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Biomimetic Semisynthesis of Arglabin from Parthenolide

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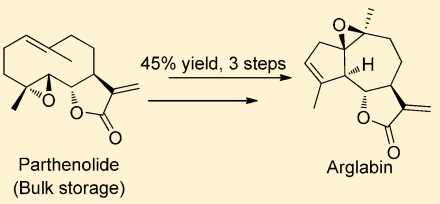
Supporting Information

ABSTRACT: The semisynthesis of arglabin, an anticancer drug in clinical application, is developed from abundant natural product parthenolide via three steps. Each step in this sequence is highly stereoselective, and the substrate-dependent stereoselectivity in the epoxidation step can be explained by computational calculations. The success of chemical semisynthesis of arglabin suggests that the biosynthesis of arglabin might proceed in a similar pathway.



Natural products are the most consistently successful sources in drug discovery.[1−3] However, natural product drugs are often produced in trace quantities, and sometimes another natural product can serve as a starting material for the semisynthesis of the target drug. For example, the development of paclitaxel (Taxol) was severely hampered by the scarcity of its original source, the bark of *Taxus brevifolia*. The compound supply issue was solved by semisynthesis from 10-deacetylbaccatin III, which is readily available from the needles of various *Taxus* species, a renewable resource.[4−6]

Sesquiterpene lactones (SLs) are a large family of plant-derived compounds; they have been shown to have considerable biological activities against inflammation and cancer.[7] Guaianolides, which consist of a tricyclic 5,7,5-ring system, represent a subgroup of SLs.[8] Arglabin (**1**, Figure 1), a

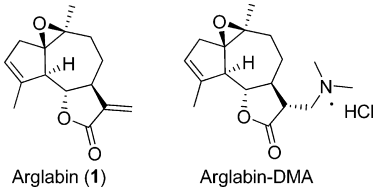
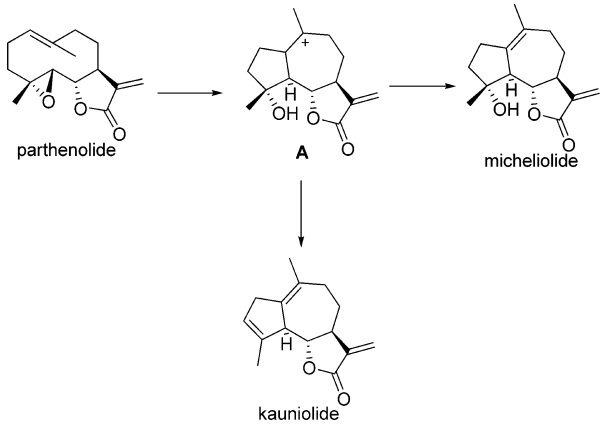


Figure 1. Stuctures of arglabin and arglabin-DMA.

prominent member of guaianolides, shows promising cytotoxicity against different tumor cell lines.[9] Arglabin has been modified to water-soluble form Arglabin-DMA, and Arglabin-DMA is a registered antitumor substance in the Republic of Kazakstan for the treatment of breast, colon, ovarian, and lung cancers.[10] Arglabin can be isolated from *Artemisia glabella*[11] but comprises only 0.27% of the aerial parts of the plant, and its purification procedures is very tedious.[12]

Up to date, the only synthesis of arglabin is reported by Reiser.[13] Moreover, although it has been proposed that parthenolide is the starting material in the biosynthesis of the guaianolide type of SLs micheliolide or kauniolide through a transition state A (Scheme 1),[14,15] there is still no direct evidence to identify the biosynthetic pathway of arglabin from parthenolide.

Scheme 1. Proposed Biosynthesis of Germacranolide Type SL to Guaianolides Type SL in the Literature



However, parthenolide is also low-yielding from its traditional natural source feverfew (*Tanacetum parthenium*); only 0.14−0.74% of parthenolide can be observed in dried feverfew leaves.[16] Fortunately, we found that parthenolide can be readily extracted in high yield (3.1−8.0%) from the root bark of *Magnolia delavayi*.[17] *Magnolia delavayi* is very abundant in several provinces in China, since its bark and flower are important traditional Chinese herbs. Moreover, removal of a small percentage of root bark every year has negligible effect on the population of *Magnolia delavayi* plants, because the root of *Magnolia delavayi* can be regenerated. Parthenolide also has multiple biological activities,[18,19] such as against cancer stem cells,[20−22] and its water-soluble analogue DMAPT is currently

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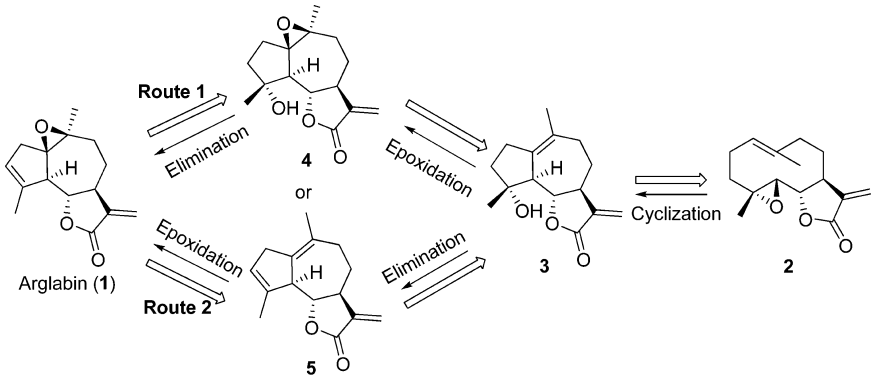
Scheme 2. Retrosynthetic Analysis of Arglabin

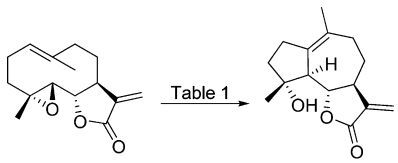


in clinical trial.[23,24] With a bulk amount of parthenolide, we pursued the synthesis of arglabin from parthenolide.

Parthenolide possesses a *trans*-6α,12-lactone moiety and so constitutes a good starting material for the syntheses of guaianolides.[25] Retrosynthetic analysis of arglabin indicates that there are two possible routes to synthesize arglabin from parthenolide (Scheme 2): route 1, epoxidation of te 1(10) double bond of compound **3** to yield compound **4** and then dehydration to afford arglabin, and route 2, dehydration of compound **3** to give compound **5**, followed by epoxidation to provide arglabin.

A biogenetic hypothesis proposes that germacrolides and their epoxide derivatives represent the precursors for other skeletal types of sesquiterpene lactones.[26] For instance, Lewis acid catalyzes reactions of parthenolide (**2**) into guaianolides at room temperature (RT), but these reactions produce complex mixtures and poor yields of each product (Table 1, entries 1 and 2).[25−29] However, in our modified procedure, parthenolide (**2**) was submitted to treatment with *p*-toluenesulfonic acid (*p*-TSA) in dichloromethane, and then natural micheliolide **3** was isolated by crystallization in 90% yield (Table 1, entry 3). This reaction can be preceded in kilogram scale without the need of chromatographic purification. Compound **3** was identified by comparing its ^{1}H and ^{13}C NMR data with those reported in the literature.[29]

Table 1. Conversion of Compound 2 to Compound 3

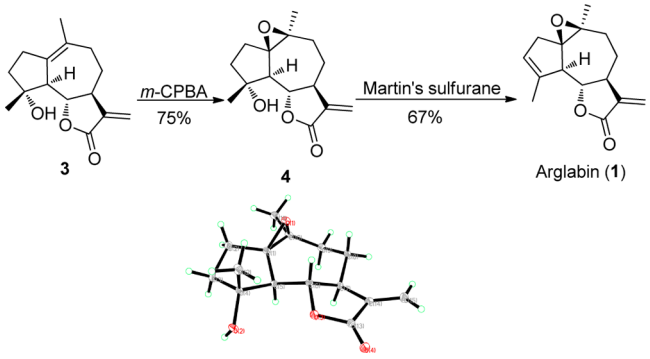


entry	conditions	yield (%)[a]
1	BF_3·OEt_2, toluene, RT	13[25]
2	*p*-TSA, MeOH, RT	26[26]
3	*p*-TSA, CH_2Cl_2, RT	90

[a]Yield of isolated compound **3**.

Using micheliolide **3**, the next step is epoxidation of the 1(10) double bond of compound **3** to yield compound **4**. The structure of compound **3** revealed that both faces of the seven-membered ring are exposed to epoxidation (Scheme 3). However, epoxidation from the β face (top) has to overcome steric shielding from the upward methyl group at the C-4 position. Furthermore, the hydroxyl group at C-4 might serve as a directing substituent, which is known not only for the epoxidation of allylic but also for homoallylic alcohols.[30−33] Surprisingly, epoxidation of compound **3** with *m*-chloroperbenzoic acid (*m*-CPBA) afforded a clean desired β-epoxide **4** as a single stereoisomer in 75% yield, which was confirmed by X-ray analysis (Scheme 3).

Scheme 3. Synthetic Route 1 for Synthesis of Arglabin from Micheliolide



With the key intermediate **4** in hand, the next aim is to achieve selective dehydration to provide the 3(4) double bond of arglabin. We initially tried the dehydration of compound **4** using base-promoted elimination of the corresponding sulfonate (Table 2, entry 1), acetate (Table 2, entries 2 and 3), or trifluoroacetate (Table 2, entries 4 and 5). Unfortunately, all of these conditions failed to provide a significant amount of elimination product. The elimination employing Tf_2O and pyridine gave arglabin in a moderate yield of 29% (Table 2, entry 6), which is lower than that of Pedro's reaction[34] and Reiser's reaction[13] in the syntheses of similar compounds. Treated compound **4** with commonly used dehydrating reagents such as Burgess reagent,[35] Lawensson's reagent,[36] and DIAD/PPh_3 afforded no product (Table 2, entries 7−9), whereas with DEAD/PPh_3 (Table 2, entry 10),[37] 13% of arglabin can be isolated, and with $SOCl_2$, and $POCl_3$ in pyridine at room temperature, arglabin were prepared in 27% and 28% yield, respectively (Table 2, entries 11 and 12). At a lower temperature of 0 °C, $POCl_3$ treatment of compound **4** provided arglabin with improved yield of 51% (Table 2, entry 13). An important advance was obtained when Martin's sulfurane[38] was used as dehydrating reagent; treatment of compound **4** with Martin's sulfurane in CH_2Cl_2 at RT afforded **1** in a yield of 67% (Table 2, entry 14). This product was

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Table 2. Dehydrative Elimination of Compound 4 for Synthesis of Arglabin

entry	conditions	yield (%)[a]
1	TsCl, DMAP, pyridine, CH_2Cl_2, RT	0
2	Ac_2O, pyridine, CH_2Cl_2, RT	0
3	Ac_2O, pyridine, RT	0
4	TFAA, Et_3N, CH_2Cl_2, RT	0
5	TFAA, pyridine, CH_2Cl_2, RT	5
6	Tf_2O, pyridine, CH_2Cl_2, RT	29
7	Burgess reagent, CH_3CN, 80 °C	0
8	Lawensson's reagent, toluene, 110 °C	0
9	DIAD, PPh_3, pyridine, THF, RT	0
10	DEAD, PPh_3, pyridine, THF, RT	13
11	$SOCl_2$, pyridine, RT	27
12	$POCl_3$, pyridine, RT	28
13	$POCl_3$, pyridine, 0 °C	51
14	Martin's sulfurane, CH_2Cl_2, RT	67

[a]Yield of isolated purified arglabin.

corresponded in all spectroscopic data with those reported in the literature.[39]

For the second route (Scheme 4), compound **3** was treated with $POCl_3$ in pyridine at −40 °C and afforded compound **5** in 65% yield. Epoxidation of compound **5** with 1.1 equiv of *m*-CPBA provided 1β,10β-epoxide (arglabin), 1α,10α-epoxide **6**, and 3β,4β-epoxide **7** in 1.2%, 27.1%, and 37.8% yields, respectively. For the 1,10-epoxidation of compound **5**, a preference of 22:1 for the α face was observed, which is consistent with the epoxidation of a similar starting material.[40]

To explain the reversal of stereoselectivity in the epoxidation of similar compounds **3** and **5**, we resorted to computational studies. We first optimized the geometries of the epoxide products (see Figure 2 and 3) and compared the free energies of the different isomers. To explain the stereoselectivity kinetically, we also explored the epoxidation reaction paths and revealed the transition states (TSs). Geometries for all species were optimized using the B3LYP method with the 6-31G* basis set. Vibrational frequency calculations were carried out to ensure that the optimized geometries are indeed associated with local minima on the potential energy surfaces and to determine the zero-point vibration energies and thermal corrections to the Gibbs free energies. Then, the optimized geometries at the B3LYP/6-31G* level were used to carry out single-point energy calculations with a larger basis set, 6-311++G**. The solvent effects (dichloromethane) were modeled using the PCM solvation method.

In Table 3, we present the calculated relative free energies of β- and α-epoxide products, as well as the relative free energies of the TSs of β- and α-epoxidation in compound **3** and **5**. It is seen from Table 3 that the free energy of β-epoxide **4** is lower than that of α-epoxide isomer by 4.6 kcal/mol. This energy difference reveals that the β-epoxide **4** is more stable than the

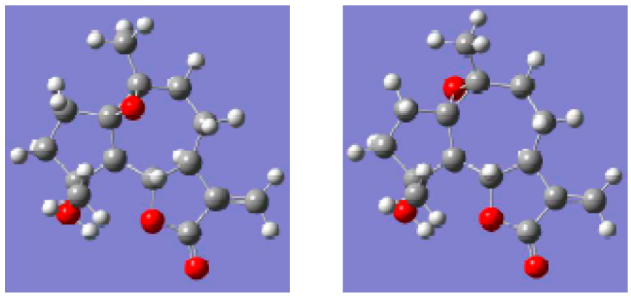


Figure 2. Optimized geometries of β-epoxide **4** and possible α-epoxide isomer.

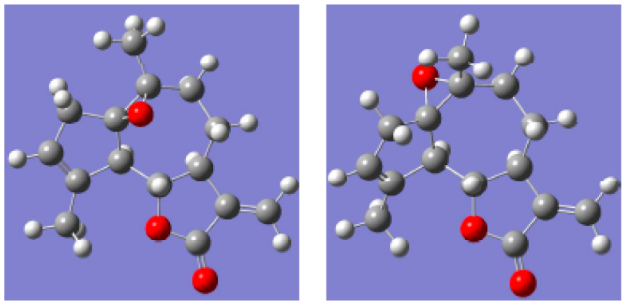


Figure 3. Optimized geometries of arglabin and compound **6**.

Table 3. Relative Free Energies (kcal/mol) of Different Isomers of Epoxide and Relative Free Energies (kcal/mol) of the TS Species in the Epoxidation of 3 and 5

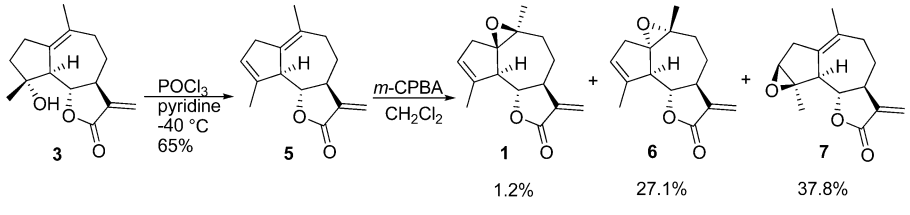
ΔG^a of β-epoxide and α-epoxide			
4 (β-epoxide)	**4** (α-epoxide)	arglabin (β-epoxide)	**6** (α-epoxide)
−4.6	0.0	0.8	0.0
$\Delta G_{TS}{}^b$ of β-epoxidation and α-epoxidation			
β-epoxidation of **3**	α-epoxidation of **3**	β-epoxidation of **5**	α-epoxidation of **5**
−0.9	0.0	1.5	0.0

[a]$\Delta G = G - G(\alpha)$. [b]$\Delta G = G_{TS} - G_{TS}(\alpha)$

α-epoxide isomer. We also notice that the free energy of the transition state in β-epoxidation of **3** is lower than the α-epoxidation by 0.9 kcal/mol. Theses results allow us to conclude that β-attack is kinetically and thermodynamically favored in the epoxidation of **3**, and the stereoselectivity is consistent with the result in our reaction. The stereoselectivity is reversed to the α-epoxidation in compound **5**, and this can also be explained by the stability of α-epoxide **6** product and the lower free energy of the TS for α-epoxidation.

To date, there is no biosynthesis study of arglabin. According the result above, we propose that the possible biosynthesis of arglabin might start with parthenolide, the carbocation involved cyclization of parthenolide results in the formation micheliolide,

Scheme 4. Synthetic Route 2 for Synthesis of Arglabin from Micheliolide



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the next step is more likely to be epoxidation of the tetrasubstituted olefin in micheliolide, and then the final step is dehydration.

In summary, we have developed the semisynthesis of the guaianolide arglabin from an abundant starting material, parthenolide. The convenient and efficient semisynthesis of arglabin was achieved in three steps from parthenolide with an overall yield of 45%. The high stereoselectivities in these three steps suggest that biosynthesis of arglabin might proceed in a similar pathway.

EXPERIMENTAL SECTION

The starting material parthenolide was obtained from Accendatech Co., Ltd. The used solvents were purified and dried according to common procedures. NMR spectra were recorded with a 400 MHz (^{1}H, 400 MHz; ^{13}C, 100 MHz) spectrometer and referenced to the solvent peak for $CDCl_3$. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br. = broad, m = multiplet), coupling constants, and integration.

***p*-Toluenesulfonic Acid Catalyzed Transformation of Parthenolide (2) to Micheliolide (3).** To a solution of *p*-toluenesulfonic acid (43.7 g, 2.5 mmol) in CH_2Cl_2 (15.8 kg) was added dropwise a solution of parthenolide (1.75 kg, 7.06 mol) in CH_2Cl_2 (3.5 kg) at 20 °C for 8 h. The resulting reaction mixture was stirred at room temperature for 15 h. The reaction was quenched with 9.1% $NaHCO_3$ (550 g). The organic layer was washed with saturated brine (2 × 2 kg), decolorized with activated carbon (100 g), and concentrated under reduced pressure to give a crude residue, which was recrystallized from acetone to yield a colorless needle, compound **3** (1.58 kg, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.20 (d, J = 3.2 Hz, 1H), 5.49 (d, J = 3.2 Hz, 1H), 3.81 (t, J = 10.4 Hz, 1H), 2.70 (d, J = 10.4 Hz, 1H), 2.65−2.62 (m, 2H), 2.40−2.34 (m, 1H), 2.07−2.26 (m, 4H), 1.73−1.86 (m, 2H), 1.68 (s, 3H), 1.36−1.28 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.8, 138.7, 131.7, 130.8, 119.5, 84.1, 80.2, 58.5, 49.5, 38.2, 34.8, 30.0, 25.7, 23.9, 23.6.

Synthesis of Compound 4. A solution of micheliolide (30 g, 121 mmol) and *m*-CPBA (32.4 g, 187.7 mmol) in CH_2Cl_2 (1.8 L) was stirred at room temperature overnight. The reaction mixture was washed with Na_2SO_3 (3 × 500 mL), $NaHCO_3$ (3 × 500 mL), and saturated brine (3 × 200 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude residue, which was recrystallized from acetone to yield compound **4** as crystalline solid (24 g, 75%). Mp: 160−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (d, J = 3.2 Hz, 1H), 5.44(s, 1H), 5.44 (t, J = 2.4 Hz, 1H), 4.01 (t, J = 10.4 Hz, 1H), 2.85 (br.s, 1H), 2.33−2.17 (m, 4H), 1.96−1.78 (m, 4H), 1.65−1.59 (m, 1H), 1.43 (s, 4H), 1.36 (m, 1H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.7, 138.1, 119.6, 81.8, 79.7, 69.8, 62.2, 55.5, 49.3, 37.3, 33.3, 29.5, 23.3, 23.2, 21.9; HRMS (ESI) for $[C_{15}H_{20}O_4Na]^+$ calcd 287.1259, found 287.1258.

Dehydration of Compound 4 with Martin's Sulfurane. A solution of Martin's sulfurane (4.54 g, 6.75 mmol) in CH_2Cl_2 (36 mL) was slowly added to a solution of compound **4** (1.19 g, 4.5 mmol) in CH_2Cl_2 (72 mL) under an atmosphere of Ar. The mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography to afford arglabin (0.74 g, 67%). $[\alpha]^{24}_D$ = +105° (3 mg/mL, $CHCl_3$)[41], ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (d, J = 3.2 Hz, 1H), 5.57 (s, 1H), 5.41 (d, J = 3.2 Hz, 1H), 4.00 (t, J = 10.4 Hz, 1H), 2.93 (br.d, J = 10.8 Hz, 1H), 2.77 (br.d, J = 17.6 Hz, 1H), 2.27−2.12 (m, 3H), 2.03 (m, 1H), 1.97 (br.s, 3H), 1.84 (br.d, J = 14.0 Hz, 1H), 1.48 (m, 1H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6, 140.7, 139.2, 125.0, 118.4, 83.0, 72.6, 62.8, 52.9, 51.2, 39.8, 33.6, 22.9, 21.6, 18.4.

Dehydration of Compound 4 with $POCl_3$. To a stirred solution of compound **4** (21.0 g, 79.5 mmol) in pyridine (656 mL) was added $POCl_3$ (18.6 mL, 199 mmol) at 0 °C. The mixture was stirred for 2 h, Et_2O (1 L) was added, and the organic layer was washed successively with $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give crude residue. Then the residue was chromatographed on a silica gel column to afford arglabin (9.97 g, yield 51%).

Synthesis of Compound 5. To a stirred solution of $POCl_3$ (0.09 mL, 0.95 mmol) in pyridine (1 mL) was slowly added micheliolide (100 mg, 0.40 mmol) in CH_2Cl_2 (1 mL) at −40 °C. The reaction mixture was stirred for 36 h at −40 °C. The reaction was quenched with $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was successively washed with $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give crude residue. Then the residue was chromatographed on a silica gel column to afford compound **5** (60.6 mg, yield 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (d, J = 3.2 Hz, 1H), 5.47 (s, 1H), 5.35 (d, J = 3.2 Hz, 1H), 3.60 (t, J = 10.0 Hz, 1H), 3.34 (d, J = 10.0 Hz, 1H), 2.92 (br d, 2H), 2.77−2.71 (m, 1H), 2.26 (t, J = 13.2 Hz, 1H), 2.15−2.02 (m, 2H), 1.89 (s, 3H), 1.67 (s, 3H), 1.37−1.27 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.0, 140.5, 139.8, 135.3, 131.2, 126.1, 117.5, 85.3, 56.1, 53.0, 37.7, 33.8, 25.8, 23.1, 17.7.

Epoxidation of Compound 5 with *m*-CPBA. A solution of compound **5** (160 mg, 0.70 mmol) and *m*-CPBA (189 mg, 1.1 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature overnight. The reaction mixture was successively washed with Na_2SO_3, $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude residue. Then the residue was chromatographed on a silica gel column to provide arglabin (2 mg, 1.2%), compound **6** (43 mg, 27.1%), and compound **7** (60 mg, 37.8%).

Compound **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (d, J = 3.2 Hz, 1H), 5.59 (s, 1H), 5.45 (d, J = 3.2 Hz, 1H), 3.78 (t, J = 10.4 Hz, 1H), 2.84 (br d, J = 18.0 Hz, 1H), 2.65 (m, 2H), 2.35 (m, 1H), 2.14 (br d, J = 16.8 Hz, 1H), 1.97 (br s, 3H), 1.84 (br d, J = 14.0 Hz, 1H), 1.60−1.43 (m, 2H), 1.34 (s, 3H).

Compound **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (d, J = 3.2 Hz, 1H), 5.40 (d, J = 2.8 Hz, 1H), 3.87 (t, J = 10.4 Hz, 1H), 3.32 (s, 1H), 2.86 (d, J = 10.0 Hz, 1H), 2.73−2.66 (m, 2H), 2.49 (d, J = 18.4 Hz, 1H), 2.27−2.02 (m, 3H), 1.66(br d, J = 10.0 Hz, 5H), 1.38−1.25 (m, 2H).

ASSOCIATED CONTENT

Supporting Information

Copies of the NMR spectra of compounds **1** and **3**−**7** and X-ray data of compound **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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