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Synthesis of Artemisinins with Substituted Sulfidyl or Sulfonyl Moiety and Their Anti-angiogenesis Activity

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The functions of vein endothelial cells such as proliferation, differentiation, migration, and tube formation are the most important processes of angiogenesis, the formation of new vascular capillaries from pre-existing blood vessels stimulated by various endogenous activators.[1] In normal biological conditions, angiogenesis is tightly regulated by the balance between activators and inhibitors, except in the process of wound healing[2] and embryonic development.[3] On the other hand, angiogenesis also plays an important role in the course of abnormal conditions including tumor growth,[4] diabetic retinopathy,[5] and rheumatoid arthritis.[6] In particular, tumor angiogenesis plays a critical role in the growth, invasion, and metastasis of tumors.[7,8] Therefore, the regulation of angiogenesis may be a potential therapeutic strategy for tumors and other related diseases. In our search for novel angiogenesis inhibitors, we discovered that 10-phenylsulfidyl or 10-phenylsulfonyl artemisinin (**1**) derived from artemisinin (**2**) exhibits strong ability of inhibition of human umbilical vein endothelial cell (HUVEC) proliferation, suppress the tube formation of HUVEC on Matrigel induced by the growth factor, and Chorioallantoic membrane (CAM) differentiation. Hence, such a suppressive activities suggest that sulfur attached artemisinin derivatives (**1**) may serve as anticancer agents by inhibiting the tumor angiogenesis.[9,10]

Artemisinin (**2**), a natural endoperoxide sesquiterpene isolated from *Artemisia annua L.*[11] and its synthetic derivatives are popular antimalarial agents[12,13] and are recently

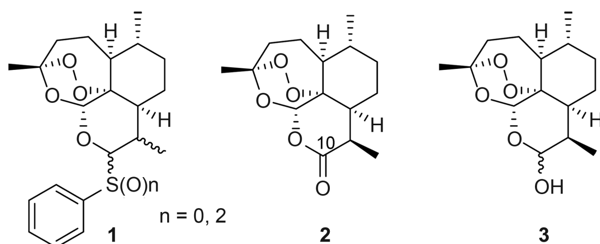


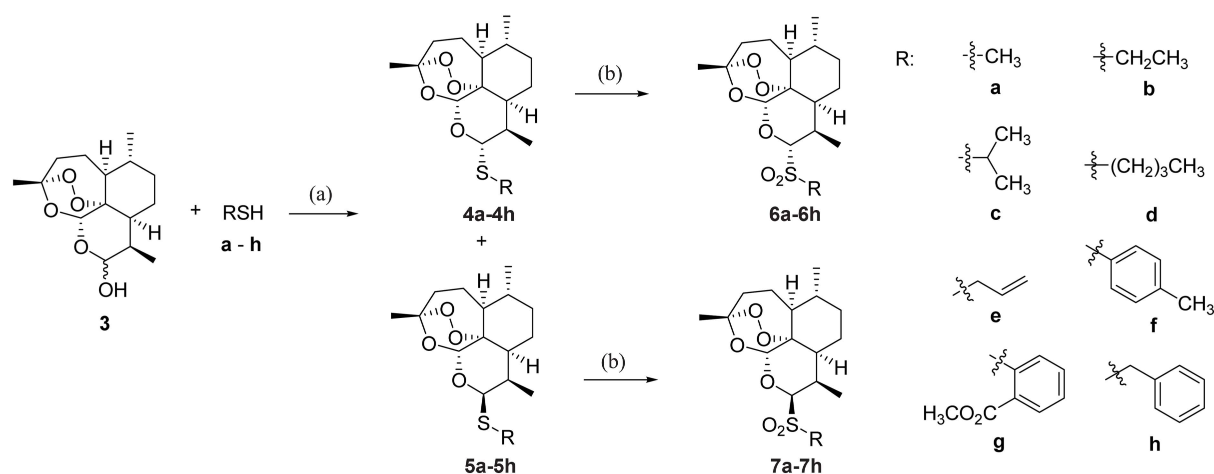
Figure 1.

[a]These authors are equally contributed on this work.

being considered as potential lead compounds in the discovery of drug for various human diseases.[14] Although Chen *et al.* had previously reported that artemisinin (**2**), dihydroartemisinin (**3**), and artesunate have a weak anti-angiogenesis effect; we were the first to discover that the addition of substituted sulfide or sulfone functionality to the C-10 position of **2** enhances the inhibitory effect of **2** against angiogenesis.[9,10] Based on our preliminary results, we decided to construct a novel series of anti-angiogenesis agents for a potential anticancer drug using an acid-catalyzed substitution reaction of **3** with various thiols as a key reaction.

As shown in Scheme 1, C-10 substituted sulfide artemisinin derivatives were obtained from the reaction of known **3**[15] with various thiols (2eq) under the catalysis of BF_3Et_2O (1eq) at room temperature for 10 mins.[16,10] Excessive reaction time, over 10 mins, produced a desoxoartemisinin deficient with peroxide moiety because the thiol reactant acted as a reductant. Because the C-10 position of **3** is similar to the anomeric center of a carbohydrate, the thioacetalization of **3** and various thiol compounds (**a-h**) afforded a major α-anomer (**4**) and minor β-anomer (**5**). The ratios and yields are shown in Scheme 1. The stereochemistry of all synthesized thioacetal products, **4** and **5** was determined using a coupling constant between H-9 and H-10 in the ^{1}H-NMR spectra of the products.[17] For example, α-anomer **4f** showed a large coupling constant (J = 10.8 Hz) because of *trans* coupling, while β-anomer **5f** showed a small value (J = 5.2 Hz). The ratio of each of the diastereomers is shown in Scheme 1. For discovering better anti-angiogenic molecules, we constructed a library of alkyl (**a**, **b**, **c**, and **d**), allyl (**e**), substituted phenyl (**f** and **g**), and benzyl (**h**) functionalities. Based on our previous report that some substituted sulfonyl artemisinin derivatives exhibited a strong anti-angiogenesis effect, we performed oxidation of the obtained substituted sulfidyl artemisinin derivatives (**4a-4h** and **5a-5h**) using H_2O_2/Urea (UHP), trifluoroacetic anhydride (TFAA), and $NaHCO_3$ to produce various 10α-substituted sulfonyl artemisinin derivatives (**6a-6h**) and 10β-sulfonyl artemisinins (**7a-7h**), respectively.[18,19]

To identify novel anti-angiogenesis agents from the syn-



Scheme 1. Reagents and conditions: (a) RSH (2eq), BF_3Et_2O (1eq), CH_2Cl_2, rt, 10 min; Yields: **4a** (41%), **5a** (32%), **4b** (85%), **5b** (11%), **4c** (80%), **5c** (5%), **4d** (74%), **5d** (10%), **4e** (70%), **5e** (11%), **4f** (%), **5f** (%), **4g** (%), **5g** (%), **4h** (82%), and **5h** (8%), (b) UHP (2.6eq), TFAA (2.6eq), $NaHCO_3$ (4.35eq), CH_3CN, −40 °C; Yields: **6a** (78%), **6b** (84%), **6c** (83%), **6d** (95%), **6e** (96%), **6f** (91%), **6h** (82%), **7a** (70%), **7b** (86%), **7c** (80%), **7d** (91%), **7e** (90%), **7f** (87%), and **7h** (80%).

thetic sulfidyl and sulfonyl artemisinin library (**4a-4h**, **5a-5h**, **6a-6h**, and **7a-7h**), we examined a HUVEC proliferation inhibitory activity assay[20] using MTT colorimetric method[21] for use as an angiogenesis inhibitor. The examination results are summarized in Table 1. The inhibitory effect of 10α- (**4**) or 10β- (**5**) substituted sulfidyl artemisinin was similar, indicating that the stereochemistry of the C-10 position of artemisinin is not important for growth inhibition. However, the growth inhibition effect of the substituted sulfidyl artemisinin was closely related to the functional group attached to the C-10 position of artemisinin. For example,

Table 1. Growth inhibitory activity against the HUVEC proliferation and tube formation

Compounds No.		Growth inhibition against HUVEC (IC_{50}, μM)[a]	Compounds No.		Growth inhibition against HUVEC (IC_{50}, μM)[a]
4	**a**	> 50	6	**a**	5.0
	b	23.1		**b**	11.5
	c	1.4		**c**	2.1
	d	> 50		**d**	> 50
	e	1.6		**e**	5.8
	f	2.5		**f**	1.1
	g	1.3		**g**	-[b]
	h	2.8		**h**	5.7
5	**a**	> 50	7	**a**	> 50
	b	9.4		**b**	> 50
	c	2.5		**c**	> 50
	d	15.8		**d**	> 50
	e	8.5		**e**	> 50
	f	0.9		**f**	4.2
	g	1.8		**g**	-[b]
	h	0.9		**h**	4.5

[a] IC_{50} values were calculated by nonlinear regression analysis using the GraphPad Prism software. ($R^2 > 0.95$). [b] Product was not obtained.

compounds **4a** (methylsulfidyl), **4b** (ethylsulfidyl), and **4d** (*n*-butylsulfidyl) almost did not inhibit the growth of the HUVEC. However, interestingly **4c** (isopropylsulfidyl) exhibited a strong inhibition effect although it had an alkyl substituent. In contrast to the alkyl groups, the growth inhibition effect of artemisinin derivatives started to improve with the addition of the allyl group. Thus, **4e** and **5e** showed stronger inhibitory activity against HUVEC proliferation than methyl-, ethyl-, and *n*-butylsulfidyl derivatives (IC_{50}, 1.6 μM for **4e** and 8.5 μM for **5e**), indicating that the increased hydrophobic property of the substituent might improve the inhibitory effect on HUVEC proliferation. This postulation was confirmed by the fact that the derivatives having aromatic substituents (**f**, **g**, and **h**) showed strong inhibitory activity against HUVEC proliferation in our synthetic artemisinin library. For example, the IC_{50} for both **5f** and **5g** is 0.9 μM. Between the substituted sulfidyl artemisinin and sulfonyl artemisinin, the former showed stronger inhibitory activity against the HUVEC proliferation by the growth factor although 10α-toluenesulfonyl artemisinin (**6f**) strongly inhibited the HUVEC growth (IC_{50} = 1.1 μM). Based on the structure-activity relationship, the aromatic group substituted sulfidyl artemisinin derivatives such as **4f-4h** and **5f-5h** can be efficient inhibitors of the HUVEC proliferation.

In order to confirm the anti-angiogenic property of synthetic artemisinins possessing substituted sulfidyl and sulfonyl groups, the tube formation assay was conducted on Matriegel[22] at the concentration of 10 μM. Among the tested compounds, 10α-toluenesulfonyl artemisinin (**6f**) strongly inhibited HUVEC tube formation. Compounds **5h** and **7c** showed a moderate inhibitory effect on the tube formation. Interestingly, **7c** showed no inhibition activity on HUVEC proliferation, but inhibited the tube formation. Meanwhile, strong inhibitors of the HUVEC proliferation such as **4e-4f**, **5f**, and **5g** did not inhibit the HUVEC tube formation. Only

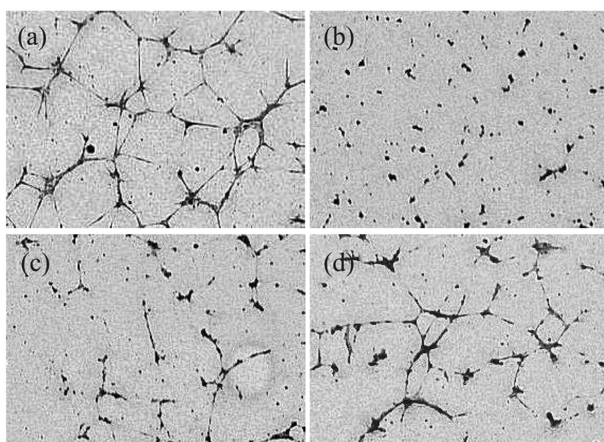


Figure 2. Inhibitory effect of selected artemisinin derivatives having substituted sulfidyl- or sulfonyl groups on tube formation by human umbilical vein endothelial cells (HUVEC) on Matrigel at the concentration of 10 μM. (a) Control, (b) compound **6f**, inhibition percentage: 93%, (c) compound **5h**, inhibition percentage: 43%, and (d) compound **7c**, inhibition percentage: 22%.

6f inhibited the proliferation and tube formation of the HUVEC simultaneously.

In conclusion, we have constructed a library consisting of new series of substituted sulfidyl- and sulfonylartemisinin derivative (**4a-4h**, **5a-5h**, **6a-6h**, and **7a-7h**) from the acid catalyzed substitution reaction of dihydroartemisinin (**2**) and various thiols (**a-h**); the inhibitory activities of these derivatives against the HUVEC proliferation and tube formation on Matrigel were examined. Among the tested compounds, **4c**, **4e-4h**, **5c**, **5g-5h**, and **6f** showed strong inhibitory activity against the HUVEC growth, and **6f**, **5h**, and **7c** efficiently inhibited the HUVEC tube formation on Matrigel. **6f** is a particularly promising candidate for anticancer drug development as it inhibited the growth and tube formation of HUVEC simultaneously.

Experimental Section

Typical Procedure for the Synthesis of 10α-Ethylsulfidylartemisinin (4b) and 10β-Ethylsulfidylartemisinin (5b): Ethanethiol (0.62 g, 10 mmol) and BF_3Et_2O (705 mg, 5 mmol) were added to a stirred solution of **2** (1.42 g, 5 mmol) in CH_2Cl_2 (50 mL) at room temperature. The solution was stirred for 10 min, after which it was diluted with CH_2Cl_2 (100 mL), washed with sat-$NaHCO_3$ and brine. The organic layer was separated, dried with $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by flash chromatography (hexane:EtOAc = 15:1) to afford 1.38 g (85%) of **4b** and 180 mg (11%) of **5b**.

4a: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.32 (s, 1H), 4.46 (d, *J* = 10.8 Hz, 1H), 2.60 (m, 1H), 2.37 (m, 1H), 2.14 (s, 3H), 2.02 (m, 1H), 1.87 (m, 1H), 1.72 (m, 2H), 1.42 (s, 3H), 0.95 (d, *J* = 6.2 Hz, 3H), 0.92 (d, *J* = 7.3 Hz, 3H) ppm; **5a**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.60 (s, 1H), 5.19 (d, *J* = 5.3 Hz, 1H), 3.05 (m, 1H), 2.37 (m, 1H), 2.21 (s, 3H), 2.04 (m, 1H), 1.88 (m, 2H), 1.69 (m, 2H), 1.44 (s, 3H), 0.97 (d, *J* = 7.3 Hz, 3H), 0.94 (d, *J* = 6.2 Hz, 3H) ppm; **4b**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.28 (s, 1H), 4.55 (d, *J* = 10.8 Hz, 1H), 2.72 (m, 3H), 2.37 (m, 1H), 2.01 (m, 1H), 1.87 (m, 1H), 1.73 (m, 2H), 1.42 (s, 3H), 1.30 (t, *J* = 7.3 Hz, 3H), 0.95 (d, *J* = 6.1 Hz, 3H), 0.92 (d, *J* = 7.3 Hz, 3H) ppm; **5b**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.62 (s, 1H), 5.30 (d, *J* = 5.3 Hz, 1H), 3.04 (m, 1H), 2.70 (q, *J* = 7.3 Hz, 2H), 2.37 (m, 1H), 2.04 (m, 1H), 1.87 (m, 1H), 1.69 (m, 2H), 1.43 (s, 3H), 1.28 (t, *J* = 7.5 Hz, 3H), 0.96 (d, *J* = 1.3 Hz, 3H), 0.94 (d, *J* = 2.4 Hz, 3H) ppm; **4c**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.26 (s, 1H), 4.62 (d, *J* = 10.8 Hz, 3H), 3.30 (m, 1H), 2.61 (m, 1H), 2.37 (m, 1H), 2.01 (m, 1H), 1.87 (m, 1H), 1.71 (m, 2H), 1.56 (m, 1H), 1.41 (s, 3H), 1.36 (d, *J* = 6.6 Hz, 3H), 1.28 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 6.1 Hz, 3H), 0.91 (d, *J* = 7.1 Hz, 3H) ppm; **5c**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.63 (s, 1H), 5.34 (d, *J* = 4.95 Hz, 1H), 3.22 (m, 1H), 3.05 (m, 1H), 2.56 (m, 2H), 1.42 (s, 1H), 1.30 (t, *J* = 6.6 Hz, 3H), 0.94 (6H) ppm; **4d**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.28 (s, 1H), 4.52 (d, *J* = 10.6 Hz, 1H), 2.70 (m, 3H), 2.39 (m, 1H), 2.00 (m, 1H), 1.87 (m, 1H), 1.43 (s, 3H), 0.91 (m, 9H) ppm; **5d**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.62 (s, 1H), 5.27 (d, *J* = 5.5 Hz, 1H), 3.04 (m, 1H), 2.67 (m, 3H), 2.37 (m, 1H), 1.44 (s, 3H), 0.93 (m, 9H) ppm; **4e**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.88 (m, 1H), 5.25 (s, 1H), 5.16 (m, 1H), 5.08 (m, 1H), 4.52 (d, *J* = 10.8 Hz, 1H), 3.46 (dd, *J* = 8.1, 13.6 Hz, 1H), 3.27 (dd, *J* = 5.3, 13.6 Hz, 1H), 3.13 (d, *J* = 7.1 Hz, 1H), 2.88 (m, 1H), 2.75 (m, 1H), 2.59 (m, 2H), 2.37 (m, 1H), 1.41 (s, 3H), 0.95 (d, *J* = 6.2 Hz, 3H), 0.91 (d, *J* = 7.1 Hz, 3H) ppm; **5e**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.81 (m, 1H), 5.61 (s, 1H), 5.16 (m, 3H), 3.30 (m, 2H), 3.04 (m, 1H), 2.36 (m, 1H), 2.05 (m, 1H), 1.87 (m, 1H), 1.69 (m, 2H), 1.43 (s, 3H), 1.26 (m, 1H), 0.95 (d, *J* = 6.2 Hz, 3H), 0.91 (d, *J* = 7.3 Hz, 3H) ppm; **4f**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.6 Hz, 2H), 7.10 (d, *J* = 7.6 Hz, 2H), 5.32 (s, 1H), 4.66 (d, *J* = 10.8 Hz, 1H), 2.52 (m, 1H), 2.37 (m, 1H), 2.32 (s, 1H), 2.01 (m, 1H), 1.86 (m, 1H), 1.70 (m, 2H), 1.50 (m, 2H), 1.47 (s, 3H), 1.37 (m, 2H), 1.22 (m, 1H), 1.01 (m, 1H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 7.2 Hz, 3H) ppm; **5f**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 5.74 (s, 1H), 5.48 (d, *J* = 5.2 Hz, 1H), 3.09 (m, 1H), 2.37 (m, 1H), 2.31 (s, 3H), 2.05 (m, 1H), 1.90 (m, 1H), 1.76 (m, 3H), 1.57 (m, 1H), 1.43 (s, 3H), 1.28 (m, 1H), 1.05 (d, *J* = 7.2 Hz, 3H), 0.98 (d, *J* = 6.4 Hz, 3H) ppm; **4g**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.2 Hz, 1H), 5.39 (s, 1H), 4.87 (d, *J* = 10.8 Hz, 1H), 3.90 (s, 3H), 2.78 (m, 1H), 2.38 (m, 1H), 2.02 (m, 1H), 1.90 (m, 1H), 1.74 (m, 2H), 1.63 (m, 1H), 1.55 (s, 3H), 1.50 (m, 1H), 1.47 (s, 3H), 1.39 (m, 1H), 1.28 (m, 1H), 1.05 (m, 1H), 0.97 (d, *J* = 6.0 Hz, 3H), 0.91 (d, *J* = 7.2 Hz, 3H) ppm; **5g**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 5.74 (d, *J* = 10.4 Hz, 1H), 5.55 (s, 1H), 2.36 (m, 1H), 2.07 (m, 1H), 1.98 (m, 2H), 1.72 (m, 2H), 1.64 (m, 1H), 1.54 (s, 3H), 1.53 (s, 3H), 1.45 (m, 3H), 1.31 (m, 2H), 1.25 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.0 Hz, 3H) ppm; **4h**; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 5H), 5.25 (s, 1H), 4.41 (d, *J* = 10.8 Hz, 1H), 4.00 (d, *J* = 13.2 Hz, 1H),

3.87 (d, J = 13.2 Hz, 1H), 2.61 (m, 1H), 2.38 (m, 1H), 2.03 (m, 1H), 1.88 (m, 1H), 1.46 (s, 3H), 0.94 (d, J = 5.9 Hz, 3H), 0.82 (d, J = 7.1 Hz, 3H) ppm; **5h**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 5H), 5.66 (s, 1H), 5.20 (d, J = 5.3 Hz, 1H), 3.87 (s, 2H), 2.99 (m, 1H), 2.37 (m, 1H), 2.05 (m, 1H), 1.46 (s, 3H), 1.26 (m, 1H), 0.95 (d, J = 6.2 Hz, 3H), 0.83 (d, J = 7.3 Hz, 3H) ppm.

Typical Procedure for the Synthesis of 10α-Ethylsulfonylartemisinin (6b). Trifluoroacetic anhydride (1.13 mL, 7.97 mmol) was added to a stirred suspension of urea hydrogen peroxide (750 mg, 7.97 mmol) in acetonitrile (50 mL) for 10 min at room temperature. The solution was added dropwise to a stirred suspension of **4b** (1 g, 3.05 mmol) and $NaHCO_3$ (1.11 g, 13.3 mmol) in acetonitrile (50 mL) at −40 °C for 10 min. The suspension was stirred for 20 min, after which the solution was quenched with water (100 mL), extracted with EtOAc (3 × 50 mL) and washed with brine (50 mL). The organic layer was separated, dried with $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by flash chromatography (hexane:EtOAc = 5:1) to afford the desired product **6b** (922 mg, 84%).

6a; ^{1}H-NMR (300 MHz; $CDCl_3$) δ 5.39 (s, 1H), 4.36 (d, J = 11.0 Hz, 1H), 2.97 (s, 3H), 2.85 (m, 1H), 2.38 (td, J = 13.7, 3.8 Hz, 1H), 1.40 (s, 3H), 1.14 (d, J = 7.1 Hz, 3H), 0.97 (d, J = 5.9 Hz, 3H) ppm; **6b**; ^{1}H-NMR (300 MHz; $CDCl_3$) δ 5.36 (s, 1H), 4.41 (d, J = 11.0 Hz, 1H), 3.24 (m, 1H), 3.11 (m, 1H), 2.91 (m, 1H), 2.38 (td, J = 13.9, 4.0 Hz, 1H), 1.43 (t, J = 7.3 Hz, 3H), 1.40 (s, 3H), 1.13 (d, J = 7.1 Hz, 3H), 0.97 (d, J = 5.9 Hz, 3H) ppm; **6c**; ^{1}H-NMR (300 MHz; $CDCl_3$) δ 5.32 (s, 1H), 4.50 (d, J = 10.6 Hz, 1H), 3.59 (m, J = 7.0 Hz, 1H), 2.97 (m, 1H), 2.38 (td, J = 13.7, 3.8 Hz, 1H), 1.42 (d, J = 4.2 Hz, 1H), 1.40 (s, 3H), 1.39 (d, J = 3.8 Hz, 3H), 1.12 (d, J = 7.1 Hz, 3H), 0.97 (d, J = 5.9 Hz, 3H) ppm; **6d**; ^{1}H-NMR (300 MHz; $CDCl_3$) δ 5.37 (s, 1H), 4.38 (d, J = 10.8 Hz, 1H), 3.18 (m, 1H), 3.09 (m, 1H), 2.89 (m, 1H), 2.38 (td, J = 13.9, 4.0 Hz, 1H), 1.40 (s, 3H), 1.13 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 4.8 Hz, 3H), 0.96 (t, J = 7.3 Hz, 3H) ppm; **6e**; ^{1}H-NMR (300 MHz; $CDCl_3$) δ 5.96 (m, 1H), 5.52 (d, J = 12.8 Hz, 1H), 5.48 (d, J = 5.7 Hz, 1H), 5.31 (s, 1H), 4.43 (d, J = 10.8 Hz, 1H), 4.06 (dd, J = 13.7, 8.0 Hz, 1H), 3.74 (dd, J = 13.7, 6.8 Hz, 1H), 2.94 (m, 1H), 2.39 (td, J = 13.7, 3.8 Hz, 1H), 1.42 (s, 3H), 1.11 (d, J = 6.9 Hz, 3H), 0.97 (d, J = 5.9 Hz, 3H) ppm; **6f**; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 7.6 Hz, 2H), 7.37 (d, J = 7.6 Hz, 2H), 5.24 (s, 1H), 4.38 (d, J = 10.8 Hz, 1H), 2.57 (m, 1H), 2.42 (m, 1H), 2.36 (s, 1H), 2.07 (m, 1H), 1.97 (m, 1H), 1.79 (m, 3H), 1.34 (s, 3H), 1.26 (m, 2H), 1.21 (d, J = 6.4 Hz, 3H), 0.89 (d, J = 7.2 Hz, 3H) ppm; **6h**; ^{1}H-NMR (300 MHz; $CDCl_3$) δ 7.49 (m, 2H), 7.39 (m, 3H), 5.24 (s, 1H), 4.65 (d, J = 13.7 Hz, 1H), 4.20 (d, J = 5.0 Hz, 1H), 4.16 (d, J = 2.0 Hz, 1H), 2.94 (m, 1H), 2.41 (td, J = 13.8, 4.1 Hz, 1H), 1.47 (s, 3H), 1.03 (d, J = 7.1 Hz, 3H), 0.96 (d, J = 5.7 Hz, 3H) ppm; **7a**; ^{1}H-NMR (300 MHz; $CDCl_3$) δ 5.91 (s, 1H), 5.00 (d, J = 6.8 Hz, 1H), 3.23 (m, 1H), 3.01 (s, 3H), 2.36 (td, J = 13.9, 4.0 Hz, 1H), 1.42 (s, 3H), 1.27 (d, J = 7.9 Hz, 3H), 0.96 (d, J = 6.0 Hz, 3H) ppm; **7b**; ^{1}H-NMR (300 MHz; $CDCl_3$) δ 5.88 (s, 1H), 5.02 (d, J = 6.6 Hz, 1H), 3.18 (m, 3H), 2.34 (td, J = 13.9, 3.8 Hz, 1H), 1.40 (s, 3H), 1.39 (t, J = 7.5 Hz, 3H), 1.28 (d, J = 7.5 Hz, 3H), 0.94 (d, J = 6.1 Hz, 3H) ppm; **7c**; ^{1}H-NMR (300 MHz; $CDCl_3$) δ 5.89 (s, 1H), 5.20 (d, J = 6.9 Hz, 1H), 3.52 (m, J = 6.9 Hz, 1H), 3.20 (m, 1H), 2.35 (td, J = 13.9, 3.9 Hz, 1H), 1.42 (d, J = 3.8 Hz, 3H), 1.41 (s, 3H), 1.39 (d, J = 5.1 Hz, 3H), 1.27 (d, J = 7.7 Hz, 3H), 0.96 (d, J = 6.2 Hz, 3H) ppm; **7d**; ^{1}H-NMR (300 MHz; $CDCl_3$) δ 5.90 (s, 1H), 5.01 (d, J = 6.6 Hz, 1H), 3.21 (m, 1H), 3.15 (m, 2H), 2.36 (td, J = 12.3, 3.8 Hz, 1H), 1.42 (s, 3H), 1.27 (d, J = 7.9 Hz, 3H), 0.96 (t, J = 7.1 Hz, 3H), 0.95 (d, J = 5.9 Hz, 3H) ppm; **7e**; ^{1}H-NMR (300 MHz; $CDCl_3$) δ 5.96 (m, 1H), 5.93 (s, 1H), 5.51(d, J = 16.8 Hz, 1H), 5.50 (d, J = 10.1 Hz, 1H), 5.06 (d, J = 6.6 Hz, 1H), 4.03 (dd, J = 13.9, 8.4 Hz, 1H), 3.73 (dd, J = 13.9, 6.2 Hz, 1H), 3.22 (m, 1H), 2.36 (td, J = 13.8, 3.8 Hz, 1H), 1.42 (s, 3H), 1.25 (d, J = 7.7 Hz, 3H), 0.95 (d, J = 6.2 Hz, 3H) ppm; **7f**; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 7.6 Hz, 2H), 7.28 (d, J = 7.6 Hz, 1H), 5.98 (s, 1H), 5.02 (d, J = 4.8 Hz, 1H), 3.11 (m, 1H), 2.32 (s, 3H), 2.28 (m, 1H), 2.06 (m, 1H), 1.91 (m, 1H), 1.79 (m, 3H), 1.43 (s, 3H), 1.38 (d, J = 7.2 Hz, 3H), 1.25 (m, 2H), 0.98 (d, J = 6.4 Hz, 3H) ppm; **7h**; ^{1}H-NMR (300 MHz; $CDCl_3$) δ 7.45 (m, 2H), 7.38 (m, 3H), 6.00 (s, 1H), 4.92 (d, J = 6.8 Hz, 1H), 4.52 (d, J = 13.5 Hz, 1H), 4.26 (d, J = 13.7 Hz, 1H), 3.17 (m, 1H), 2.37 (td, J = 14.5, 3.8 Hz, 1H), 1.46 (s, 3H), 1.14 (d, J = 7.7 Hz, 3H), 0.95 (d, J = 6.2 Hz, 3H).

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