suitably protected *meso*-cyclobutane diester **18** by enolization and protonation affords the *trans*-diester **19** (Scheme 3b), which is readily converted to *trans*-cyclobutane diol **20** following reduction and deprotection. Subsequent oxidation with FeCl₃·6H₂O under our previously optimized conditions affords (±)-pinoresinol (**4**) in 48 % yield (87 % based on



Scheme 3. Synthesis of (±)-pinoresinol. a) Stereochemical analysis of tanegool and pinoresinol. b) Bio-inspired synthesis of pinoresinol (**4**).

recovered starting material), wherein the relative configuration at C₂ and C₃ of the cyclobutane is relayed to the *cis*-fused 5,5-ring juncture of the natural product. As with the cyclization of **12a** during the synthesis of (±)-tanegool (Scheme 2), the 5-*exo*-trig cyclization of bis-*para*-quinone methide **21** is selective for the rotamer that places the quinone methide in a sterically favored syn conformation relative to the hydrogen atom at C₂. This gives rise to **22**, which undergoes a second 5-*exo*-trig cyclization with the expected stereoselectivity. This completes the synthesis of (±)-pinoresinol by installing the *cis*-fused 5,5-ring system and underscores the principal distinction between the oxidation of cyclobutane diols **8** and **20**. In the oxidation of **8**, a second 5-*exo*-trig cyclization at the stage of **13** is either precluded or thermodynamically disfavored by the *trans*-configuration at C₂ and C₃, which would produce a strained 5,5-*trans*-fused product.

In summary, we have developed a concise approach to the furanolignans, which hinges on the oxidative opening of diarylcyclobutane diols. The resulting *para*-quinone methides,

which are putative biosynthetic intermediates, undergo stereospecific cyclization to give the natural products tanegool and pinoresinol. A particularly attractive feature of our route is the ability to modify the cyclobutane prior to oxidation, thus setting the stage for the synthesis of non-natural analogues of the natural products. We are currently exploring the applicability of our strategy for the synthesis of additional lignan family members, as well as enantioselective routes to the furanolignans that capitalize on the symmetry of the diarylcyclobutane diols.

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- [1] For reviews discussing the biosynthesis of lignans: a) J. Y. Pan, S. L. Chen, M. H. Yang, J. Wu, J. Sinkkonen, K. Zou, *Nat. Prod. Rep.* **2009**, 26, 1251–1292; b) C. W. Lindsley, C. R. Hopkins, G. A. Sulikowski in *Biomimetic Organic Synthesis*, Wiley-VCH, Weinheim, **2011**, pp. 677–693; c) L. B. Davin, N. G. Lewis, *Phytochem. Rev.* **2003**, 2, 257–288; d) L. B. Davin, M. Jourdes, A. M. Patten, K.-W. Kim, D. G. Vassao, N. G. Lewis, *Nat. Prod. Rep.* **2008**, 25, 1015–1090.
- [2] For a review on furanofuran lignans: R. C. Brown, N. A. Swain, *Synthesis* **2004**, 811–827.
- [3] For selected total syntheses of lignan natural products: a) C. P. Ting, T. J. Maimone, *Angew. Chem. Int. Ed.* **2014**, 53, 3115–3119; *Angew. Chem.* **2014**, 126, 3179–3183; b) T. Rovis, C. Nasveschuk, *Synlett* **2008**, 126–128; c) H. Li, Y. Zhang, X. Xie, H. Ma, C. Zhao, G. Zhao, X. She, *Org. Lett.* **2014**, 0, 0; d) Y. Kawabe, R. Ishikawa, Y. Akao, A. Yoshida, M. Inai, T. Asakawa, Y. Hamashima, T. Kan, *Org. Lett.* **2014**, 16, 1976–1979; e) X. Han, E. J. Corey, *Org. Lett.* **1999**, 1, 1871–1872; f) L. G. Monovich, Y. Le Huérou, M. Rönn, G. A. Molander, *J. Am. Chem. Soc.* **2000**, 122, 52–57; g) G. A. Molander, K. M. George, L. G. Monovich, *J. Org. Chem.* **2003**, 68, 9533–9540; h) R. S. Coleman, S. R. Gurrall, S. Mitra, A. Raao, *J. Org. Chem.* **2005**, 70, 8932–8941; i) W. Gong, R. R. Singidi, J. C. Gallucci, T. V. RajanBabu, *Chem. Sci.* **2012**, 3, 1221–1230; j) A. Joncour, A. Decor, S. Thoret, A. Chiaroni, O. Baudoin, *Angew. Chem. Int. Ed.* **2006**, 45, 4149–4152; *Angew. Chem.* **2006**, 118, 4255–4258.
- [4] For reviews describing the biological activity of lignans: a) S. Carmela, T. Corrado in *Bioactive Compounds from Natural Sources*, 2nd ed., CRC, Boca Raton, **2011**, 299–338; b) W. R. Cunha, M. L. Andrade e Silva, R. C. S. Veneziani, S. R. Ambrosio, J. K. Bastos in *Lignans: Chemical and Biological Properties, Phytochemicals—A Global Perspective of Their Role in Nutrition and Health* (Ed.: V. Rao), InTech Publishers, Rijeka, Croatia, **2012**, pp. 213–234.
- [5] N. J. Cartwright, R. D. Haworth, *J. Chem. Soc.* **1944**, 535–537.
- [6] For a comprehensive list of references see the supporting information. For selected examples see: a) P. W. Paré, H.-B. Wang, L. B. Davin, N. G. Lewis, *Tetrahedron Lett.* **1994**, 35, 4731–4734; b) M. Bunzel, J. Ralph, H. Kim, F. Lu, S. A. Ralph, J. M. Marita, R. D. Hatfield, H. Steinhart, *J. Agric. Food Chem.* **2003**, 51, 1427–1434; c) E. Kim, H. K. Lee, E. I. Hwang, S. U. Kim, W. S. Lee, S. Lee, S. H. Jung, *Synth. Commun.* **2005**, 35, 1231–1238; d) A. Haikarainen, J. Sipilä, P. Pietikainen, A. Pajunen, I. Mutikainen, *Bioorg. Med. Chem.* **2001**, 9, 1633–1638; e) L. Juhász, L. Kurti, S. Antus, *J. Nat. Prod.* **2000**, 63, 866–870.
- [7] L. B. Davin, H. B. Wang, A. L. Crowell, D. L. Bedgar, D. M. Martin, S. Sarkanen, N. G. Lewis, *Science* **1997**, 275, 362–366.
- [8] B. Pickel, M. A. Constantin, J. Pfannstiel, J. Conrad, U. Beifuss, A. Schaller, *Angew. Chem. Int. Ed.* **2010**, 49, 202–204; *Angew. Chem.* **2010**, 122, 207–209.
- [9] S. Kadota, K. Tsubono, K. Makino, M. Takeshita, T. Kikuchi, *Tetrahedron Lett.* **1987**, 28, 2857–2860.
- [10] R. M. Wilson, J. G. Dietz, T. A. Shepherd, D. M. Ho, K. A. Schnapp, R. C. Elder, J. W. Watkins II, L. S. Geraci, C. F. Campaña, *J. Am. Chem. Soc.* **1989**, 111, 1749–1754.
- [11] For related work on electron transfer initiated cycloreversion, see: J. P. Doering, W. von E. DeLuca, *J. Am. Chem. Soc.* **2003**, 125, 10608–10614.
- [12] For examples of the oxidative opening of diaryl cyclobutanes, see: a) V. Nair, R. Rajan, K. Mohanan, V. Sheeba, *Tetrahedron Lett.* **2003**, 44, 4585–4588; b) V. Nair, L. Balagopal, R. Rajan, J. Mathew, *Acc. Chem. Res.* **2004**, 37, 21–30.
- [13] a) R. A. Pabon, D. J. Bellville, N. L. Bauld, *J. Am. Chem. Soc.* **1984**, 106, 2730–2731; b) N. P. Schepp, D. Shukla, H. Sarker, N. L. Bauld, L. J. Johnston, *J. Am. Chem. Soc.* **1997**, 119, 10325–10334.
- [14] For seminal contributions: a) P. Beresford, M. C. Lambert, A. Ledwith, *J. Chem. Soc. C* **1970**, 18, 2508–2510; P. Beresford, M. C. Lambert, A. Ledwith, *J. Chem. Soc. C* **1970**, 18, 2730–2731; b) L. L. O’Neil, O. Wiest, *J. Org. Chem.* **2006**, 71, 8926–8933, and reference [13a].
- [15] For reviews: a) A. Ledwith, *Acc. Chem. Res.* **1972**, 5, 133–139; b) N. L. Bauld, D. J. Bellville, B. Harichian, K. T. Lorenz, R. A. Pabon, Jr., D. W. Reynolds, D. D. Wirth, H. S. Chiou, B. Kaye Marsh, *Acc. Chem. Res.* **1987**, 20, 371; c) N. L. Bauld, *Tetrahedron* **1989**, 45, 5307–5363.
- [16] The field of radical-ion chemistry has recently seen a resurgence, largely owing to the development of visible-light-induced electron-transfer reactions. In this context, the chemistry of the cyclobutane radical cation has been revisited. For relevant reviews: a) D. M. Schultz, T. P. Yoon, *Science* **2014**, 343, 1239176; b) M. A. Ischay, T. P. Yoon, *Eur. J. Org. Chem.* **2012**, 3359–3372; c) J. W. Tucker, C. R. J. Stephenson, *J. Org. Chem.* **2012**, 77, 1617–1622; d) T. P. Yoon, M. A. Ischay, J. Du, *Nat. Chem.* **2010**, 2, 527–532.
- [17] E. P. Stout, Y. G. Wang, D. Romo, T. F. Molinski, *Angew. Chem. Int. Ed.* **2012**, 51, 4877–4881; *Angew. Chem.* **2012**, 124, 4961–4965.
- [18] a) D. P. O’Malley, K. Li, M. Maue, A. L. Zografos, P. S. Baran, *J. Am. Chem. Soc.* **2007**, 129, 4762–4775; b) B. H. Northrop, D. P. O’Malley, A. L. Zografos, P. S. Baran, K. N. Houk, *Angew. Chem. Int. Ed.* **2006**, 45, 4126–4130; *Angew. Chem.* **2006**, 118, 4232–4236.
- [19] For a comprehensive list of references see the supporting information. For selected examples: a) M. D. Auria, A. Vantaggi, *Tetrahedron* **1992**, 48, 2523–2528; b) Y. Ito, T. Kitada, M. Horiguchi, *Tetrahedron* **2003**, 59, 7323–7329; c) A. Natarajan, J. T. Mague, K. Venkatesan, V. Ramamurthy, *Org. Lett.* **2005**, 7, 1895–1898; d) V. Mascitti, E. J. Corey, *Tetrahedron Lett.* **2006**, 47, 5879–5882.
- [20] For progress in the related [2+2] cycloaddition of more electron rich styrenes: a) Z. Lu, T. P. Yoon, *Angew. Chem. Int. Ed.* **2012**, 51, 10329–10332; *Angew. Chem.* **2012**, 124, 10475–10478; b) M. A. Ischay, M. S. Ament, T. P. Yoon, *Chem. Sci.* **2012**, 3, 2807–2811; c) M. Riener, D. A. Nicewicz, *Chem. Sci.* **2013**, 4, 2625–2629.
- [21] For an alternative synthesis of electron-rich diarylcyclobutanes: a) W. R. Gutekunst, P. S. Baran, *J. Am. Chem. Soc.* **2011**, 133, 19076–19079; b) W. R. Gutekunst, P. S. Baran, *J. Org. Chem.* **2014**, 79, 2430–2452.
- [22] M. D. Cohen, G. M. J. Schmidt, *J. Chem. Soc.* **1964**, 1996–2000.

- [23] a) M. D. Cohen, G. M. J. Schmidt, F. I. Sonntag, *J. Chem. Soc.* **1964**, 2000–2013; b) G. M. J. Schmidt, *J. Chem. Soc.* **1964**, 2014–2021.
- [24] M. Ichikawa, M. Takahashi, S. Aoyagi, C. Kibayashi, *J. Am. Chem. Soc.* **2004**, *126*, 16553–16558.
- [25] For a comprehensive list of references see the supporting information. For selected reports: a) F. A. Macías, A. Lopez, R. M. Varela, A. Torres, J. M. Molinillo, *J. Agric. Food Chem.* **2004**, *52*, 6443–6447; b) F. Abe, T. Yamauchi, *Chem. Pharm. Bull.* **1990**, *38*, 2143–2145.
- [26] Y. Kita, T. Hirofumi, K. Hatanaka, T. Takada, S. Fujita, S. Mitoh, H. Sakurai, S. Oka, *J. Am. Chem. Soc.* **1994**, *116*, 3684–3691.
- [27] The relative stereochemistry of **9** was assigned previously (see ref. [25a]). See the supporting information for a discussion on the assignment of **15** based on nOe and coupling constants obtained in this work.
- [28] R. Andersson, T. Popoff, O. Theander, *Acta Chem. Scand. Ser. B* **1975**, *29*, 835–837.
- [29] H. Kasahara, Y. Jiao, D. L. Bedgar, S. J. Kim, A. M. Patten, Z. Q. Xia, L. B. Davin, N. G. Lewis, *Phytochemistry* **2006**, *67*, 1765–1780.
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