Natural Product Synthesis

DOI: 10.1002/anie.201307659

Stereocontrolled Syntheses of Tetralone- and Naphthyl-Type Lignans by a One-Pot Oxidative [3,3] Rearrangement/Friedel–Crafts Arylation**

*Jordan C. T. Reddel, Kelly E. Lutz, Abdallah B. Diagne, and Regan J. Thomson**

Abstract: *The development of a stereoselective one-pot oxidative [3,3] sigmatropic rearrangement/Friedel–Crafts arylation that provides enantioenriched benzhydryl compounds is reported. The utility of this new transformation is demonstrated by the concise synthesis of several tetralone- and naphthyl-type lignan natural products, many of which display anti-malarial activity.*

In 2010, an estimated 660000 deaths worldwide were attributed to malaria, while millions remain infected.[1] This disease, which is caused by the parasitic protozoan genus *Plasmodium*, largely affects tropical and subtropical communities.[1] Natural products, such as quinine and artemisinin, have long served as the backbone of drug development in anti-malarial research, but unfortunately, resistance to once efficacious medications has necessitated the ongoing search for new approaches to treatment.[2] Extracts from plants, such as *Pycnanthus angolensis* and *Holostylis reniformis*, have traditionally been used to treat malaria throughout Africa and Brazil, respectively.[3] Isolated lignans from these and other plants represent potential new candidates for the development of anti-malarial drugs (Figure 1).[4,5] For instance, (−)-8′-*epi*-aristoligone (**1**) has shown promising antiplasmodial activity against a chloroquine-resistant strain of *P. falciparum* with an IC_{50} value of 2.61 ± 0.06 μM.[5a]

We wished to devise a flexible and general approach to the stereoselective synthesis of these lignan natural products that would also be amenable to the preparation of non-natural analogues.[6] In particular, we were interested in developing stereoselective fragment-coupling reactions that would allow the simultaneous introduction of the two requisite aryl groups along with the formation of the C7′ and C8′ stereocenters through a cascade process that involves *N*-allylhydrazones (Scheme 1).[7] We envisioned that hydrazine **8** would act as a linchpin for the reaction of aryl aldehyde **7** with arene **10** by initial formation of hydrazone **9**, which is followed by a hypervalent-iodide-initiated one-pot oxidative [3,3] rearrangement/Friedel–Crafts arylation to afford benzhydryl derivative **11**. Previous work from our laboratory has shown

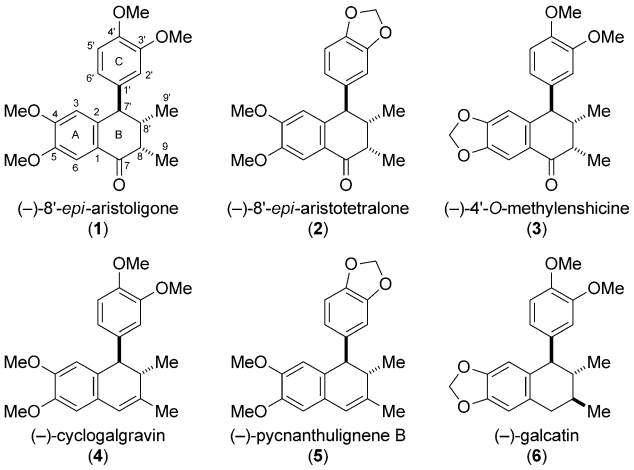
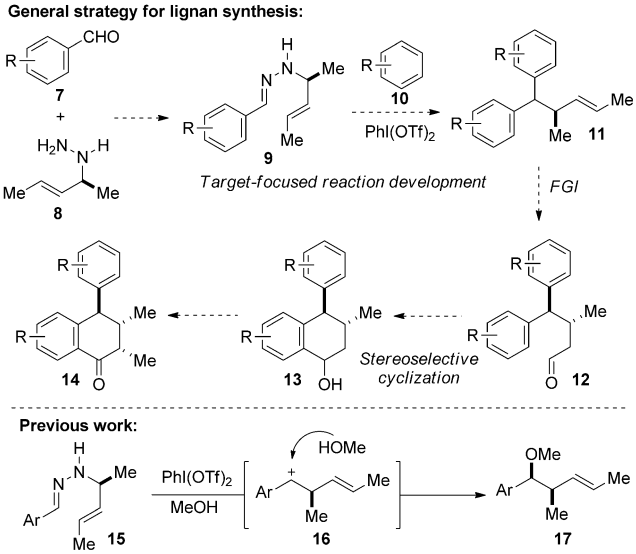


Figure 1. Selected tetralone (**1**–**3**), dihydronaphthyl (**4** and **5**), and tetrahydronaphthyl (**6**) lignans.



Scheme 1. Sequential C–C/C–C bond-forming cascade. FGI = functional group interconversion.

that a related oxidative rearrangement of aryl hydrazones (e.g., **15**) in the presence of methanol led to the generation of ethers **17**.[7e] Mechanistic investigations indicated that the reaction most likely proceeded via the intermediacy of a carbocation (i.e., **16**), and it was this species we wished to intercept in our new oxidative [3,3] rearrangement/Friedel–Crafts arylation process (**9**→**11**). Access to intermediates such as **11** would allow for elaboration to aldehyde **12**, which

[*] J. C. T. Reddel, K. E. Lutz, A. B. Diagne, Prof. R. J. Thomson
Department of Chemistry, Northwestern University
2145 Sheridan Rd, Evanston, IL 60208 (USA)
E-mail: r-thomson@northwestern.edu

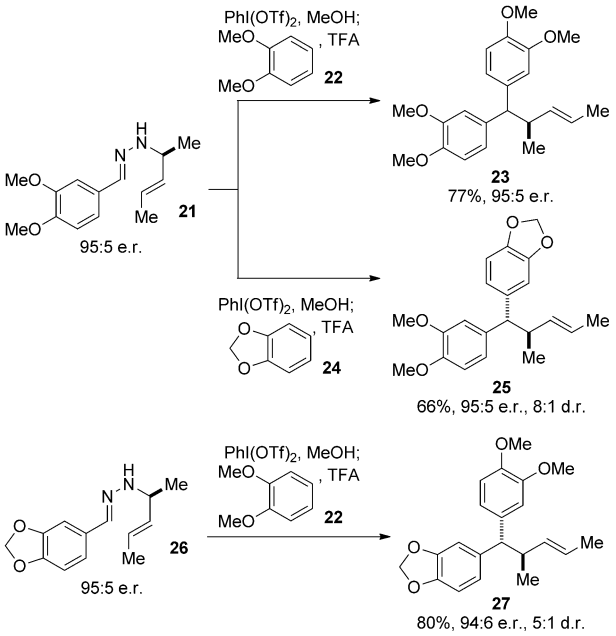
[**] This work was supported in part by Northwestern University and the National Science Foundation (CHE0845063). We thank Reed Larson for assistance with X-ray crystallography.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201307659.

Table 1: Reaction development.

Entry	Reaction conditions	Product	Yield[a] [%]
1	$PhI(OTf)_2$ (1 equiv), MeOH (10 equiv), −78 °C	**19**	39
2	$PhI(OTf)_2$ (1 equiv), **22** (10 equiv), −78 °C	**20**	11
3	$PhI(OTf)_2$ (1 equiv), MeOH (10 equiv), −78 °C; then **22** (10 equiv), TFA (25 equiv), 0 °C	**20**	38
4	$PhI(OTf)_2$ (1 equiv), MeOH (10 equiv), −78 °C; then **22** (10 equiv), TFA (25 equiv), 0 °C	**20**	53

[a] Yields of isolated products over two steps from 3,4-dimethoxybenzaldehyde. All reactions were conducted in CH_2Cl_2. OTf = trifluoromethanesulfonate, TFA = trifluoroacetic acid.

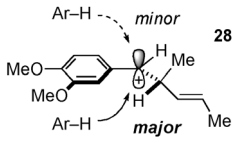


Scheme 2. Stereoselective fragment-coupling cascade.

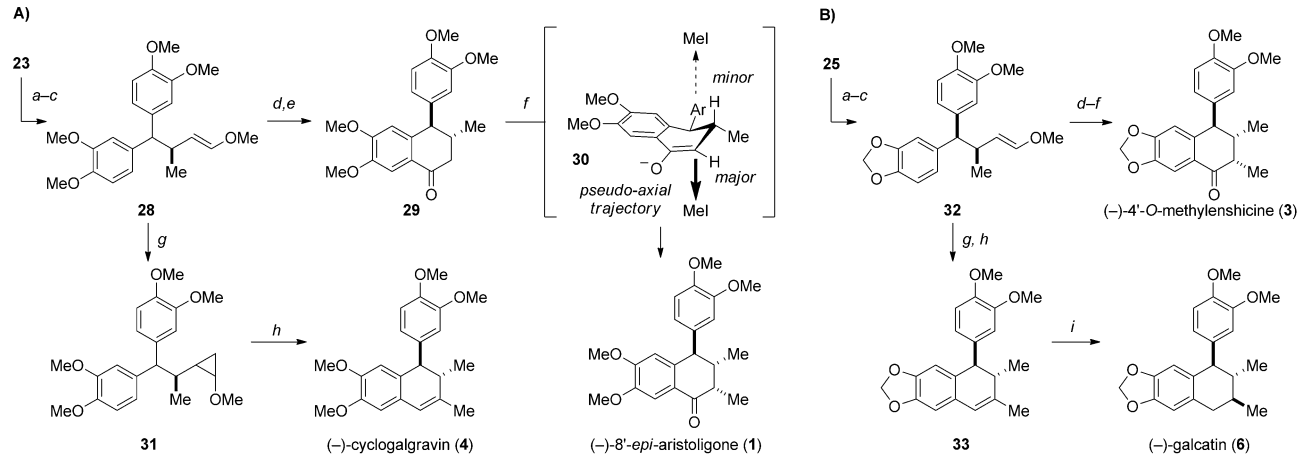
we planned to engage in a stereoselective cyclization to yield the desired lignan ring system (**13** and thence **14**).

Our investigations began with hydrazone **18**, which was readily prepared from the corresponding aldehyde and hydrazine fragments. Treatment of **18** with $PhI(OTf)_2$ in the presence of methanol under our previously reported conditions[7e] gave rise to the expected methyl ether **19** in an unoptimized 39% yield (Table 1, entry 1). We were initially encouraged by the finding that benzhydryl **20** was isolated in 11% yield when 1,2-dimethoxybenzene (**22**) was used as the external nucleophile rather than methanol (Table 1, entry 2). Unfortunately, we were unable to improve this low yield. Bach and co-workers have shown that benzylic alcohols and ethers akin to **20** are suitable substrates for stereoselective Friedel–Crafts alkylations,[8] and they employed such a reaction in an elegant synthesis of podophyllotoxin.[8d] After a short investigation, we found that methyl ether **19** could be transformed into benzhydryl derivative **20** when treated with trifluoroacetic acid and 1,2-dimethoxybenzene (Table 1, entry 3). These positive results led us to explore the feasibility of a one-pot conversion of hydrazone **18** into benzhydryl **20** via ether **19**. Thus, a sequential treatment of hydrazone **18** with $PhI(OTf)_2$ and methanol, followed by the addition of 1,2-dimethoxybenzene and trifluoroacetic acid led to clean formation of the desired product **20** in 53% yield (Table 1, entry 4).

With suitable conditions in hand,[9] we prepared the three precursors necessary for our enantioselective total syntheses of various lignans (Scheme 2). Enantioenriched hydrazone **21** was prepared from the corresponding optically enriched hydrazine **8**[7e,f] and 3,4-dimethoxybenzaldehyde. The one-pot oxidative [3,3] rearrangement/Friedel–Crafts arylation of **21** with 1,2-dimethoxybenzene (**22**) proceeded with complete chirality transfer to afford benzhydryl **23** in 77% yield.[10] Under the same conditions, but in the presence of benzo[*d*]-[1,3]dioxole (**24**) rather than 1,2-dimethoxybenzene, **21** was cleanly converted into benzhydryl **25** in 66% yield as an 8:1 mixture of stereoisomers. An important design aspect of our synthetic strategy was that by exchanging the nature of the starting aldehyde and the aryl nucleophile, we would gain controlled access to either stereoisomeric product in a regiodivergent manner. Thus, formation of hydrazone **26** from piperonal followed by oxidative [3,3] rearrangement and Friedel–Crafts arylation with 1,2-dimethoxybenzene (**22**) led to the generation of diastereomeric benzhydryl **27** (80% yield, 5:1 d.r.). The stereochemical outcome that was observed for the formation of **25** and **27** was somewhat surprising, as the related ether formation had given the opposite relative configuration between the nucleophile and the methyl substituent (**15**→**17**, Scheme 1).[7e] We speculated that perhaps the arylation proceeded by an S_N2 displacement of an initially formed *syn* methyl ether akin to **15**. Isolation of the intermediate methyl ether, which is formed by the oxidative rearrangement of **21**, indicated only a modest preference for the *syn* isomer (2:1), which upon arylation using TFA converged to **25** as an enhanced 8:1 mixture of diastereomers (**25**/**27** = 8:1). This observed stereoconvergence, in combination with additional mechanistic investigations,[11] provided strong evidence for a common intermediate (i.e., **28**) as we had originally proposed. Thus, it appears that the addition of aryl nucleophiles to **28** proceeds with good selectivity away from the methyl group, whereas methanol adds across the face of the methyl group with a slight preference, as we had previously observed.[7e]



According to our synthetic strategy (Scheme 1), the 3,4-dimethoxybenzaldehyde-derived benzhydryl products **23** and **25** would allow access to (−)-8′-*epi*-aristoligone (**1**), (−)-cyclogalgravin (**4**), (−)-4′-*O*-methylenshicine (**3**) and (−)-galcatin (**6**). Similarly, the piperonal-derived product **27** would lead to (−)-8′-*epi*-aristotetralone (**2**) and (−)-pycnanthulignene B (**5**). Our syntheses of the four natural products from 3,4-dimethoxybenzaldehyde are outlined in Scheme 3 A



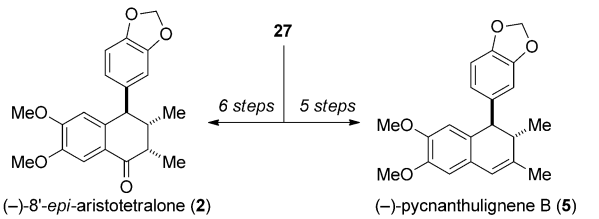
Scheme 3. A) a) OsO_4 (1 mol%), NMO; b) $NaIO_4$; c) $[Ph_3PCH_2OMe]^+Cl^-$, NaHMDS, 90% over three steps from **23**; d) TFA, THF/water; e) IBX, 82% over two steps from **28**; f) LDA, MeI, 66%, 3:1 d.r.; g) Et_2Zn, CH_2I_2, TFA, 73% from **28**; h) HCl/MeOH (1:1), reflux, 73%. B) a) OsO_4 (1 mol%), NMO; b) $NaIO_4$; c) $[Ph_3PCH_2OMe]^+Cl^-$, NaHMDS, 83% over three steps from **25**; d) TFA, THF/water; e) MnO_2, 58% over two steps from **32**; f) LDA, MeI, 94%, 3:1 d.r.; g) Et_2Zn, CH_2I_2, TFA; h) HCl/MeOH (1:1), reflux, 76% over two steps from **32**; i) Pd/C (10% wt), H_2, 89%, 16:1 d.r. IBX = *ortho*-iodoxybenzoic acid, NMO = *N*-methylmorpholine *N*-oxide, LDA = lithium diisopropylamide, TFA = trifluoroacetic acid, NaHMDS = sodium hexamethyldisilazide.

and B. Benzhydryl **23** was converted into methyl enol ether **28** in 90% yield over three steps that involve oxidative alkene cleavage and Wittig olefination (Scheme 3A). Initial attempts to induce a one-pot hydrolysis of **28** to the corresponding aldehyde with subsequent stereoselective Friedel–Crafts cyclization using aqueous HCl led to cyclization, but the formed benzylic alcohol underwent rapid elimination in situ to generate a dihydronaphthalene. We therefore surveyed more mild acids and found that exposure of **28** to aqueous trifluoroacetic acid afforded the desired benzylic alcohol with a minimal amount of elimination. Analysis of the stereoselectivity of the cyclization was hampered owing to the presence of the hydroxyl epimers,[12] but this issue was resolved after oxidation with IBX. Thus, tetralone **29** was formed in > 20:1 d.r. and 82% yield over two steps from enol ether **28**. Alkylation of tetralone **29** with methyl iodide proceeded in 66% overall yield to deliver (−)-8′-*epi*-aristoligone (**1**) and its C8 epimer, (−)-8,8′-*epi*-aristoligone (also a natural product), in a 3:1 ratio.[13] Alkylation with methyl iodide appears to favor an approach along an axial trajectory to enolate **30** that minimizes 1,2 eclipsing interactions in the developing transition state, an outcome consistent with observed "torsional steering" in related systems.[14] Overall, the synthesis of **1** proceeded in 28% yield over eight steps from 3,4-dimethoxybenzaldehyde.

In principle, cyclogalgravin (**4**) could be produced from 8′-*epi*-aristoligone (**1**) by ketone reduction and elimination. Rather than explore this possibility, we devised a shorter route that intercepted an earlier common intermediate, namely enol ether **28**. Cyclopropanation of **28** under conditions developed by Shi et al.[15] produced cyclopropane **31** in good yield as an inconsequential mixture of stereoisomers. Heating of **31** in a 1:1 mixture of concentrated HCl and methanol at reflux led to smooth formation of (−)-cyclogalgravin (**4**) in 73% yield, presumably via an intermediate aldehyde (or the related methyl oxocarbenium ion), which underwent cyclization and elimination.[16]

(−)-4′-*O*-Methylenshicine (**3**) was synthesized in 24% yield from **25** (Scheme 3B) in a manner analogous to our previously discussed synthesis of (−)-8′-*epi*-aristoligone (**1**). As for the synthesis of **1**, the key cyclization from enol ether **32** proceeded such that ring formation occurred selectively on the benzo[*d*][1,3]dioxole group to generate the *anti* relationship between the aryl and methyl substituents. For (−)-galcatin (**6**), we began by preparing dihydronaphthalene **33** from enol ether **32** using our cyclopropane fragmentation/cyclization/elimination cascade. Curiously, **33** has never been identified as a natural product despite it being a constitutional isomer of pycnanthulignene B (**5**) and that both of the corresponding tetralone isomers (**3** and **2**) are found in nature. Regardless of biosynthetic relationships, dihydronaphthalene **33** served as a useful synthetic precursor to galcatin (**6**), undergoing stereoselective hydrogenation with palladium on carbon to generate **6** as a 16:1 mixture of the C8 stereoisomers (89% combined yield).[17]

The final two natural products that we prepared using this new strategy were (−)-8′-*epi*-aristotetralone (**2**) and (−)-pycnanthulignene B (**5**; Scheme 4). Benzhydryl **27**, which is derived from piperonal, served as the starting point for the syntheses, which proceeded in analogy to our routes to 8′-*epi*-aristoligone (**1**) and cyclogalgravin (**4**), respectively. Thus, (−)-8′-*epi*-aristotetralone (**2**) was prepared in 43% yield over six steps from **27**, whereas (−)-pycnanthulignene B (**5**) could



Scheme 4. Concise total syntheses of (−)-8′-*epi*-aristotetralone (**2**) and (−)-pycnanthulignene B (**5**).

be accessed over five steps in 70% yield from **27** (for details, see the Supporting Information).

In summary, the development of a novel one-pot oxidative [3,3] rearrangement/Friedel–Crafts arylation has allowed the rapid and stereocontrolled synthesis of several related lignan natural products. The flexible and modular nature of this approach should make it amenable towards the preparation of other natural lignans and to the synthesis of non-natural versions for biological evaluation against the malaria parasite.

Received: August 30, 2013
Published online: December 16, 2013

Keywords: cascade reactions · hydrazones · lignans · natural product synthesis · sigmatropic rearrangement

[1] *World Malaria Report 2012*, World Health Organization: Geneva, **2012**.
[2] a) R. G. Ridley, *Nature* **2002**, *415*, 686 – 693; b) S. Vangapandu, M. Jain, K. Kaur, P. Patil, S. R. Patel, R. Jain, *Med. Res. Rev.* **2007**, *27*, 65 – 107.
[3] a) V. F. de Andrade-Neto, T. da Silva, L. M. Xavier Lopes, V. E. do Rosario, F. de Pilla Varotti, A. U. Krettli, *Antimicrob. Agents Chemother.* **2007**, *51*, 2346 – 2350; b) M. Abrantes, T. Mill-Homens, N. Duarte, D. Lopes, P. Cravo, M. d. C. Madureira, M.-J. U. Ferreira, *Planta Med.* **2008**, *74*, 1408 – 1412.
[4] For relevant papers on the isolation of the lignans shown in Figure 1, see: (−)-8′-*epi*-aristoligone: a) T. da Silva, L. M. Lopes, *Phytochemistry* **2004**, *65*, 751 – 759; (−)-4′-*O*-methylenshicine and (−)-cyclogalgravin: b) T. da Silva, L. M. X. Lopes, *Phytochemistry* **2006**, *67*, 929 – 937; (−)-pycnanthulignene B: c) E. C. N. Nono, P. Mkounga, V. Kuete, K. Marat, P. G. Hultin, A. E. Nkengfack, *J. Nat. Prod.* **2010**, *73*, 213 – 216; (−)-galcatin: d) G. Hughes, E. Ritchie, *Aust. J. Chem.* **1954**, *7*, 104 – 112; for the isolation of (−)-8′-*epi*-aristotetralone, see Ref. [3a].
[5] For a review, see: R. S. Ward, *Nat. Prod. Rep.* **1999**, *16*, 75 – 96, and previous reports referred to therein.
[6] For previous syntheses of these natural products and closely related tetralone- and naphthyl-type lignans, see: a) T. Takeya, E. Kotani, S. Tobinaga, *Chem. Commun.* **1983**, 98 – 99; b) A. N. Kasatkin, G. Checksfield, R. J. Whitby, *J. Org. Chem.* **2000**, *65*, 3236 – 3238; c) P. K. Datta, C. Yau, T. S. Hooper, B. L. Yvon, J. L. Charlton, *J. Org. Chem.* **2001**, *66*, 8606 – 8611; d) B. L. Yvon, P. K. Datta, T. N. Le, J. L. Charlton, *Synthesis* **2001**, 1556 – 1560; e) C. E. Rye, D. Barker, *J. Org. Chem.* **2011**, *76*, 6636 – 6648; f) B.-C. Hong, C.-S. Hsu, G.-H. Lee, *Chem. Commun.* **2012**, *48*, 2385 – 2387; g) J. K. Rout, C. V. Ramana, *J. Org. Chem.* **2012**, *77*, 1566 – 1571.
[7] For relevant publications on the rearrangements of *N*-allylhydrazones, see: a) R. V. Stevens, E. E. McEntire, W. E. Barnett, E. Wenkert, *J. Chem. Soc. Chem. Commun.* **1973**, 662 – 663; b) D. A. Mundal, J. J. Lee, R. J. Thomson, *J. Am. Chem. Soc.* **2008**, *130*, 1148 – 1149; c) D. A. Mundal, K. E. Lutz, R. J. Thomson, *Org. Lett.* **2009**, *11*, 465 – 468; d) D. A. Mundal, C. A. Avetta, Jr., R. J. Thomson, *Nat. Chem.* **2010**, *2*, 294 – 297; e) K. E. Lutz, R. J. Thomson, *Angew. Chem.* **2011**, *123*, 4529 – 4532; *Angew. Chem. Int. Ed.* **2011**, *50*, 4437 – 4440; f) O. Gutierrez, B. F. Strick, R. J. Thomson, D. J. Tantillo, *Chem. Sci.* **2013**, *4*, 3997 – 4003.
[8] a) F. Mühlthau, D. Stadler, A. Goeppert, G. A. Olah, G. K. S. Prakash, T. Bach, *J. Am. Chem. Soc.* **2006**, *128*, 9668 – 9675; b) D. Stadler, F. Mühlthau, P. Rubenbauer, E. Herdtweck, T. Bach, *Synlett* **2006**, 2573 – 2576; c) D. Stadler, T. Bach, *Chem. Asian J.* **2008**, *3*, 272 – 284; d) D. Stadler, T. Bach, *Angew. Chem.* **2008**, *120*, 7668 – 7670; *Angew. Chem. Int. Ed.* **2008**, *47*, 7557 – 7559.
[9] We explored the possibility of using fewer than 10 equivalents of the external aryl nucleophile during the one-pot oxidative [3,3] sigmatropic rearrangement/Friedel–Crafts reaction, but found that the yields of the desired product were significantly reduced for most reactions. We did, however, find that that the synthesis of **27** from **26** could be conducted in 75% yield with as low as 1.5 equivalents of 1,2-dimethoxybenzene. Unfortunately, this good result did not translate to the synthesis of **23** and **25**.
[10] Generally speaking, we have observed that hydrazones that are derived from branched hydrazines (i.e., **21** and **26**) provide significantly better yields and cleaner reactions than hydrazones derived from unbranched hydrazines (i.e., **18**). Although the exact reason for this difference in reactivity is not clear, we speculate that the unbranched hydrazones are more susceptible to decomposition under the oxidative reaction conditions, possibly because of isomerization and/or deprotonation of the allyl fragment. Computational studies of the related triflimide-catalyzed [3,3] rearrangement of *N*-allylhydrazones have revealed that branched *N*-allylhydrazones possess significantly lower activation barriers; see Ref. [7f].
[11] Treatment of independently prepared samples of both the *syn* and *anti* diastereomers of model compound **18** with benzo[*d*]-[1,3]dioxole (**24**) and trifluoroacetic acid provided the same arylated product in a stereoconvergent fashion, which is consistent with the intermediacy of a common carbocationic intermediate for both diastereomers. For details, as well as structural data (relative and absolute configurations), see the Supporting Information.
[12] Analysis of the unpurified reaction mixture by ^{1}H NMR spectroscopy indicated a ratio of approximately 1:1 for the epimeric benzylic alcohols.
[13] For each of the three tetralone-based lignans prepared herein, namely (−)-8′-*epi*-aristoligone (**1**), (−)-8′-*epi*-aristotetralone (**2**), and (−)-4′-*O*-methylenshicine (**3**), the final enolate alkylation gave rise to a 3:1 ratio of C8 epimers. In each instance, the minor epimer produced is also a known natural product. We also determined the enantiopurity of **1**, **2**, and **3**, which indicated only a slight erosion of optical purity during the synthesis (most likely during the Wittig reaction). For details, see the Supporting Information.
[14] For key articles on the axial allylation of enolates, see: a) E. J. Corey, R. A. Sneen, *J. Am. Chem. Soc.* **1956**, *78*, 6269 – 6278; b) L. Velluz, J. Valls, G. Nominé, *Angew. Chem.* **1965**, *77*, 185 – 205; *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 181 – 200; c) D. A. Evans in *Asymmetric Synthesis*, *Vol. 3* (Ed.: J. D. Morrison), Academic Press, Orlando, FL, **1984**, p. 2. For an illuminating study on the importance of torsional steering as a stereocontrol element, see: M. J. Martinelli, B. C. Peterson, V. V. Khau, D. R. Hutchison, M. R. Leanna, J. E. Audia, J. J. Droste, Y.-D. Wu, K. N. Houk, *J. Org. Chem.* **1994**, *59*, 2204 – 2210.
[15] Z. Q. Yang, J. C. Lorenz, Y. Shi, *Tetrahedron Lett.* **1998**, *39*, 8621 – 8624.
[16] This cyclization was conducted on a mixture of cyclopropane diastereomers without apparent consequence for overall efficiency. For an account of the chemistry of oxycyclopropanes, see: E. Wenkert, *Acc. Chem. Res.* **1980**, *13*, 27 – 31.
[17] The reduction of **33** to galcatin (**6**) using PtO_2 was previously reported; see: J. S. Liu, M. F. Huang, Y. L. Gao, J. A. Findlay, *Can. J. Chem.* **1981**, *59*, 1680 – 1684. We found that using PtO_2 yielded a 3:1 ratio of the C8 epimers, whereas an improved ratio of 16:1 could be obtained by using palladium on carbon as the catalyst.

