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Explorations into Neolignan Biosynthesis: Concise Total Syntheses of Helicterin B, Helisorin, and Helisterculin A from a Common Intermediate

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Abstract: Helicterins A and B (**1** and **2**), helisorin (**3**), and helisterculin A (**4**) are structurally unique natural products with the ability to combat the avian myeloblastosis virus. Biogenetically, their architectures are considered to be products of seemingly straightforward Diels−Alder, radical-based, or acid-induced dimerizations of common, simpler precursors. Yet, the pursuit of such blueprints in the laboratory has failed thus far in enabling their successful synthesis. Herein, we describe the first total syntheses of three of these natural products. Key features include the use of a building block distinct from Nature's likely starting material, highly complex retro Diels−Alder/Diels−Alder reaction cascades, an unconventional protecting group to achieve the proper balance of chemical reactivity on sensitive scaffolds, and several carefully developed reaction conditions that effectively balance competing reaction pathways.

1. Introduction

In late 1999 and early 2000, Tezuka and co-workers reported the isolation and structural characterization of helicterins A and B, helisorin, and helisterculin A (**1**−**4**, Figure 1), four members of a family of structurally distinct neolignans from the Indonesian plant *Helicteres isora* that possess mild inhibitory activity against the avian myeloblastosis virus.[1] Similar to many plant-derived polyphenols, their architectural complexity likely derives from the oligomerization of a simpler building block, in this case either rosmarinic acid (**5**)[2] or its doubly methylated form, oresbiusin B (**6**),[3] if one assumes that all of the unassigned stereogenic centers in these isolates possess the same absolute chirality.

Indeed, as shown in Scheme 1, a possible biosynthesis of these adducts could begin via oxidation of the conjugated aromatic ring within **5** (cf. Figure 1) to its corresponding *o*-quinone (**10**), followed by a Diels−Alder reaction with the olefinic domain of unoxidized **5** (shown here as **9**) to provide key intermediate **8**. This molecule, in turn, could give rise to helisorin (**3**) via a Friedel−Crafts reaction of the pendant aromatic ring onto the proximal ketone, while changes in its oxidation state could provide pathways to helisterculin A (**4**) and intermediate **7**, the likely precursor needed to forge the acetal-based core of helicterin A and B (**1** and **2**).[4] Alternatively, critical intermediate **8** could also be envisioned to arise via a radical-based union of appropriate carbon-centered radicals (**12a** and **12b**) followed by a C−C bond-forming event.

Yet, despite the elegance and apparent simplicity of these general sequences, ones proposed by the original isolation chemists[1] and mirrored by many[5] in assessing putative biosynthetic pathways to related polyphenol natural products, the challenge for synthetic chemistry is accomplishing them in the absence of the enzymes that Nature likely deploys to achieve the requisite stereo- and chemoselectivity.[6] For instance, the proposed conversion of **8** into **7** requires the selective delivery of hydride from the more hindered face of the [2.2.2]-bicycle onto the less accessible of its two ketones, and *ortho*-quinones of the type postulated for the opening Diels−Alder reaction typically decompose prior to intermolecular cycloaddition.[7] In fact, in our own efforts to temper the latter of these reactivity issues by using an *ortho*-quinone monoketal as a surrogate for the needed diene as provided upon oxidation of model compound **14** by $PhI(OAc)_2$ in MeOH, the resultant molecule underwent a Diels−Alder-based homodimerization that afforded **15** in 87% yield no matter how many equivalents of dienophile

(1) (a) Tezuka, Y.; Terazono, M.; Kusumoto, T. I.; Kawashima, Y.; Hatanaka, Y.; Kadota, S.; Hattori, M.; Namba, T.; Kikuchi, T.; Tanaka, K.; Supriyatna, S. *Helv. Chim. Acta* **1999**, *82*, 408–417. (b) Tezuka, Y.; Terazono, M.; Kusumoto, T. I.; Hatanaka, Y.; Kadota, S.; Hattori, M.; Namba, T.; Kikuchi, T.; Tanaka, K.; Supriyatna, S. *Helv. Chim. Acta* **2000**, *83*, 2908–2919.

(2) Petersen, M.; Simmonds, M. S. J. *Phytochemistry* **2003**, *62*, 121–125.

(3) Huang, H.; Sun, H.-D.; Wang, M.-S.; Zhou, S.-X. *J. Nat. Prod.* **1996**, *59*, 1079–1080.

(4) Several examples of such dimerizations are known with [2.2.1]-bicycles: (a) Banks, M. R.; Gosney, I.; Grant, K. J.; Reed, D.; Hodgson, P. K. G. *Magn. Reson. Chem.* **1992**, *30*, 996–999. (b) Jauch, J.; Schurig, V.; Walz, L. *Zeit. Kristallograph.* **1991**, *196*, 255–260. (c) Creary, X.; Rollin, A. J. *J. Org. Chem.* **1977**, *42*, 4226−4230. However, there are no examples involving [2.2.2]-systems, to the best of our knowledge. In fact, several studies have revealed challenges in forging such dimeric cores. (d) Creary, X.; Rollin, A. J. *J. Org. Chem.* **1977**, *42*, 4231–4238. (e) Richardson, A. M.; Chen, C.-H.; Snider, B. B. *J. Org. Chem.* **2007**, *72*, 8099–8102.

(5) For reviews, see: (a) Oikawa, H.; Tokiwano, T. *Nat. Prod. Rep.* **2004**, *21*, 321–353. (b) Ward, R. S *Nat. Prod. Rep.* **1999**, *16*, 75–96. (c) For a general review on biogenetic Diels−Alder reactions, see: Stocking, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078–3115.

(6) For the original coining of the term chemoselectivity as a principle in controlled, selective, functional group manipulation, see: (a) Trost, B. M; Salzmann, T. N. *J. Am. Chem. Soc.* **1973**, *95*, 6840–6845.

(7) For example, see: Deslongchamps, P. *Can. J. Chem.* **1990**, *68*, 115–126, and references therein.

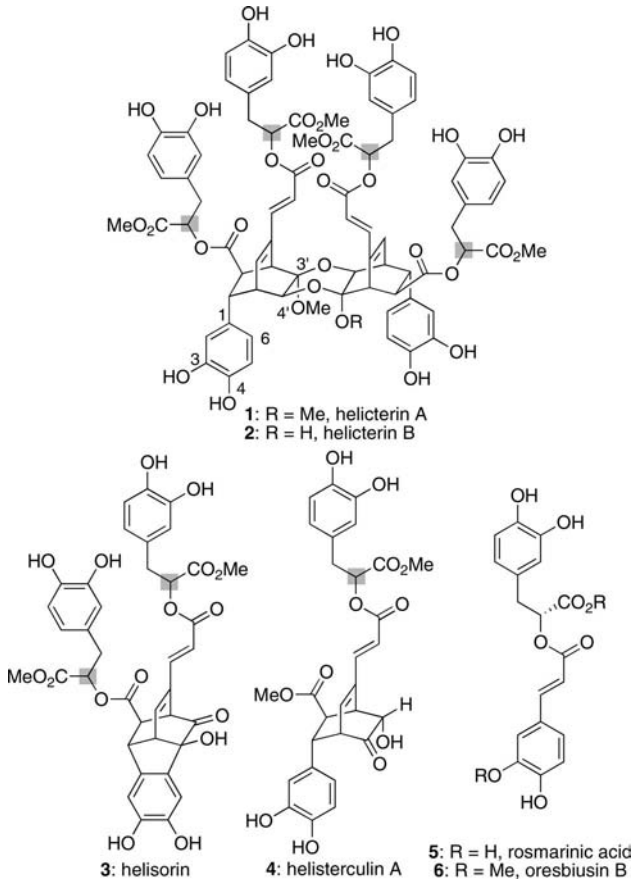
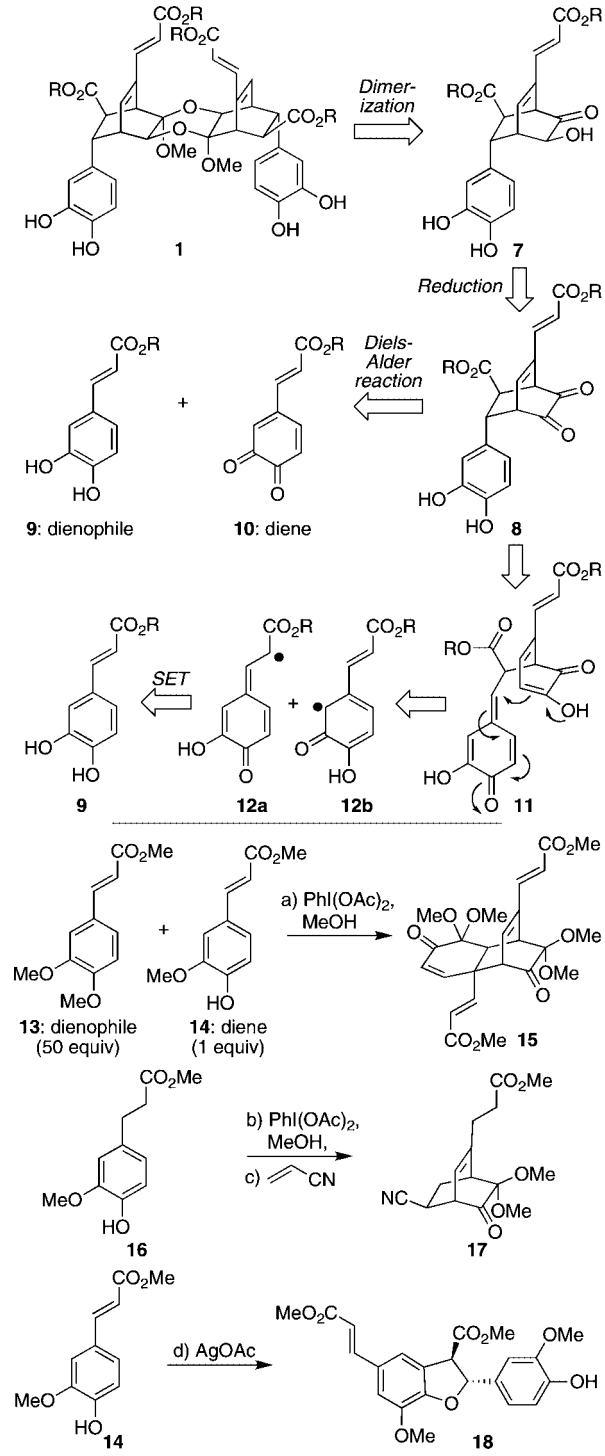


Figure 1. Structures of helicterin A and B (**1** and **2**) and related natural products (**3**−**6**). Unassigned stereocenters are highlighted.

13 were present in solution.[8]Only through major structural alteration, such as removal of the conjugated olefin and the use of a smaller dienophile, were we able to achieve direct [4 + 2] reactions, though, as illustrated with a reaction between acrylonitrile and the oxidized form of **16**, the resultant products (such as **17**) possessed regiochemistry opposite that found in the helicterin family.[9] In the same vein, our attempts to achieve controlled radical-based dimerizations of **14** using single-electron transfer (SET) reagents, such as AgOAc, consistently led to a complex mixture of products from which we have only been able to isolate and characterize dihydrofuran **18**.[10]

Herein, we report the first synthetic solution to this general problem in chemoselectivity, an answer revealing that many of the general tenets of the proposed biosynthetic scheme can be reduced to practice, but only by utilizing a building block that is structurally distinct from Nature's presumed starting material in combination with carefully conceived reaction conditions that achieve appropriate control on sensitive frameworks.

Scheme 1. Proposed Biogenetic Routes to Helicterin A and B (**1** and **2**) and Preliminary Efforts To Achieve Their Core Synthesis[a]

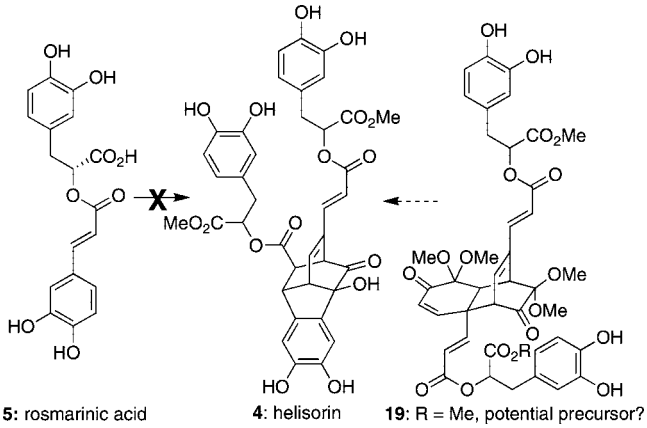


[a] Reagents and conditions: (a) $PhI(OAc)_2$ (1.05 equiv), $MeOH/CH_2Cl_2$ (6:1), 25 °C, 14 h, 87%; (b) $PhI(OAc)_2$ (1.1 equiv), $MeOH/CH_2Cl_2$ (5:1), 25 °C, 14 h, 97%; (c) acrylonitrile (100 equiv), toluene, 80 °C, 48 h, 43%; (d) AgOAc (1.1 equiv), toluene, 60 °C, 20 h, 20%.

(8) For selected examples of such dimerizations affording natural products, see: (a) Bérubé, A.; Drutu, I.; Wood, J. L. *Org. Lett.* **2006**, *8*, 5421–5424. (b) Gagnepain, J.; Castet, F.; Quideau, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 1533–1536. (c) For the original use of $PhI(OAc)_2$ as oxidant, see: Takata, T.; Tajima, R.; Ando, W. *J. Org. Chem.* **1983**, *48*, 4764–4766.

(9) The regiochemistry of this product matches that reported by several other investigators. For example, see: (a) Liao, C.-C; Chu, C.-S.; Lee, T.-H.; Rao, P. D.; Ko, S.; Song, L. D.; Shiao, H.-C. *J. Org. Chem.* **1999**, *64*, 4102–4110. More generally, for selected reviews of such chemistry, see: (b) Quideau, S.; Pouysegu, L.; Deffieux, D *Synlett* **2008**, 467–495. (c) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383–1429. (d) Rodríguez, S.; Wipf, P. *Synthesis* **2004**, 2767–2783. For recent examples in the realm of total synthesis, see: (e) Yen, C.-F.; Liao, C.-C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4090–4093. (f) Cook, S. P.; Polara, A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 16440–16441.

Scheme 2. Proposed Use of a Unique Dimeric Form of Rosmarinic Acid To Overcome Laboratory Issues of Chemoselectivity As Observed with Nature's Starting Material

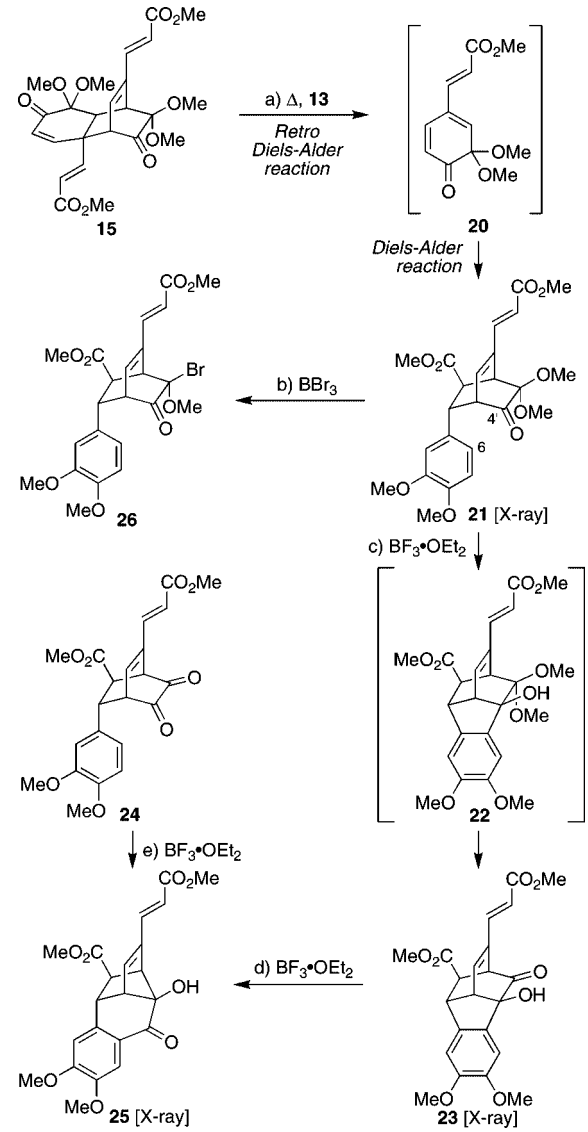


2. Results and Discussion

2.1. Overarching Synthetic Approach and Initial Model Studies. Given our inability to temper the reactive pathways of model compounds related to rosmarinic acid (**5**, Scheme 2), we wondered whether the varied architectural complexity of the helicterin family could be controllably accessed from a different starting material. Such an idea was inspired by our previous studies with the resveratrol-based collection of natural products where we found that a common, nonobvious precursor could be converted into a variety of structurally unique natural products and analogues with high selectivity upon its exposure to simple reagents.[11] In this case, we postulated that **19**, a fully functionalized form of the Diels−Alder homodimer (**15**) discussed above, could constitute that starting material if it could be funneled into a protected version of the desired core structure (**8**, cf. Scheme 1) by heating it at a high enough temperature in the presence of the requisite dienophile (**9**). In other words, we hypothesized that the Diels−Alder dimerization reaction we had modeled earlier with phenol **14** provided **15** as a kinetic outcome, while the desired product (**21**, Scheme 3) might represent a thermodynamic sink reachable by breaking apart that material through a retro Diels−Alder reaction and inducing a [4 + 2]-cycloaddition reaction with dienophile **13**.[12]

We thus decided to re-explore this model system, and pleasingly, compound **21** was produced in 43% isolated yield (83% yield based on recovered starting material) following 30 min of heating a mixture of **15** and **13** at 220 °C in mesitylene in a sealed tube; its structure was verified by X-ray crystallographic analysis. As shown in Table 1, this unique retro Diels−Alder/Diels−Alder sequence was not effectively promoted by microwave radiation irrespective of reaction solvent (entries 1−3), did not appear to benefit from any "on-water" effect under thermal activation (entry 4 and entry 6 versus entry 7),[13] and required slightly more than 5 equiv of dienophile to obtain a maximal yield (entries 7−11). It also required significant activation, as no product was observed under thermal conditions if the reaction temperature was below 160 °C. While these reaction conditions are relatively harsh, their success in

Scheme 3. Model Studies To Create the Helisorin Core[a]



[a] Reagents and conditions: (a) **13** (6.7 equiv), mesitylene, 220 °C, 43% (83% b.r.s.m.); (b) BBr_3 (1.0 M in CH_2Cl_2, 6.0 equiv), −78 °C, 1 h, 86%; (c) $BF_3 \cdot OEt_2$ (6.0 equiv), CH_2Cl_2, 0→25 °C, 16 h, 82%; (d) $BF_3 \cdot OEt_2$ (20 equiv), CH_2Cl_2, 25 °C, 16 h, 80%; (e) $BF_3 \cdot OEt_2$ (6.0 equiv), CH_2Cl_2, 0→25 °C, 16 h, 53%.

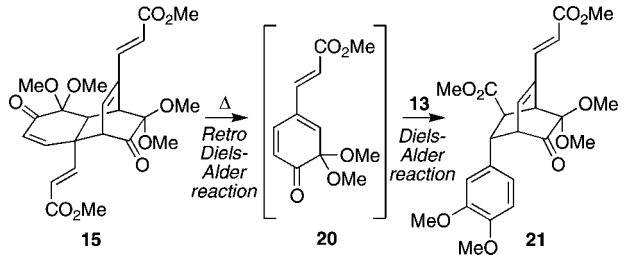
(10) Despite the absence of control in our endeavors to dimerize this substrate, others have reported a number of instances where high levels of selectivity can be achieved using SET agents. For one recent example leading to a dihydrofuran product, see: (a) Sako, M.; Hosokawa, H.; Ito, T.; Iinuma, M. *J. Org. Chem.* **2004**, *69*, 2598–2600. (b) For efforts to dimerize an oxazolidine derivative of rosmarinic acid, work that led to products very similar to **18**, see: Bruschi, M.; Orlandi, M.; Rindone, B.; Rummakko, P.; Zoia, L. *J. Phys. Org. Chem.* **2006**, *19*, 592–596.

(11) Snyder, S. A.; Zografos, A. L.; Lin, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 8186–8191.

(12) For other examples of this reaction concept using masked *ortho*-benzoquinones, see: (a) Singh, V.; Samanata, B. *Tetrahedron Lett.* **1999**, *40*, 1807–1810. (b) Chittimalla, S. K.; Shiao, H.-Y.; Liao, C.-C. *Org. Biomol. Chem.* **2006**, *4*, 2267–2277. (c) Chittimalla, S. K.; Liao, C.-C. *Synlett* **2002**, 565–568. (d) Liao, C.-C.; Peddinti, R. K *Acc. Chem. Res.* **2002**, *35*, 856–866. For the use of *ortho*-quinol dimers in these types of sequences, see: (e) Singh, V. K.; Deota, P. T.; Bedekar, A. V. *J. Chem. Soc., Perkin Trans. 1* **1992**, 903–912. It is important to note that, in all these examples, only monosubstituted dienophiles were employed; none has explored a substrate as complex as that reported here. Also, the regiochemistry observed in these cases is in line with that observed for compound **17**.

(13) (a) Breslow, R.; Rideout, D. *J. Am. Chem. Soc.* **1980**, *102*, 7816–7817. (b) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159–164. (c) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275–3279.

Table 1. Screening of Conditions To Form Diels–Alder Product **21**



entry	heating source	conditions	yield (%)[b]
1	μwave	EtOH, 200 °C, 5 min, 5.0 equiv of **13**	0
2	μwave	ethylene glycol, 210 °C, 10 min, 5.0 equiv of **13**	16
3	μwave	toluene/*i*-PrOH, 190 °C, 35 min, 5.0 equiv of **13**	11
4	oil bath[a]	H_2O/LiCl, 160 °C, 60 min, 5.0 equiv of **13**	23
5	oil bath[a]	DMA, 220 °C, 30 min, 5.0 equiv of **13**	26
6	oil bath[a]	mesitylene/H_2O, 220 °C, 30 min, 5.0 equiv of **13**	34
7	oil bath[a]	mesitylene, 220 °C, 30 min, 5.0 equiv of **13**	40
8	oil bath[a]	mesitylene, 220 °C, 30 min, 3.3 equiv of **13**	33
9	oil bath[a]	mesitylene, 220 °C, 30 min, 6.7 equiv of **13**	43
10	oil bath[a]	mesitylene, 220 °C, 30 min, 10 equiv of **13**	42
11	oil bath[a]	mesitylene, 220 °C, 30 min, 20 equiv of **13**	44

[a] Reaction performed in a sealed tube. [b] Isolated yields only are reported. DMA = *N*,*N*-dimethylacetamide

producing the desired core architecture validated the general concept of using **19** (Scheme 2) as a starting material to fashion **1**–**4**.

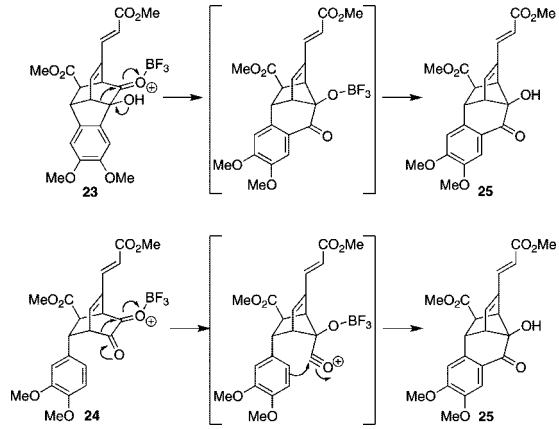
From this new compound (**21**, Scheme 3), we then initiated a search for conditions that could achieve a Friedel–Crafts-like union between C-6 and the C-4′ carbonyl as required to create the core of helisorin (**3**). We began by exposing **21** to a variety of protic acids in an array of reaction solvents (such as HCl or TFA in wet THF and *p*-TsOH in acetone) in hopes of effecting both acetal cleavage and the desired C–C bond construction. However, the starting material was consistently recovered in near quantitative yield from all these experiments. Fortunately, select Lewis acids provided the needed activation. For instance, controlled exposure of **21** to 6 equiv of $BF_3 \cdot OEt_2$ in CH_2Cl_2 at 0 °C, followed by slow warming to ambient temperature and 16 h of additional stirring, accomplished the desired event in 82% yield. Others, such as $FeCl_3 \cdot SiO_2$,[14] also provided **23**, but in significantly reduced yield (13%). Mechanistically, we postulate that this step leading to **23** proceeds via initial Friedel–Crafts cyclization (generating intermediate **22**), followed by acetal cleavage. This statement is not based on the direct observation or isolation of any **22**. Rather, it reflects the fact that when the putative diketone intermediate (**24**, see Supporting Information for its synthesis) that would arise from the alternate order of events was exposed separately to the same reaction conditions involving $BF_3 \cdot OEt_2$, only the unique rearranged adduct **25**[15] was obtained. Moreover, **23** could be converted into the same material only through far more forcing conditions (20 equiv of $BF_3 \cdot OEt_2$). Finally, the use of more powerful Lewis acids in our attempts to convert **21** into **23** resulted in unexpected reaction products; for instance, the use of 6 equiv of BBr_3 at −78 °C in CH_2Cl_2 smoothly provided halogenated intermediate **26** in 82% yield.[16] Several other Lewis acids, such as $In(OTf)_3$, $TiCl_4$, and Me_2AlCl in CH_2Cl_2 at 25 °C, did not induce any reactions with **21** despite several hours of stirring and their use in superstoichiometric amounts (10–15 equiv).

2.2. Protecting Group Selection, Synthesis of Fully Functionalized Starting Materials, and Total Synthesis of Helisorin (3). Although the above studies were promising in revealing that the core motifs of at least one of the target molecules could be accessed (i.e., **3**), the main issue for their translation to fully functional materials, in our opinion, was the identification of an appropriate protecting group for the phenols. Though such an issue is a standard concern for any synthetic plan,[17] these natural products, and the developed conditions up to this point for the critical C–C bond constructions, presented a unique array of combined challenges. First, under no circumstance could the chosen protecting group require aqueous acid to cleave, as such conditions could rupture the acetal linkage in the two helicterins (**1** and **2**). Aqueous base would presumably be just as deleterious, as it could hydrolyze the ester linkages within all the target molecules and/or racemize their chiral centers. Moreover, given the oxidation potential of the 3,4-diphenoxy ring systems within all of the targets (each was isolated from the plant extracts in less than 30 min in a cold room; ambient temperatures, light, and oxygen caused their decomposition),[18] every phenol protecting group would have to be cleaved quickly and cleanly so as to avoid overmanipulation of the final product, especially during purification. Finally, based on a series of additional model studies (not shown), it became evident that both the Diels–Alder reaction leading to **21**, as well as the Friedel–Crafts reaction that afforded **24** (cf. Scheme 3), required an electron-donating protecting group to proceed.

Given these collated criteria, we anticipated that the ideal protective group would likely need to be an ether, one with just the right balance of stability versus reactivity so as to be able to survive exposure to stoichiometric amounts of mild Lewis acids (such as $BF_3 \cdot OEt_2$) at 25 °C over several hours, but which could be ruptured quickly in the presence of more powerful Lewis acids (such as BBr_3) at much lower tempera-

(14) Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem.* **1986**, *51*, 404–407.

(15) The structure of **25** was confirmed by X-ray crystallographic analysis. As indicated below, we believe that the formation of this product follows a Pinacol-like mechanism. To account for the highly different reactivity of **23** and **24** upon its exposure to $BF_3 \cdot OEt_2$, we are invoking slightly different pathways depending upon whether the sequence commences with **23** or **24**. An alternative mechanism for the conversion of **24** into **25**, one which does not invoke an acylium ion that could lead to simple loss of CO, would be for **24** to convert into **23**, with that step being rate-determining.

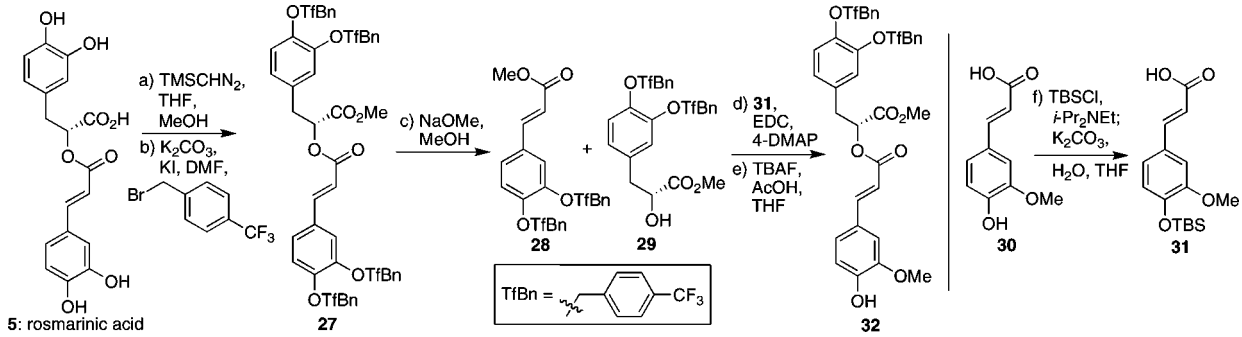


(16) The existence of such bromoacetals has been documented previously: Mackenzie, K.; Proctor, G.; Woodnutt, D. J. *Tetrahedron* **1987**, *43*, 5981–5993.

(17) Kocienski, P. J. *Protecting Groups*; Georg Thieme: Stuttgart, 2004; pp 679.

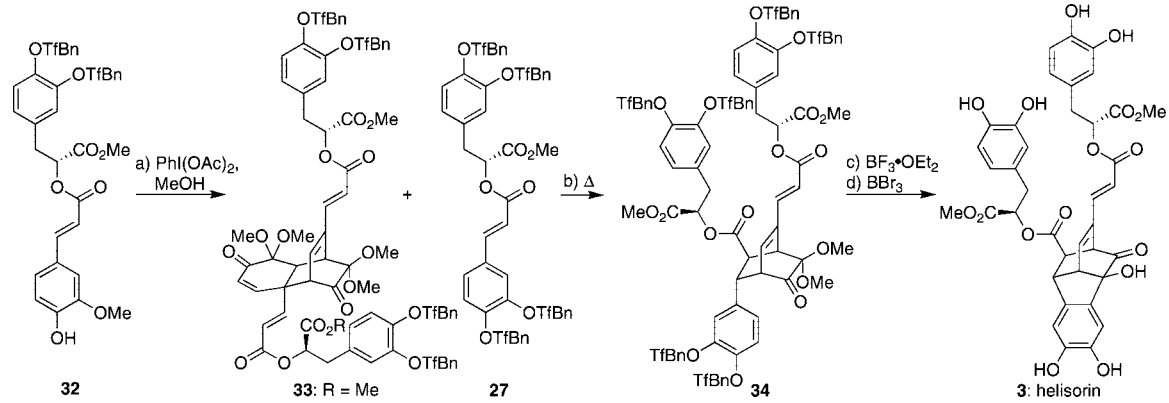
(18) Personal communication from Prof. Yasuhiro Tezuka.

Scheme 4. Synthesis of Building Blocks **27**, **28**, and **32** from Rosmarinic Acid (**5**)[a]



[a] Reagents and conditions: (a) $TMSCHN_2$ (0.95 equiv), THF/MeOH (10:1), −78 °C, 1 h; (b) TfBnBr (6.0 equiv), K_2CO_3 (6.0 equiv), KI (catalytic), 60 °C, 8 h, 84% overall; (c) NaOMe (1.0 equiv), MeOH/CH_2Cl_2 (1:1), 25 °C, 2 h, 92% **28**, 90% **29**; (d) **31** (2.0 equiv), EDC·HCl (2.0 equiv), 4-DMAP (1.0 equiv), CH_2Cl_2, 25 °C, 3 h; (e) TBAF (2.0 equiv), AcOH, THF, 0 °C, 10 min, 94% overall; (f) TBSCl (2.5 equiv), *i*-Pr_2NEt (3.0 equiv), CH_2Cl_2, 25 °C, 14 h, then K_2CO_3 (excess), H_2O, THF, 25 °C, 2 h, 99%. TMS = trimethylsilyl, EDC = 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide, 4-DMAP = 4-dimethylaminopyridine, TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl.

Scheme 5. Total Synthesis of Helisorin (**3**)[a]



[a] Reagents and conditions: (a) $PhI(OAc)_2$ (1.05 equiv), MeOH/CH_2Cl_2 (5:1), 25 °C, 14 h, 99%; (b) **27** (6.7 equiv), mesitylene, 220 °C, 30 min, 38% (71% b.r.s.m.); (c) BF_3·OEt_2 (30 equiv), H_2O (5.0 equiv), C_6H_6, 0→25 °C, 16 h, 53% (82% b.r.s.m.); (d) BBr_3 (1.0 M in CH_2Cl_2, 20 equiv), CH_2Cl_2, −78 °C, 30 min, 77%.

tures. Based on literature precedent, benzyl ethers appeared ideal in this regard;[19] however, simple model studies (not shown) quickly demonstrated that this group was sensitive to prolonged exposure to BF_3·OEt_2. We thus decided to explore substituted benzyl ethers, hoping that the addition of a mildly electron-withdrawing group (such as a *p*-CF_3 group; σ value = 0.54)[20,21] could deactivate the protecting group enough to survive exposure to BF_3·OEt_2 while still permitting the Diels−Alder and Friedel−Crafts reactions to succeed.

This conjecture was tested by preparing the differentially protected rosmarinic acid derivatives **27** and **32** as shown in Scheme 4.[22] Starting from commercially available **5**, initial chemoselective methylation of its free carboxylic acid was achieved through treatment with 0.95 equiv of $TMSCHN_2$ and was followed by a subsequent alkylation of the four phenol residues using *p*-CF_3-benzyl bromide under Finkelstein conditions. These operations completed the synthesis of **27** in 84% overall yield. Methanolysis of the internal ester linkage within this new product then provided both **28** and **29**, the latter of which was coupled with carboxylic acid **31** under standard conditions (EDC, 4-DMAP, CH_2Cl_2, 25 °C) to afford, following silyl ether cleavage, the differentially protected intermediate **32**. These operations set the stage to explore the key sequence of steps that would hopefully lead to a total synthesis of helisorin (**3**).

As indicated in Scheme 5, the first of these operations, oxidative homodimerization of **32** via a Diels−Alder reaction, proceeded quickly and cleanly in near quantitative yield (99%) with $PhI(OAc)_2$ in MeOH at 25 °C. Next, in a test of the robustness of the retro Diels−Alder/Diels−Alder sequence that worked so effectively in model systems, this intermediate (**33**) was heated in mesitylene in a sealed tube at 220 °C in the presence of 6.7 equiv of dienophile **27**, and the desired Diels−Alder product (**34**) was obtained in 38% isolated yield

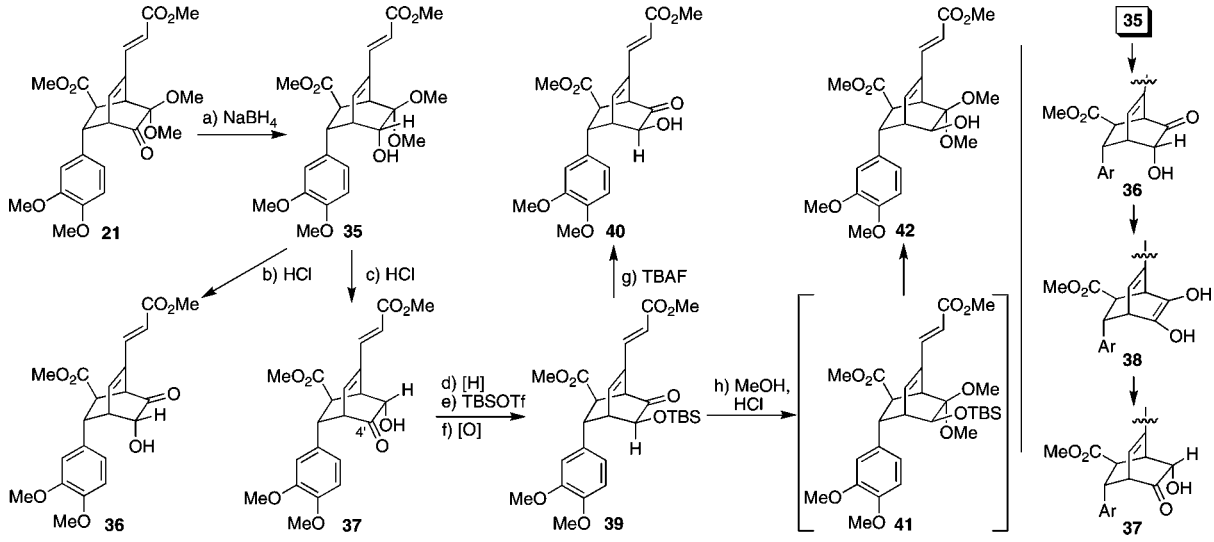
(19) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley and Sons: New York, 1999; p 779. For the general utility and value of benzyl ethers as a protective device for rosmarinic acid specifically, see: (b) Eicher, T.; Ott, M.; Speicher, A. *Synthesis* **1996**, 755–762.

(20) For the determination of the σ-value, see: (a) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195. For an exploration into the reactivity of this ether, see: (b) Liotta, L. J.; Dombi, K. L.; Kelley, S. A.; Targontsidis, S.; Morin, A. M. *Tetrahedron Lett.* **1997**, *38*, 7833–7834. To the best of our knowledge, while *p*-CF_3-benzyl ethers have been used to protect aliphatic alcohols on a select number of occasions, they have never been employed to protect phenols. The abbreviation of these protecting groups as TfBn was originally defined in ref 19a.

(21) Our selection of this particular benzyl ether was ultimately based on the failure of 2,6-difluoro-benzyl ethers (σ-value = 0.06) to survive prolonged exposure to BF_3·OEt_2, while far more electron-withdrawing ligands such as *p*-NO_2-benzyl ethers (σ-value = 0.78) and *p*-CN-benzyl ethers (σ-value = 0.66) led to synthetic intermediates with poor solubility profiles.

(22) Elements of the sequence leading to this piece were inspired by: O'Malley, S. J.; Tan, K. L.; Watzke, A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13496–13497.

Scheme 6. Synthesis of Model Dimerization Percursors **40** and **42** from Diels−Alder Product **21**[a]



[a] Reagents and conditions: (a) $NaBH_4$ (excess), $MeOH/CH_2Cl_2$, 0 °C, 1 h, 99%; (b) 0.2 M HCl, H_2O, toluene, 0 °C, 20 h, 86%; (c) 0.5 M HCl, H_2O, THF, 25 °C, 14 h, 84%; (d) $Me_4NBH(OAc)_3$ (5.0 equiv), MeCN/AcOH (10:1), 25 °C, 5 h, 75%; (e) TBSOTf (1.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, −78→25 °C, 1 h; (f) Dess−Martin periodinane (1.5 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 25 °C, 1 h, 94% over 2 steps; (g) TBAF (1.0 M in THF, 2.0 equiv), AcOH (2.0 equiv), THF, 25 °C, 2 h, 54% (76% b.r.s.m.); (h) 0.4 M HCl, $MeOH/CH(OMe)_3$ (4:1), 25 °C, 14 h, 93%.

(71% yield based on recovered **27**). Interestingly, though both fragments contained a single chiral center, this new product (**34**) was generated as a 1:1 mixture of diastereomers, indicating that such stereochemical information was too remote to control the facial presentation of the two partners in this key event.[23] This outcome suggests, albeit circumstantially, that an enzyme is involved in Nature's synthesis of such a framework since only a single natural product enantiomer has been isolated thus far.

Given the uncertainty regarding some of the stereochemistry of the final natural products as mentioned in the Introduction, the two Diels−Alder diastereomers (**34**) were separated at this stage via standard column chromatography and then subjected separately to $BF_3 \cdot OEt_2$ in hopes of creating the remaining C−C bond of the helisorin core. Fortunately, this step proceeded relatively smoothly in 53% yield (82% yield based on recovered **34**) when the original model conditions ($BF_3 \cdot OEt_2$ in CH_2Cl_2) were slightly adjusted in terms of solvent and water content (benzene and 5 equivalents of added water). Finally, controlled exposure to BBr_3 in CH_2Cl_2 at −78 °C quickly and cleanly cleaved all six *p*-CF_3-benzyl ethers in 30 min, providing a synthetic sample of **3** in 77% yield that was identical to naturally derived helisorin (**3**) in all respects (^1H and ^{13}C NMR, IR, HRMS, α_D). As such, the first laboratory synthesis of this neolignan was complete, and a definitive assignment of this molecule's relative stereochemistry and the connection of the family to **5** and/or **6** could finally be made.[24]

2.3. Total Synthesis of Helicterin B (2). With these successes in hand, we next targeted the most complex members of the family, helicterins A and B (**1** and **2**), beginning with model studies seeking to create the acetal core of these rosmarinic acid tetramers. Our initial goal was to convert compound **21** into either hydroxyketone **40** or hydroxyketal **42** (Scheme 6) given literature precedent indicating that such functional domains in [2.2.1]-bicyclic frameworks could induce dimerization simply upon standing or upon exposure to anhydrous acids.[4] As such, our efforts began with attempts to achieve a stereoselective reduction of the ketone within **21** to generate **42** directly. Unfortunately, no condition screened, including several that can accomplish such a reaction in [2.2.1]-systems (such as Meerwein−Pondorff−Verley reduction, samarium-based reducing agents, or $NaBH_4/CeCl_3$),[25] rose to the occasion. Instead, **35** was formed consistently and proved resistant to all efforts at inversion (either under standard Mitsunobu conditions or attempted displacement of a triflate with KO_2 or $NaNO_2$).[26] The same inversion challenge was observed with hydroxyketone **36**, formed from **35** in 86% yield via its controlled exposure to aqueous HCl in toluene at 0 °C.

As such, an indirect approach to **40** and **42** was developed wherein **35** was first exposed to 0.5 M HCl in a more polar solvent (THF) to effect both acetal cleavage as well as an equilibrative ketol shift[27] which ultimately provided hydroxyketone **37** [the core of the natural product helisterculin A (**4**)]. This compound, formed in 84% yield, is the most thermodynamically stable (by 1.7 kcal/mol) of the four possible hydroxy-

(23) Recently, some very unique approaches have been developed to create chiral masked *ortho*-benzoquinones that could conceivably afford a diastereoselective solution to this key step: (a) Pouységu, L.; Chassaing, S.; Dejugnac, D.; Lamidey, A.-M.; Miqueu, K.; Sotiropoulos, J.-M.; Quideau, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3552–3555. (b) Luo, S.-Y.; Jang, Y.-J.; Liu, J.-Y.; Chu, C.-S.; Liao, C.-C.; Hung, S.-C. *Angew. Chem., Int. Ed.* **2008**, *47*, 8082–8085. Unfortunately, attempts at deploying these ideas within the context of these natural products have not succeeded in our hands. As such, future efforts are being directed towards identifying solutions to this problem.

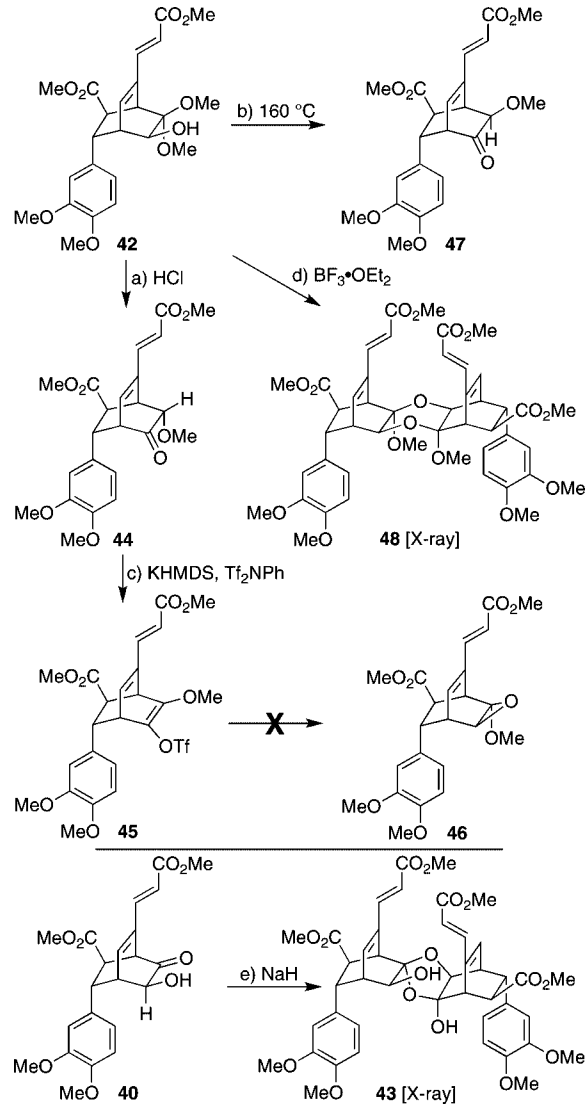
(24) If the final deprotection was stirred for prolonged periods (greater than 1 h), executed at reaction temperatures above −50 °C, and/or left unprotected from atmospheric oxygen and light (especially upon purification), significant decomposition was observed. Final isolations of each synthetic natural product were handled with extreme care so as to minimize exposure to heat and air. Typically, upon completion of the BBr_3-induced deprotection, the reaction would be quenched while still cold, quickly engaged in an extractive workup, and concentrated via rotary evaporation using an ice-cold water bath (all performed in less than 5 min). The crude product was then loaded onto a preparative TLC plate, with the separation performed in the dark using an argon-purged chamber and degassed solvents (typically in less than 30 min).

(25) (a) Namy, J. L.; Souppe, J.; Collin, J.; Kagan, H. J. *J. Org. Chem.* **1984**, *49*, 2045–2049. (b) de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. *Synthesis* **1994**, 1007–1017. (c) Krief, A.; Surleraux, D. *Synlett* **1991**, 273–275.

ketone isomers based on DFT calculations;[28] it also reflects the mechanistic product of proton capture by enol **38** on the least hindered face[29] at the most accessible position. From here, compound **39** was accessed via (1) directed reduction of the remaining ketone as mediated by $Me_4NBH(OAc)_3$,[30] (2) selective silyl protection of the resultant C-4′ hydroxyl, and (3) oxidation of the remaining alcohol. Desilylation under basic conditions (TBAF, THF) then completed the synthesis of **40** in 54% yield, while controlled treatment of **39** with a solution of 0.5 M HCl in a 4:1 mixture of MeOH/$CH(OMe)_3$ led to **42** in 93% yield. It is important to note that in the latter of these two operations the added $CH(OMe)_3$ ensured initial acetal formation before silyl ether cleavage, thereby preventing any equilibration back to **37** by way of an intermediate hydroxyketone.

At this juncture, we expected that both compounds **40** and **42** would dimerize readily to generate the core of helicterin A (**1**). However, this outcome did not occur with the ease that previous work suggested.[4] As shown in Scheme 7, exposure of **42** to anhydrous HCl afforded only **44** (likely though a mechanism similar to the one leading to **37**, vide supra), while treatment with acids such as CSA in toluene led to **44** alongside an unsymmetrical dimer (**43**, verified by X-ray crystallography) whose connectivity reflects the core structure of yunnaneic acid C,[31] a member of a related group of natural products. Similarly, heating **42** neat at 160 °C for several hours primarily generated **47**, while efforts to dimerize hydroxyketone **40** under both acidic and basic protocols (NaH/THF or HCl/MeOH) delivered **43** exclusively in near quantitative yield (99%). Even efforts to utilize a more circuitous route, such as attempts to convert **44** into enol triflate **45** as part of an effort to generate a different dimerization precursor (i.e., epoxide **46**), were thwarted, in this case by the relative ease with which **45** underwent a retro Diels−Alder reaction upon its exposure to various Pd sources in attempts to perform a reductive Stille reaction

Scheme 7. Model Studies Directed Towards the Synthesis of the Helicterin Core via Attempted Dimerizations of **40** and **42**[a]



[a] Reagents and conditions: (a) HCl (g), 100 °C, 45 min, 99%; (b) 160 °C, 4 h, 15% (32% b.r.s.m.); (c) KHMDS (0.5 M in toluene, 1.3 equiv), Tf_2NPh (2.6 equiv), THF, −78 °C, 10 min, 74%; (d) $BF_3 \cdot OEt_2$ (4.0 equiv), CH_2Cl_2, 0 °C, 30 min, 79%. (e) NaH (10 equiv), THF, 25 °C, 20 min, 99%. Tf = trifluoromethanesulfonate, KHMDS = potassium bis(trimethylsilyl)amide.

(Scheme 7. Once again, as with the Friedel−Crafts reaction leading to helisorin (**3**, cf. Scheme 5), only a Lewis acid would prove capable of forging the requisite bond constructions. That reagent was $BF_3 \cdot OEt_2$, which delivered a model helicterin A core (**48**) in 79% yield when **42** was exposed to it in CH_2Cl_2 at 0 °C for 30 min.[32]

Pleasingly, these explorations transferred readily to fully functionalized intermediates, as compound **34** was smoothly advanced to intermediate **50** via the same reaction sequence as shown in Scheme 8. The only major surprise came two steps later, as following the formation of the desired acetal core of helicterin A (**1**) with $BF_3 \cdot OEt_2$, subsequent exposure of the resultant product to BBr_3 in CH_2Cl_2 not only cleaved all 12

(26) For representative procedures that were attempted, see: (a) Dodge, J. A.; Nissen, J. S.; Presnell, M. *Org. Synth.* **1996**, *73*, 110–115. (b) Albert, R.; Dax, K.; Link, R. W.; Stütz, A. E. *Carbohydr. Res.* **1983**, *118*, C5–C6. (c) Radüchel, B. *Synthesis* **1980**, 292–295. (d) Mukaiyama, T.; Shintou, T.; Fukumoto, K. *J. Am. Chem. Soc.* **2003**, *125*, 10538–10539.

(27) For a recent example of this type of rearrangement in synthesis, see: Meng, D.; Tan, Q.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3197–3201.

(28) These calculations were performed at the DFT-B3LYP(1)/6−31+G* level in acetonitrile and THF continuum solvents. All four possible isomers were subjected to conformational searching within MacroModel 6.0 using the OPLS 2001 force field. The lowest energy structures for each possible isomer were then optimized in the gas phase at the B3LYP/6−31+G* level within Jaguar 7.0. Single-point solvation calculations, including first-shell correction terms and activation energy, were then performed in acetonitrile and THF continuum solvents. For leading references, see: (a) Jorgensen, W. L.; Maxwell, D. S.; Tirado-Rives, J. *J. Am. Chem. Soc.* **1996**, *118*, 11225–11236. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789. (c) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (d) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372–1377.

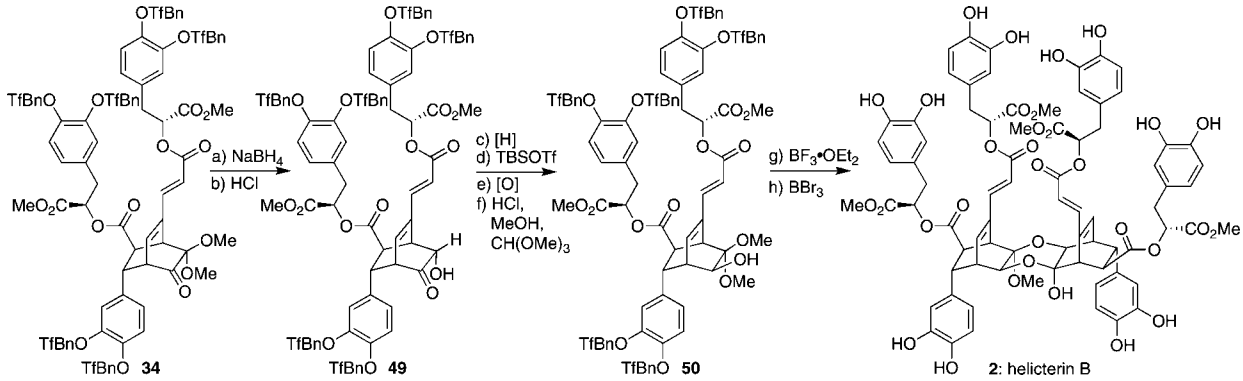
(29) Zimmerman, H. E. *J. Am. Chem. Soc.* **1956**, *78*, 1168−1173. An alternate mechanism for this step could involve a [1,2]-hydride shift onto an intermediate carbocation. However, we believe that invoking an enol intermediate, despite its possible strain within a [2.2.2]-framework, is reasonable given results that are described in Scheme 7: the facile formation of enol triflate **45** and the relatively poor yield in the conversion of **42** into **47** which could proceed via such a hydride shift mechanism (but which does so only at high temperature). In addition, compound **40** (Scheme 6) could also be converted into **37** through its exposure to acid; a hydride shift would have led to a different product in this case.

(30) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939–5942.

(31) Tanaka, T.; Nishimura, A.; Kouno, I.; Nonaka, G.; Young, T.-J. *J. Nat. Prod.* **1996**, *59*, 843–849.

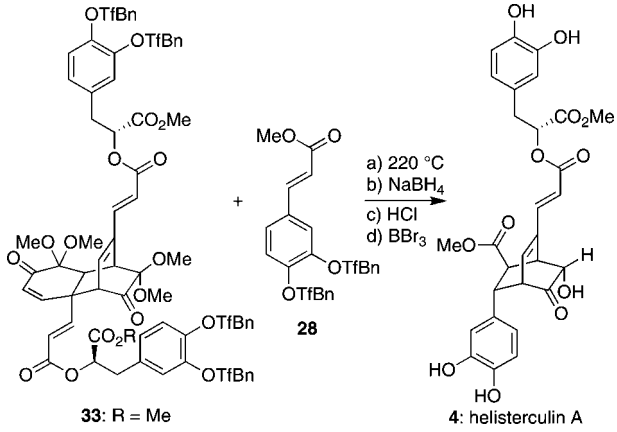
(32) The structure of **48** was verified by X-ray crystallography. Interestingly, exposure of hydroxyketone **40** to a number of different Lewis acids did not afford a helicterin A-like core.

Scheme 8. Total Synthesis of Helicterin B (**2**)[a]



[a] Reagents and conditions: (a) $NaBH_4$ (1.5 equiv), MeOH/THF (4:1), −30 °C, 1 h; (b) 0.5 M HCl, MeCN/H_2O (100:1), 25 °C, 14 h, 56% overall; (c) $Me_4NBH(OAc)_3$ (5.0 equiv), MeCN/AcOH (80:1), 25 °C, 28 h; (d) TBSOTf (1.05 equiv), Et_3N (5.0 equiv), CH_2Cl_2, −78 °C, 1 h; (e) Dess−Martin periodinane (1.5 equiv), $NaHCO_3$ (excess), CH_2Cl_2, 25 °C, 1 h; (f) 0.4 M HCl MeOH/$CH(OMe)_3$ (4:1), 25 °C, 14 h, 43% overall; (g) $BF_3 \cdot OEt_2$ (8.0 equiv), CH_2Cl_2, 0 °C, 30 min, 67%; (h) BBr_3 (1.0 M in CH_2Cl_2, 20 equiv), CH_2Cl_2, −78 °C, 45 min, 76%.

Scheme 9. Total Synthesis of Helisterculin A (**4**)[a]



[a] Reagents and conditions: (a) **28** (6.7 equiv), mesitylene, 220 °C, 30 min, 44% (78% b.r.s.m.); (b) $NaBH_4$ (1.5 equiv), MeOH/THF (4:1), 0 °C, 1 h, 79%; (c) 0.2 M HCl, MeCN/H_2O (15:1), 25 °C, 2 h, 74%; (d) BBr_3 (1.0 M in CH_2Cl_2, 8.0 equiv), CH_2Cl_2, −78 °C, 30 min, 92%.

p-CF_3-benzyl ethers but also led to the replacement of one of the methyl ethers in the acetal core with a hydroxyl group. As such, the first total synthesis of helicterin B (**2**) had been achieved. Thus far, all efforts to convert helicterin B (**2**) into helicterin A (**1**), such as exposure to anhydrous MeOH under acidic catalysis, have led solely to the recovery of **2**. We hypothesize that the difficulty in executing this conversion, as well as the general ease of forming **2** in the absence of obtaining even trace amounts of **1** in the final deprotection, could derive from an intramolecular hydrogen bond that might exist between the hydroxyl domain and the pendant methyl ether oxygen.

2.4. Total Synthesis of Helisterculin A (4). As a final demonstration of the robustness and utility of the developed sequences, the remaining dimeric member of the family, helisterculin A (**4**), was prepared using a number of the critical steps discussed earlier. As shown in Scheme 9, our common dimeric starting material (**33**) was subjected to the same retro Diels−Alder/Diels−Alder cascade, this time using a different dienophile (**28**) to yield the bicyclic core of the target molecule. This intermediate was then subjected to reduction followed by an acid-catalyzed acetal cleavage and equilibrative ketol rearrangement, as discussed above in the context of Scheme 6, to afford the thermodynamic hydroxyketone product. Global phenol deprotection with BBr_3 then smoothly converted this compound into the natural product (**4**), completing the sequence in a final overall yield of 42%.

3. Conclusion

We have developed an efficient approach capable of controllably accessing the major architectures within this neolignan family, culminating here in total syntheses of three natural products as well as providing the first route to the core of several others (the yunnaneic acids). In the process, the stereochemical ambiguities of the side chains have been resolved and their connections to rosmarinic acid established. Each route proceeds in good overall yield, requiring 14 or fewer steps from commercially available materials. Key features of these sequences include some of the most complex retro Diels−Alder/Diels−Alder reactions to date, an unconventional protecting group to achieve the proper balance of chemical reactivity on sensitive scaffolds, several carefully developed reaction conditions that effectively balanced competing reaction pathways, and the illustration that Lewis acids were typically needed to accomplish the biomimetic steps of the sequence. This synthesis also reaffirms an idea we previously expressed: diverse, oligomeric natural products can be accessed by way of common precursors that differ from Nature's presumed building block.[11]

Acknowledgment. We would like to acknowledge the gracious assistance of Prof. Yasuhiro Tezuka (Toyama University) in providing us with copies of the physical NMR spectra of **1**−**4** and for sharing some of the challenges his group encountered in achieving their isolation. We also would like to thank Mr. Anish Shah for synthesizing several intermediates, Ms. Michelle L. Hall for performing DFT calculations, and Drs. John Decatur and Y. Itagaki for NMR spectroscopic and mass spectrometric assistance, respectively. The National Science Foundation (CHE-0619638) is acknowledged for the acquisition of an X-ray diffractometer, and we thank Prof. Gerard Parkin and members of his group for obtaining our crystal structures. Financial support for this work was provided by Columbia University, Amgen, and Eli Lilly. S.A.S. is a Camille and Henry Dreyfus New Faculty Awardee.

Supporting Information Available: Experimental procedures, compound characterization, copies of spectral data, X-ray structures, and complete ref 7. This material is available free of charge via the Internet at http://pubs.acs.org.

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