JOC The Journal of Organic Chemistry

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Semisynthesis of Libiguin A and Its Analogues by Trans-Lactonization of Phragmalin

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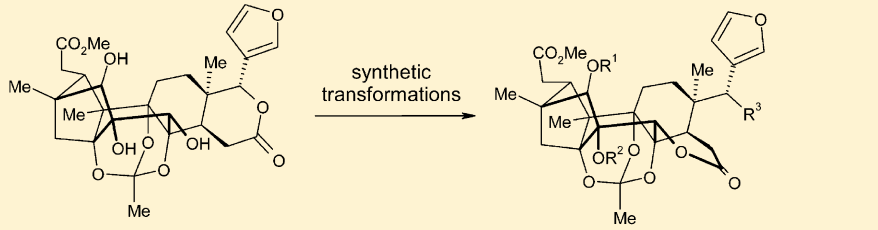
Supporting Information



Phragmalin

Isolated from seeds of *Chukrasia tabularis* 3.52 g/kg

Libiguin A R^1 = -C(O)i-Pr, R^2 = -C(O)i-Pr, R^3 = (=O)

1 R^1= -C(O)Me, R^2 = H, R^3 = -OC(O)CF_3

2 R^1 = -C(O)i-Pr, R^2 = H, R^3 = (=O)

3 R^1= -C(O)Me, R^2 = H, R^3 = (=O)

ABSTRACT: Libiguins are limonoids with highly potent sexual activity enhancing effects, originally isolated from the Madagascarian Meliaceae species *Neobeguea mahafalensis*, where they exist in only minute quantities. Their low natural abundance has hampered mapping of their biological effects. Here we describe an approach to the semisynthesis of libiguin A and its close analogues **1**−**3** starting from phragmalin, which is a limonoid present in high amounts in a commercially cultivated Meliaceae species, *Chukrasia tabularis*, allowing the preparation of libiguins in appreciable quantities.

Species of the Meliaceae plant family are a rich source of structurally diverse limonoids exhibiting a variety of biological activities.[1] In a previous study, we isolated two members of a new class of limonoids from the Madagascarian meliaceae species *Neobeguea mahafalensis*, which we named libiguin A and B (Figure 1). We discovered that these compounds induce a profound stimulation of sexual behavior in rodents at dosage levels in the low μg/kg range.[2] However, the isolation of the libiguins was an extremely complicated procedure because of their low natural abundance in the *N. mahafalensis* tree and the presence of many compounds with closely similar chromatographic properties.[2] This event precluded us from preparing sufficient quantities to allow a detailed characterization of the biological effects of the libiguins and their analogues.

To remedy this, we undertook the development of a procedure to access larger quantities of libiguin-type compounds. Although synthetic studies of several structural types of limonoids have been performed,[3] to the best of our knowledge no synthetic or semisynthetic approach for constructing the libiguin scaffold has been reported to date. As a potential starting material for the semisynthesis, we proposed phragmalin, a limonoid that is present in large quantities in some species of the Meliaceae family.[4,5] In the commercially cultivated species *Chukrasia tabularis*, which can be grown in a sustainable manner, phragmalin may be isolated in kilogram quantities per ton of plant tissue.[6] The major differences between phragmalin and libiguins are the location of the lactone ring, which is formed with the 17-oxy functionality in phragmalin and with the 30-oxy functionality in the libiguins. The 17-oxy function involved in the lactone ring of phragmalin is oxidized to the ketone in libiguin A or acetylated in libiguin B. Thus, trans-lactonization in phragmalin would be a key for the semisynthetic approach to libiguin-type compounds in order to provide the quantities of material required for biological investigations. Our initial studies of trans-lactonization were not successful despite our use of many commonly applied methods for lactone ring opening and closing. In the present study, we solved the trans-lactonization problem. This allowed us to prepare libiguin A as well as compounds **1**−**3**, novel analogues of the natural compounds libiguin A and B that are reported here for the first time.

Received: February 10, 2014
Published: April 9, 2014

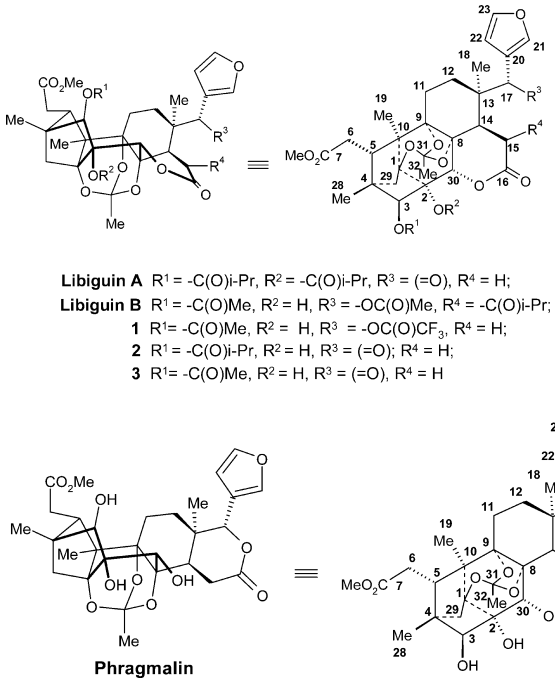
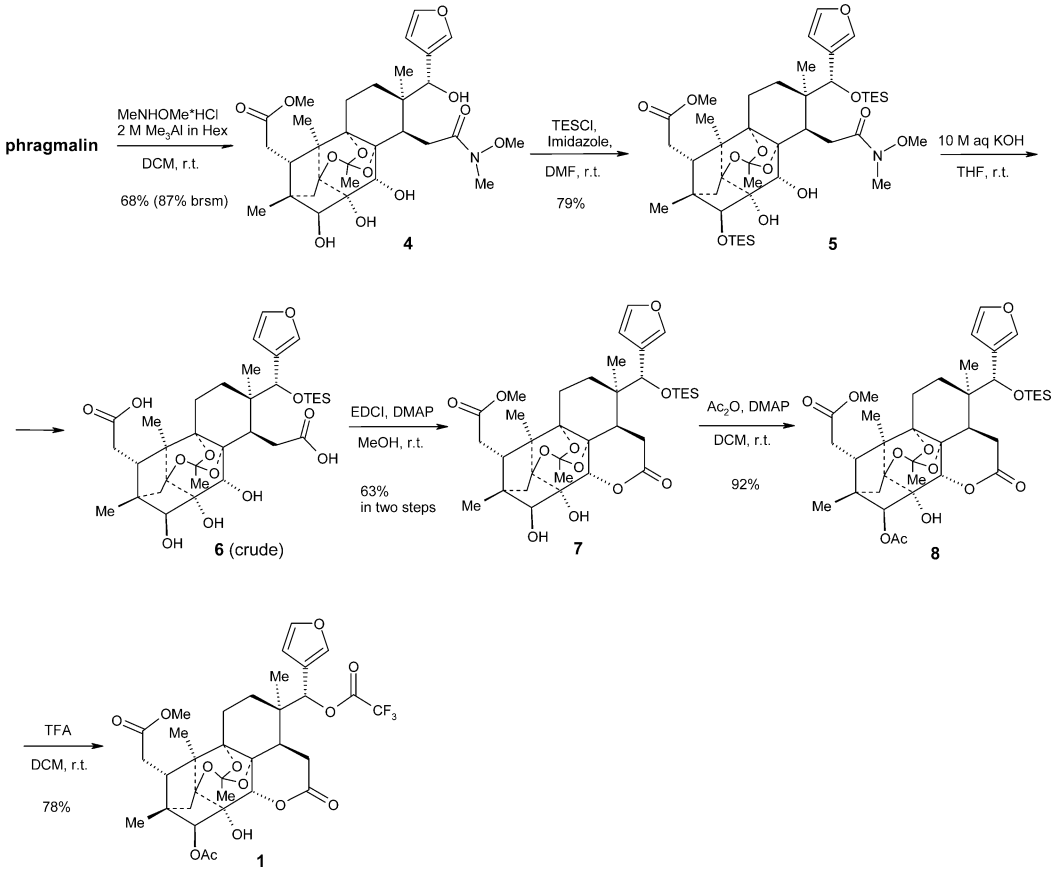


Figure 1. Structures of phragmalin, libiguin A and B, and their analogues **1**–**3**.

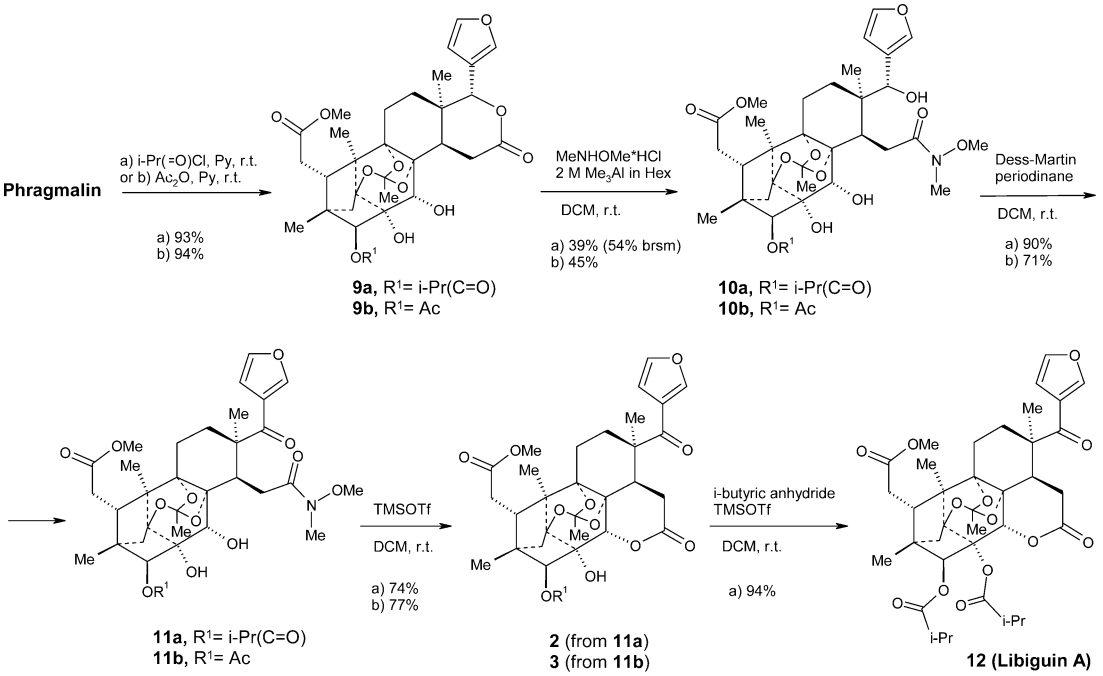
The phragmalin used herein was prepared from seeds of *C. tabularis* essentially as described previously[7] at a yield of 3.52 g/kg of seeds. In order to achieve the key trans-lactonization in phragmalin, we searched for conditions to open the lactone ring, aiming to prepare a relatively stable carboxylic acid derivative that could be used to form the lactone ring with the 30-OH group later in the synthetic route. A number of hydrolytic, reductive, and aminolytic conditions gave only limited success. Finally, reaction with MeONHMe·HCl promoted by Me_3Al led to lactone ring opening, providing Weinreb amide **4** in acceptable yield (Scheme 1).[8] The success of this reaction relied on careful time control, as prolonged reaction times led to increased amounts of byproducts that presumably were products of both lactone and ester aminolysis. The next step was selective protection of the 17-OH group over the 30-OH group in intermediate **4**. After some experimentation, selective protection of the 3-OH and 17-OH groups over the 2-OH and 30-OH groups was achieved by silylation of compound **4** with TESCl. This provided derivative **5**, which could be used for lactonization studies. We found that hydrolysis of both the ester and the Weinreb amide and concomitant cleavage of the TES group from the 3-OH group took place under basic hydrolysis conditions, providing dicarboxylic acid **6** (according to NMR analysis of the crude sample). Compound **6** was used for the next step without purification. Lactone ring closure and re-establishing of the ester function in **6** was achieved using EDCI as a condensing agent and MeOH as the reaction solvent. This led to compound **7** based on the libiguin scaffold in good overall yield. Selective acetylation of the 3-OH group in compound **7** gave derivative **8** in very high yield. Next, deprotection of the TES group in intermediate **8** was investigated under various conditions. However, all attempts failed to give a compound

Scheme 1. Synthesis of Libiguin Analogue 1 from Phragmalin



dx.doi.org/10.1021/jo500318w | J. Org. Chem. 2014, 79, 4148–4153

Scheme 2. Synthesis of Libiguin A and Its Analogues 2 and 3 from Phragmalin



with a free 17-OH group; either no reaction was observed or trans-lactonization back to a phragmalin derivative took place. When cleavage of the TES group was performed with TFA, trifluoroacetyl derivative **1**, a novel analogue of natural libiguin A and B, was isolated in good yield. The stereochemistry at C-17 for compound **1** was defined by NOESY NMR analysis (see the Supporting Information). Retention of the configuration according to the NMR analysis allowed us to exclude furylmethyl carbenium ion formation as a potential intermediate for the resulting TFA ester.

The facile trans-lactonization of libiguin back to the phragmalin scaffold when the 17-OH group was not protected prompted us to modify the synthetic route toward libiguin A. We aimed to oxidize the 17-OH group before the formation of the lactone ring with the 30-OH group. Observations from protection studies of phragmalin revealed that the 3-OH group could be selectively acylated over the 2-OH and 30-OH groups, even in the presence of a large excess of acylating agent. In addition, several attempts to place silyl, acetal, or PMB protection on the 2-OH and 30-OH groups in phragmalin failed, likely as a result of steric crowding. However, this result indicated that the 30-OH group is potentially reluctant to undergo oxidation in favor of the sterically less crowded 17-OH group after lactone ring opening in phragmalin. To prepare a substrate for oxidation, the 3-OH group in phragmalin was first acylated with isobutyryl chloride or acetic anhydride to give intermediate **9a** or **9b**, respectively (Scheme 2). Me_3Al-promoted aminolysis with MeONHMe·HCl was then applied to achieve selective lactone opening in the acylated phragmalin derivatives **9a** and **9b**, giving Weinreb amides **10a** and **10b**. As expected, the 30-OH group in compounds **10a** and **10b** exhibited low reactivity in oxidation with Dess−Martin periodinane[9] that allowed selective oxidation of the 17-OH group, providing intermediates **11a** and **11b**. Lactone ring closure with the 30-OH group was successfully achieved by Lewis acid activation of the Weinreb amide.[10] Out of several Lewis acids investigated, TMSOTf gave the best yield of products **2** and **3**, novel analogues of natural libiguin A. Finally, acylation of the 2-OH group in **2** was achieved by TMSOTf-promoted acylation with isobutyric anhydride,[11] giving the target compound libiguin A (**12**). The NMR data for the semisynthetic product matched those of libiguin A isolated from natural sources.[2]

In summary, we have developed a short semisynthetic route to the limonoid libiguin A and to the new libiguin analogues **1**−**3** starting from phragmalin isolated from *C. tabularis* seeds. This was based on selective aminolysis of the lactone in phragmalin with MeONHMe and TMSOTf-promoted lactonization of the resulting Weinreb amide with the 30-OH group after oxidation or protection of the 17-OH group. Pharmacological studies to characterize the sexual stimulating activities of the novel libiguins are currently underway and will be reported in a future publication.

EXPERIMENTAL SECTION

Materials. *C. tabularis* seeds (30 kg) were obtained from a commercial tree plantation and were well-dried. Phragmalin was prepared from the seeds essentially as described previously.[7] The yield of phragmalin was 3.52 g/kg of seeds (dry weight).

NMR Spectroscopy. NMR spectra were recorded with a 600 MHz spectrometer equipped with a cryoprobe or a 400 MHz instrument in $CDCl_3$ solution at 25 °C. Chemical shifts are reported in parts per million relative to residual solvent signal [$\delta(^1H)$, 7.25 ppm; $\delta(^{13}C)$, 70.0 ppm]. Two-dimensional spectra recorded included DQF-COSY, NOESY, TOCSY, sensitivity-enhanced ^{13}C HSQC, and $^{13}C-^1H$ HMBC. Pulsed-field gradients were used for all of the ^{13}C correlation spectra. The NOESY mixing time was 800 ms, and the TOCSY one was 70 ms. ^{13}C HMBC spectra were recorded with the coupling evolution delay for the generation of multiple-bond correlations set to 62.5 ms. All of the 2D spectra were run with a data matrix of 4096 × 1024 points, giving $\tau_{2,max}$ = 250 ms for the ^1H nucleus in the acquisition dimension and $\tau_{1,max}$ = 100 ms for ^1H or $\tau_{1,max}$ = 50 ms for ^{13}C in the indirect dimension. Prior to Fourier transformation, the data matrix was zero-filled twice and multiplication by a shifted sine-bell window function was applied. For $^1H-^{13}C$ HMBC, the magnitude spectra were calculated.

dx.doi.org/10.1021/jo500318w | J. Org. Chem. 2014, 79, 4148−4153

HRMS. Exact molecular masses were determined on a hybrid quadrupole time-of-flight mass spectrometer equipped with an electrospray ion source.

Syntheses. *Compound 4.* To a suspension of MeNHOMe·HCl (351 mg, 3.600 mmol) in DCM (20 mL) at 0 °C was added dropwise a 2 M solution of Me_3Al in hexane (3.6 mL, 7.200 mmol). After the addition was complete, the reaction was stirred at room temperature (r.t.) for 20 min. Then at 0 °C a solution of phragmalin (200 mg, 0.360 mmol) in DCM (10 mL) was added, and the reaction mixture was stirred at room temperature for 30 min. At 0 °C an aqueous solution of Rochelle's salt (30 mL) was added, and the organic phase was separated. The aqueous phase was extracted with EtOAc (3 × 30 mL), and the combined organic phases were dried over Na_2SO_4. The solution was filtered and evaporated in vacuo. The residue was purified by flash chromatography on silica gel, eluting with EtOAc, to give compound **4** (153 mg, 68%) as a colorless oil and recovered phragmalin (43 mg, 22%).

^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 0.90 (1H, dt, J = 2.3 and 15.0 Hz); 0.98 (3H, s); 1.09 and 1.10 (total 6H, both s); 1.36 (1H, bt, J = 14.5 Hz); 1.54 (1H, d, J = 10.5 Hz); 1.55 (3H, s); 1.65 (1H, dd, J = 2.7 and 14.5 Hz); 1.81 (1H, d, J = 10.6 Hz); 1.83 (1H, d, J = 14.5 Hz); 2.22 (1H, dd, J = 3.9 and 16.0 Hz); 2.31 (1H, bt, J = 6.7 Hz); 2.38 (1H, dd, J = 9.4 and 16.0 Hz); 2.90−2.98 (3H, m); 3.08−3.20 (1H, bs); 3.16 (3H, s); 3.40−3.55 (1H, m); 3.56 (1H, s); 3.61 (3H, s); 3.66 (1H, dd, J = 1.2 and 11.0 Hz); 3.72 (3H, s); 4.26 (1H, bs); 4.74 (1H, s); 5.23 (1H, s); 6.48 (1H, d, J = 1.5 Hz); 7.32 (1H, t, J = 1.5 Hz); 7.48 ppm (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$, TMS) δ: 14.7; 15.8; 20.1; 21.1; 25.4; 29.4; 31.9; 32.2; 34.3; 35.8; 39.6; 40.0; 45.6; 45.8; 46.7; 51.9; 60.4; 69.5; 69.7; 78.9; 83.5; 84.4; 86.9; 88.5; 110.2; 118.6; 126.9; 140.5; 142.4; 173.2; 176.7 ppm. HRMS (ESI) $[M + H]^+$: calcd for $C_{31}H_{43}NO_{12}$ 622.2864, found 622.2856. $[\alpha]_D^{25}$ = −33.3 (c = 1.0, DCM).

Compound 5. To a solution of compound **4** (250 mg, 0.40 mmol) in DMF (6 mL) were added imidazole (408 mg, 6.00 mmol) and TESCl (675 μL, 4.00 mmol), and the mixture was stirred at r.t. overnight. Water (30 mL) was added to the reaction mixture, and the product was taken up into EtOAc (50 mL). The aqueous phase was separated, and the organic phase was washed with water (3 × 20 mL) and dried over Na_2SO_4. Solvent was evaporated in vacuo, and the residue was purified by flash chromatography on silica gel, eluting with a mixture of light petroleum ether and EtOAc (2:1), to give compound **5** (270 mg, 79%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 0.46−0.53 (6H, m); 0.69−0.80 (6H, m); 0.88 (9H, t, J = 8.0 Hz); 0.91 (3H, s); 1.02 (9H, t, J = 7.8 Hz); 1.05 (3H, s); 1.10−1.30 (1H, m); 1.16 (3H, s); 1.46−1.49 (1H, m); 1.48 (3H, s); 1.54−1.64 (2H, m); 1.74−1.79 (2H, m); 2.17 (1H, dd, J = 3.9 and 14.9 Hz); 2.31 (1H, d, J = 5.9 and 15.1 Hz); 2.35 (1H, d, J = 10.2 Hz); 2.68 (1H, d, J = 14.9 Hz); 2.75 (1H, s); 2.85 (1H, dd, J = 3.9 and 9.4 Hz); 3.14 (3H, s); 3.28 (1H, d, J = 9.8 Hz); 3.45 (1H, s); 3.54 (3H, s); 3.71 (3H, s); 3.79 (1H, bt, J = 13.1 Hz); 4.49 (1H, s); 5.18 (1H, s); 6.44 (1H, s); 7.32 (1H, s); 7.38 ppm (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$, TMS) δ: 5.0; 6.8; 15.2; 15.6; 19.9; 20.7; 25.4; 28.3; 31.3; 32.6; 34.6; 35.8; 39.1; 40.0; 45.5; 46.2; 46.7; 51.6; 61.1; 69.1; 70.0; 78.8; 84.0; 84.6; 86.8; 88.8; 110.6; 118.3; 126.8; 140.7; 141.8; 172.7; 177.2 ppm. HRMS (ESI) $[M + H]^+$: calcd for $C_{43}H_{71}NO_{12}Si_2$ 850.4593, found 850.4594. $[\alpha]_D^{25}$ = −21.2 (c = 1.0, DCM).

Compound 7. To a solution of compound **5** (34 mg, 0.04 mmol) in THF (4 mL) was added 10 M aq. KOH (20 μL, 0.20 mmol), and the reaction mixture was stirred at r.t. for 24 h. To this mixture was added 5% aqueous $KHSO_4$ (10 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated. The residue was dissolved in MeOH (2 mL), and DMAP (20 mg, 0.16 mmol) and EDCI (31 mg, 0.16 mmol) were added. The reaction mixture was stirred at r.t. for 6 h, and then aqueous 5% $KHSO_4$ (10 mL) was added. The mixture was extracted with EtOAc (2 × 10 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography on silica gel, eluting with a mixture of light petroleum ether and EtOAc (1:1), to give compound **7** (17 mg, 63%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 0.46−0.53 (6H, m); 0.88 (9H, t, J = 7.8 Hz); 1.01 (3H, s); 1.10−1.30 (1H, m); 1.13 (3H, s); 1.20 (3H, s); 1.64 (3H, s); 1.65 (1H, d, J = 11.0 Hz); 1.75−1.95 (4H, m); 1.99 (1H, dd, J = 3.1 and 9.0 Hz); 2.28 (1H, dd, J = 3.1 and 16.4 Hz); 2.35−2.40 (1H, m); 2.45 (1H, dd, J = 9.8 and 16.0 Hz); 2.72 (1H, s); 2.73−2.78 (2H, m); 3.25 (1H, dd, J = 3.1 and 18.8 Hz); 3.65 (1H, s); 3.70 (3H, s); 4.96 (1H, s); 5.39 (1H, s); 6.44 (1H, s); 7.36 (1H, s); 7.55 ppm (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$, TMS) δ: 4.8; 7.0; 14.8; 15.6; 21.0; 21.4; 23.9; 27.4; 29.5; 34.0; 36.0; 39.5; 39.9; 45.4; 45.7; 46.2; 51.8; 69.5; 74.6; 78.5; 81.0; 83.3; 84.6; 84.7; 110.6; 118.5; 124.7; 141.2; 142.5; 169.4; 173.1 ppm. HRMS (ESI) $[M + H]^+$: calcd for $C_{35}H_{50}O_{11}Si$ 675.3201, found 675.3193. $[\alpha]_D^{25}$ = −46.7 (c = 1.0, DCM).

Compound 8. To a solution of compound **7** (23 mg, 0.034 mmol) in DCM (2 mL) were added DMAP (17 mg, 0.016 mmol) and Ac_2O (65 μL, 0.68 mmol). The reaction mixture was stirred at r.t. for 4 h, and then 1 M aqueous $NaHCO_3$ (10 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL), and the organic phase was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography on silica gel, eluting with a mixture of light petroleum ether and EtOAc (1:1), to give compound **8** (22 mg, 92%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 0.45−0.61 (6H, m); 0.89 (9H, t, J = 8.0 Hz); 0.92 (3H, s); 1.10−1.30 (1H, m); 1.12 (3H, s); 1.21 (3H, s); 1.64 (3H, s); 1.65−1.90 (4H, m); 1.91 (1H, d, J = 11.0 Hz); 1.94 (1H, dd, J = 3.1 and 8.2 Hz); 2.19 (1H, d, J = 15.6 Hz); 2.22 (3H, s); 2.44 (1H, dd, J = 10.6 and 16.8 Hz); 2.78 (1H, dd, J = 8.2 and 18.0 Hz); 2.79 (1H, s); 2.85 (1H, dd, J = 2.3 and 10.6 Hz); 3.30 (1H, dd, J = 3.1 and 18.4 Hz); 3.67 (3H, s); 4.83 (1H, s); 4.91 (1H, s); 5.24 (1H, s); 6.44 (1H, s); 7.36 (1H, s); 7.46 ppm (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 5.0; 7.0; 14.7; 15.6; 21.0; 21.1; 21.5; 24.6; 27.6; 29.7; 30.1; 33.4; 36.7; 39.8; 44.4; 45.6; 45.8; 52.0; 70.6; 75.0; 77.4; 81.1; 83.5; 84.3; 84.7; 110.7; 118.5; 125.2; 141.2; 142.7; 169.1; 169.8; 172.8 ppm. HRMS (ESI) $[M + H]^+$: calcd for $C_{37}H_{52}O_{12}Si$ 717.3306, found 717.3305. $[\alpha]_D^{25}$ = −53.5 (c = 0.5, DCM).

Compound 1. A solution of compound **8** (8 mg, 0.011 mmol) in a mixture of DCM and TFA (2 mL, ratio 10:1) was stirred at r.t. for 18 h and then evaporated. The residue was purified by flash chromatography on silica gel, eluting with a mixture of light petroleum ether and EtOAc (2:1), to give compound **1** (6 mg, 78%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 0.94 (3H, s); 1.14 (3H, s); 1.28 (3H, s); 1.30−1.45 (2H, m); 1.64 (3H, s); 1.82 (1H, d, J = 11.0 Hz); 1.94 (1H, d, J = 11.0 Hz); 1.90−2.05 (2H, m); 2.08 (1H, dd, J = 1.2 and 9.0 Hz); 2.19 (3H, s); 2.28 (1H, dd, J = 2.8 and 16.4 Hz); 2.46 (1H, dd, J = 9.4 and 16.0 Hz); 2.76 (1H, s); 2.84 (1H, dd, J = 9.0 and 18.4 Hz); 2.90 (1H, dd, J = 2.7 and 9.8 Hz); 2.97 (1H, dd, J = 1.6 and 18.4 Hz); 3.71 (3H, s); 4.84 (1H, s); 5.28 (1H, s); 6.07 (1H, s); 6.43−6.46 (1H, m); 7.39 (1H, s); 7.70 ppm (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$, TMS) δ: 14.7; 15.6; 20.5; 21.1; 21.6; 23.7; 27.2; 31.2; 33.8; 37.3; 38.4; 39.7; 45.4; 45.6; 45.9; 52.0; 74.6; 75.0; 77.8; 79.3; 82.7; 83.8; 84.7; 108.8; 114.3; 118.9; 119.3; 142.1; 143.5; 156.5; 167.5; 170.2; 172.6 ppm. ^{19}F NMR (564 MHz, $CDCl_3$, $CFCl_3$) δ: −75.39 ppm. HRMS (ESI) $[M + H]^+$: calcd for $C_{33}H_{37}F_3O_{13}$ 699.2265, found 699.2277. $[\alpha]_D^{25}$ = −39.0 (c = 0.5, DCM).

Compound 9a. To a solution of phragmalin (200 mg, 0.356 mmol) in pyridine (6 mL) was added isobutyryl chloride (0.19 mL, 1.785 mmol). The reaction mixture was stirred at r.t. for 24 h, and then an additional portion of isobutyric anhydride (0.19 mL, 1.785 mmol) was added. The mixture was stirred for 16 h at room temperature, and then 10% aqueous $KHSO_4$ (20 mL) was added. The mixture was extracted with EtOAc (3 × 20 mL), and the combined organic phases were dried over Na_2SO_4. The extract was filtered and evaporated, and the residue was purified by flash chromatography on silica gel, eluting with a mixture of hexane and EtOAc (1:1), to give compound **9a** (208 mg, 93%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 0.94 (3H, s); 1.04 (3H, s); 1.15 (3H, s); 1.17−1.19 (1H, m); 1.20 (6H, dd, J = 2.3 and 7.0 Hz); 1.25−1.30 (1H, m); 1.62−1.65 (1H, m); 1.63 (3H, s); 1.74 (1H, d, J =

dx.doi.org/10.1021/jo500318w | J. Org. Chem. 2014, 79, 4148−4153

10.6 Hz); 1.93 (1H, d, J = 10.6 Hz); 1.97 (1H, dd, J = 1.6 and 10.2 Hz); 1.98−2.03 (1H, m); 2.26 (1H, dd, J = 2.7 and 16.4 Hz); 2.47 (1H, dd, J = 9.4 and 16.4 Hz); 2.59 (1H, septet, J = 7.0 Hz); 2.62 (1H, dd, J = 10.2, 19.2 Hz); 2.86 (1H, t, J = 3.5 Hz); 3.11 (1H, dd, J = 2.7 and 9.4 Hz); 3.19 (1H, d, J = 7.0 Hz); 3.41 (1H, dd, J = 1.6 and 19.2 Hz); 3.70 (3H, s); 4.58 (1H, d, J = 7.0 Hz); 4.69 (1H, s); 5.55 (1H, s); 6.48 (1H, d, J = 1.6 Hz); 7.42 (1H, t, J = 1.6 Hz); 7.51 ppm (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 14.3; 16.0; 18.5; 18.9; 19.9; 21.2; 25.2; 27.1; 29.1; 33.7; 34.4; 34.5; 37.2; 39.5; 42.2; 45.3; 45.6; 52.0; 69.1; 77.8; 78.4; 82.7; 84.1; 86.1; 86.8; 109.6; 119.0; 121.4; 140.2; 142.8; 171.1; 172.9; 175.9 ppm. HRMS (ESI) $[M + H]^+$: calcd for $C_{33}H_{42}O_{12}$ 631.2755, found 631.2763. $[\alpha]_D^{25}$ = −82.3 (c = 1.0, DCM).

Compound ***9b***. To a solution of phragmalin (100 mg, 0.180 mmol) in pyridine (3 mL) was added acetic anhydride (0.33 mL, 3.560 mmol), and the reaction mixture was stirred at r.t. for 48 h. Then 10% aqueous $KHSO_4$ (15 mL) was added, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over Na_2SO_4. The extract was filtered and evaporated, and the residue was purified by flash chromatography on silica gel, eluting with a mixture of hexane and EtOAc (1:1), to give compound **9b** (100 mg, 94%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, TMS): 0.94 (3H, s); 1.07 (3H, s); 1.14 (3H, s); 1.25−1.30 (1H, m); 1.55−1.63 (2H, m); 1.63 (3H, s); 1.73 (1H, d, J = 11.0 Hz); 1.92−2.04 (3H, m); 2.11 (3H, s); 2.26 (1H, dd, J = 3.1 and 16.4 Hz); 2.46 (1H, dd, J = 9.4 and 16.4 Hz); 2.63 (1H, dd, J = 10.2 and 19.2 Hz); 2.86 (1H, s); 3.09 (1H, dd, J = 2.7 and 9.4 Hz); 3.21 (1H, d, J = 7.5 Hz); 3.40 (1H, dd, J = 1.2 and 19.2 Hz); 3.71 (3H, s); 4.57 (1H, d, J = 7.0 Hz); 4.70 (1H, s); 5.54 (1H, s); 6.49 (1H, s); 7.42 (1H, t, J = 1.8 Hz); 7.52 ppm (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 14.5; 16.0; 19.9; 20.9; 21.2; 25.2; 27.2; 29.0; 33.8; 34.7; 36.9; 39.6; 42.2; 45.4; 45.5; 52.1; 69.2; 77.8; 78.2; 82.9; 84.0; 86.2; 86.7; 109.6; 119.1; 121.5; 140.3; 143.0; 170.2; 171.2; 172.8 ppm. HRMS (ESI) $[M + H]^+$: calcd for $C_{31}H_{38}O_{12}$ 603.2442, found 603.2443. $[\alpha]_D^{25}$ = −89.9 (c = 1.0, DCM).

Compound ***10a***. To a suspension of MeNHOMe·HCl (177 mg, 1.820 mmol) in DCM (10 mL) at 0 °C was added dropwise a 2 M solution of Me_3Al in hexane (1.82 mL, 3.647 mmol). After the addition was complete, the reaction mixture was stirred at r.t. for 20 min. The temperature of the reaction was adjusted to 0 °C, and a solution of compound **9a** (115 mg, 0.182 mmol) in DCM (5 mL) was added to the mixture. The resulting reaction mixture was stirred at room temperature for 30 min. At 0 °C, an aqueous solution of Rochelle's salt (20 mL) was added, and the organic phase was separated. The aqueous phase was extracted with EtOAc (3 × 20 mL), and the combined organic phases were dried over Na_2SO_4. The solution was filtered and evaporated in vacuo. The residue was purified by flash chromatography on silica gel, eluting with EtOAc, to give compound **10a** (49 mg, 39%) as a colorless oil and recovered starting material **9a** (32 mg, 28%).

^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 0.93 (3H, s); 1.09 (3H, s); 1.11 (3H, s); 1.25 (3H, d, J = 6.8 Hz), 1.27 (3H, d, J = 6.8 Hz); 1.44 (1H, bt, J = 14.9 Hz); 1.55−1.59 (1H, m); 1.56 (3H, s); 1.69−1.77 (2H, m); 1.83−1.90 (1H, m); 1.91 (1H, d, J = 10.6 Hz); 2.24 (1H, dd, J = 2.7 and 16.4 Hz); 2.40−2.47 (2H, m); 2.67 (1H, septet, J = 7.0 Hz); 2.85 (1H, bs); 2.86 (1H, s); 2.96 (1H, dd, J = 5.9 and 15.7 Hz); 3.07 (1H, dd, J = 2.3 and 10.2 Hz); 3.17 (3H, s); 3.38 (1H, d, J = 9.0 Hz); 3.48 (1H, bs); 3.66 (3H, s); 3.71 (3H, s); 4.58 (1H, d, J = 8.6 Hz); 4.72 (1H, s); 5.17 (1H, d, J = 3.1 Hz); 6.53 (1H, d, J = 1.6 Hz); 7.37 (1H, t, J = 1.6 Hz); 7.49 ppm (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 14.3; 15.9; 18.9; 19.0; 20.0; 20.8; 25.4; 29.0; 29.7; 32.2; 32.6; 34.0; 34.4; 37.2; 39.6; 40.0; 45.3; 45.5; 46.0; 51.9; 61.3; 70.0; 70.6; 78.1; 83.1; 84.0; 86.8; 88.4; 110.3; 118.6; 126.9; 140.0; 142.3; 172.7; 176.3 ppm. HRMS (ESI) $[M + H]^+$: calcd for $C_{35}H_{49}NO_{13}$ 692.3282, found 692.3287. $[\alpha]_D^{25}$ = −56.4 (c = 1.0, DCM).

Compound ***10b***. To a suspension of MeNHOMe·HCl (134 mg, 1.375 mmol) in DCM (15 mL) at 0 °C was added dropwise a 2 M solution of Me_3Al in hexane (1.40 mL, 2.750 mmol). After the addition was complete, the reaction mixture was stirred at r.t. for 20 min. Then at 0 °C a solution of compound **9b** (166 mg, 0.275 mmol) in DCM (6 mL) was added, and the reaction mixture was stirred at r.t. for 30 min. The temperature of the reaction was cooled to 0 °C, and an aqueous solution of Rochelle's salt (30 mL) was added. The organic phase was separated. The aqueous phase was extracted with EtOAc (3 × 30 mL), and the combined organic phases were dried over Na_2SO_4. The solution was filtered and evaporated in vacuo. The residue was purified by flash chromatography on silica gel, eluting with EtOAc, to give compound **10b** (81 mg, 45%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, TMS): 0.93 (3H, s); 1.10 and 1.11 (total 6H, both s); 1.40 (1H, bt, J = 14.9 Hz); 1.56 (3H, s); 1.60−1.73 (2H, m); 1.85 (1H, dt, J = 2.8 and 14.6 Hz); 1.90 (1H, d, J = 11.0 Hz); 2.16−2.26 (2H, m); 2.21 (3H, s); 2.37−2.46 (2H, m); 2.84−3.08 (4H, m); 3.18 (3H, s); 3.40−3.54 (2H, m); 3.66 (3H, s); 3.71 (3H, s); 4.54 (1H, d, J = 8.4 Hz); 4.72 (1H, s); 5.21 (1H, s); 6.53 (1H, d, J = 1.5 Hz); 7.37 (1H, t, J = 1.5 Hz); 7.48 ppm (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 14.4; 15.8; 20.0; 20.9; 21.2; 25.4; 29.0; 29.1; 29.7; 32.1; 34.0; 36.8; 39.6; 40.0; 45.3; 45.4; 45.9; 51.9; 61.4; 69.9; 70.1; 78.1; 83.4; 84.0; 86.8; 88.3; 110.2; 118.7; 127.1; 140.0; 142.6; 170.4; 172.6 ppm. HRMS (ESI) $[M + H]^+$: calcd for $C_{33}H_{45}NO_{13}$ 664.2969, found 664.2968. $[\alpha]_D^{25}$ = −67.6 (c = 1.0, DCM).

Compound ***11a***. To a solution of compound **10a** (44 mg, 0.063 mmol) in DCM (6 mL) was added a 0.39 M solution of Dess−Martin periodinane in DCM (0.50 mL, 0.190 mmol). The reaction mixture was stirred at r.t. for 40 min and diluted with 10% $Na_2S_2O_4$ (15 mL). The product was extracted with EtOAc (3 × 15 mL), and the combined organic phases were dried over Na_2SO_4. The extract was filtered and evaporated, and the residue was purified by flash chromatography on silica gel, eluting with a mixture of hexane and EtOAc (1:1 then 0:1), to give compound **11a** (39 mg, 90%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 0.86 (3H, s); 1.12 (3H, s); 1.20 (6H, d, J = 7.0 Hz); 1.51 (3H, s); 1.55 (3H, s); 1.71 (1H, d, J = 11.0 Hz); 1.83−1.98 (4H, m); 2.20−2.27 (2H, m); 2.36−2.45 (2H, m); 2.61 (1H, septet, J = 7.0 Hz); 2.74 (1H, t, J = 4.7 Hz); 2.87 (1H, dd, J = 3.1 and 9.4 Hz); 3.03−3.12 (1H, m); 3.14 (3H, s); 3.57 (3H, s); 3.65 (3H, s); 3.70 (1H, bs); 4.11 (1H, bs); 4.35 (1H, d, J = 5.1 Hz); 4.69 (1H, s); 6.76 (1H, d, J = 2.0 Hz); 7.42 (1H, t, J = 1.6 Hz); 8.0 ppm (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 14.6; 15.9; 18.6; 18.8; 20.7; 24.8; 25.5; 28.3; 31.3; 32.4; 34.2; 34.4; 36.8; 39.6; 44.4; 45.2; 45.7; 50.4; 51.7; 61.2; 68.7; 78.1; 83.7; 84.2; 86.2; 87.6; 110.6; 118.7; 125.9; 143.1; 146.9; 171.1; 172.8; 175.9; 200.7 ppm. HRMS (ESI) $[M + H]^+$: calcd for $C_{35}H_{47}NO_{13}$ 690.3126, found 690.3135. $[\alpha]_D^{25}$ = −30.5 (c = 1.0, DCM).

Compound ***11b***. To a solution of compound **10b** (70 mg, 0.105 mmol) in DCM (10 mL) was added a 0.39 M solution of Dess−Martin periodinane in DCM (0.81 mL, 0.315 mmol). The reaction mixture was stirred at r.t. for 40 min and diluted with 10% $Na_2S_2O_4$ (20 mL). The product was extracted with EtOAc (3 × 15 mL), and the combined organic phases were dried over Na_2SO_4. The extract was filtered and evaporated, and the residue was purified by flash chromatography on silica gel, eluting with a mixture of hexane and EtOAc (1:1 then 0:1), to give compound **11b** (49 mg, 71%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 0.92 (3H, s); 1.14 (3H, s); 1.52 (3H, s); 1.53−1.60 (1H, m); 1.55 (3H, s); 1.67−1.76 (2H, m); 1.85−2.02 (3H, m); 2.17 (3H, s); 2.28 (1H, dd, J = 3.5 and 16.0 Hz); 2.32−2.54 (3H, m); 2.69 (1H, bt, J = 4.3 Hz); 2.94 (1H, s); 2.95 (1H, dd, J = 3.5 and 9.4 Hz); 3.13 (3H, s); 3.61 (3H, s); 3.62 (3H, s); 3.70−3.77 (1H, m); 4.43 (1H, d, J = 6.7 Hz); 4.66 (1H, s); 6.80 (1H, d, J = 2.0 Hz); 7.42 (1H, t, J = 1.2 Hz); 8.00 ppm (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 14.7; 15.8; 20.8; 20.9; 24.8; 25.4; 28.1; 29.7; 30.7; 32.4; 36.6; 39.7; 44.8; 45.1; 45.6; 50.2; 51.7; 61.2; 68.5; 78.2; 83.8; 84.2; 86.4; 87.7; 110.8; 118.7; 126.7; 143.0; 146.3; 170.6; 172.8; 175.2; 200.4 ppm. HRMS (ESI) $[M + H]^+$: calcd for $C_{33}H_{43}NO_{13}$ 662.2813, found 662.2808. $[\alpha]_D^{25}$ = −35.5 (c = 1.0, DCM).

Compound ***2***. To a solution of compound **11a** (24 mg, 0.035 mmol) in DCM (3.5 mL) were added 4 Å molecular sieves and TMSOTf (32 μL, 0.175 mmol). The mixture was stirred at r.t. for 0.5

dx.doi.org/10.1021/jo500318w | J. Org. Chem. 2014, 79, 4148−4153

h and diluted with saturated aqueous $NaHCO_3$ (10 mL). The product was extracted with EtOAc (3 × 10 mL), and the combined organic phases were dried over Na_2SO_4. The extract was filtered and evaporated, and the residue was purified by flash chromatography on silica gel, eluting with EtOAc, to give compound **2** (16 mg, 74%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 0.90 (3H, s); 1.11 (3H, s); 1.13−1.28 (1H, m); 1.38 (6H, d, J = 7.0 Hz); 1.48 (3H, s); 1.67 (3H, s); 1.73−1.85 (2H, m); 1.94 (1H, d, J = 11.0 Hz); 1.96 (1H, dd, J = 3.9 and 9.0 Hz); 2.11 (1H, dd, J = 2.7 and 15.7 Hz); 2.17−2.24 (2H, m); 2.31 (1H, dd, J = 9.8 and 15.7 Hz); 2.60 (1H, dd, J = 3.1 and 9.8 Hz); 2.69−2.81 (3H, m); 2.91 (1H, s); 3.52 (3H, s); 4.82 (1H, s); 5.38 (1H, s); 6.79 (1H, d, J = 1.2 Hz); 7.43 (1H, t, J = 1.6 Hz); 8.1 ppm (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 14.7; 15.6; 18.7; 18.8; 21.5; 24.9; 25.0; 28.1; 31.8; 33.9; 34.7; 37.1; 40.0; 45.3; 46.1; 49.1; 51.5; 51.6; 75.1; 77.9; 79.9; 83.1; 84.1; 84.3; 110.0; 119.0; 124.4; 143.5; 147.0; 168.7; 172.4; 175.9; 199.1 ppm. HRMS (ESI) $[M + H]^+$: calcd for $C_{33}H_{40}O_{12}$ 629.2598, found 629.2593. $[\alpha]_D^{25}$ = −44.1 (c = 1.0, DCM).

Compound ***3***. To a solution of compound **11b** (35 mg, 0.053 mmol) in DCM (5.3 mL) were added 4 Å molecular sieves and TMSOTf (48 μL, 0.265 mmol). The mixture was stirred at r.t. for 0.5 h and diluted with saturated aqueous $NaHCO_3$ (10 mL). The product was extracted with EtOAc (3 × 10 mL), and the combined organic phases were dried over Na_2SO_4. The extract was filtered and evaporated, and the residue was purified by flash chromatography on silica gel, eluting with EtOAc, to give compound **3** (24 mg, 77%) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$, TMS) δ: 0.91 (3H, s); 1.11 (3H, s); 1.49 (3H, s); 1.20−1.40 (1H, m); 1.67 (3H, s); 1.78−1.85 (2H, m); 1.93 (1H, d, J = 11.0 Hz); 1.96 (1H, dd, J = 3.9 and 8.6 Hz); 2.11 (1H, dd, J = 3.1 and 16.0 Hz); 2.15−2.22 (2H, m); 2.29 (3H, s); 2.31−2.36 (1H, m); 2.61 (1H, dd, J = 3.5 and 9.8 Hz); 2.73 (1H, dd, J = 3.1 and 17.6 Hz); 2.79 (1H, dd, J = 8.2 and 17.6 Hz); 2.89 (1H, s); 3.54 (3H, s); 4.82 (1H, s); 5.41 (1H, s); 6.81 (1H, s); 7.43 (1H, s); 8.08 ppm (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$, TMS) δ: 14.7; 15.4; 20.8; 21.3; 24.8; 24.9; 28.0; 31.6; 33.7; 36.5; 39.9; 44.9; 45.9; 48.9; 51.4; 51.5; 74.9; 77.7; 79.8; 83.1; 84.0; 84.4; 109.8; 118.9; 124.3; 143.3; 146.8; 168.8; 170.3; 172.2; 199.0 ppm. HRMS (ESI) $[M + H]^+$: calcd for $C_{31}H_{36}O_{12}$ 601.2285, found 601.2289. $[\alpha]_D^{25}$ = −68.8 (c = 1.0, DCM).

Compound ***12*** *(Libiguin A)*. Compound **2** (8 mg, 0.0127 mmol) was dissolved in DCM (3 mL), and isobutyric anhydride (21 μL, 0.127 mmol) and TMSOTf (2.3 μL, 0.0127 mmol) were added. The mixture was stirred at r.t. for 0.5 h and then diluted with saturated aqueous $NaHCO_3$ (5 mL). The product was extracted with EtOAc (3 × 5 mL), and the combined organic phases were dried over Na_2SO_4. The extract was filtered and evaporated, and the residue was purified by flash chromatography on silica gel, eluting with a mixture of hexane and EtOAc (1:1 then 0:1), to give compound **12** (8 mg, 94%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ: 0.9 (3H, s), 1.10 (3H, s), 1.16 (3H, d, J = 6.9 Hz), 1.19 (3H, d, J = 6.9 Hz), 1.37 (3H, d, J = 7.4 Hz), 1.38 (3H, d, J = 7.4 Hz), 1.39 (1H, m), 1.48 (3H, s), 1.62 (3H, s), 1.80 (1H, d, J = 11.1 Hz), 1.83 (1H, m), 1.96 (1H, dd, J = 1.7 and 8.1 Hz), 2.00 (1H, d, J = 11.1 Hz), 2.08 (1H, dd, J = 9.8 and 15.5), 2.11 (1H, m), 2.17 (1H, m), 2.32 (1H, dd, J = 2.4 and 15.5 Hz), 2.54 (1H, dd, J = 2.4 and 9.8 Hz), 2.59 (1H, septet, J = 6.9 Hz), 2.71 (1H, m), 2.73 (1H, m), 2.78 (1H, septet, J = 7.4 Hz), 3.51 (3H, s), 5.37 (1H, s), 5.87 (1H, s), 6.79 (1H, dd, J = 1.9 and 0.8 Hz), 7.41 (1H, dd, J = 1.9 and 1.4 Hz), 8.06 ppm (1H, dd, J = 1.4 and 0.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 15.0; 16.0; 18.5; 18.6; 18.9; 19.0; 21.3; 24.5; 25.0; 28.4; 31.4; 33.6; 34.8; 35.1; 35.9; 40.8; 46.2; 46.6; 49.1; 51.6; 51.7; 74.8; 79.7; 80.4; 83.3; 83.7; 84.4; 110.1; 118.6; 124.6; 143.4; 147.1; 169.0; 172.3; 175.3; 175.8; 199.0 ppm. HRMS (ESI) $[M + H]^+$: calcd for $C_{37}H_{46}O_{13}$ 699.3017, found 699.3009. $[\alpha]_D^{25}$ = −46.8 (c = 1.0, DCM).

■ ASSOCIATED CONTENT

Supporting Information

2D NMR (NOESY and HMBC) correlation data for compounds **4**, **5**, **7**, **1**, **3**, and **12** and NMR spectra for compounds **1**−**5** and **7**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): J.E.S.W. holds shares in Dicotyledon AB, a Swedish limited company.

■ ACKNOWLEDGMENTS

Monetary support was obtained from the Swedish VR (K2012-62X-22053-01-3), Uppsala Bio (Bio-X 2009 Award), and TWAS (Research Grant Agreement 09-177 RG/CHE/AF/AC_G−UNESCO FR: 3240230332).

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