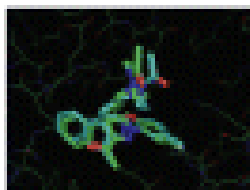




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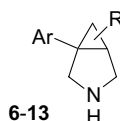
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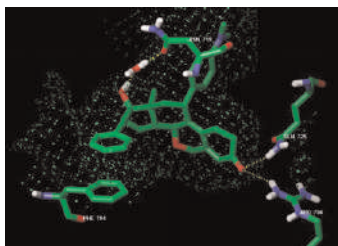
Studies on the structure–activity relationship of bicifadine analogs as monoamine transporter inhibitors pp 3682–3686

Mingzhu Zhang, Florence Jovic, Troy Vickers, Brian Dyck, Junko Tamiya, Jonathan Grey,
Joe A. Tran, Beth A. Fleck, Rebecca Pick, Alan C. Foster, Chen Chen*



Insight from molecular modeling into different conformation and SAR of natural steroids and unnatural 7-oxa-steroids pp 3687–3690

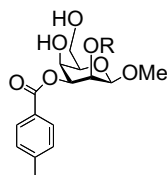
Fu-An Kang*, Xin Chen, Nareshkumar Jain, George Allan, Pamela Tannenbaum, Scott Lundeen, Zhihua Sui



Molecular modeling, in vivo activity, pharmacokinetic and metabolic properties of unnatural 7-oxa-steroids are reported.

Protein subtype-targeting through ligand epimerization: Talose-selectivity of galectin-4 and galectin-8 pp 3691–3694

Christopher T. Öberg, Helen Blanchard, Hakon Leffler, Ulf J. Nilsson*



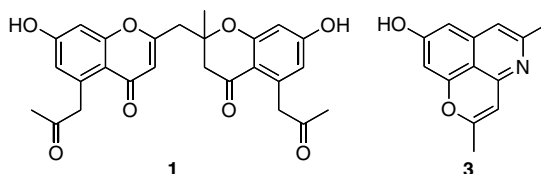
Galectin-4 C-terminal domain and galectin-8 N-terminal domain were found to prefer the α -talopyranose configuration to the natural ligand β -galactopyranose configuration. Methyl β - α -talopyranosides derivatized at O2 and O3 were synthesized and discovered to be selective submillimolar inhibitors of galectin-4C and galectin-8N.



Chrobisiamone A, a new bischromone from *Cassia siamea* and a biomimetic transformation of 5-acetonyl-7-hydroxy-2-methylchromone into cassiarin A

pp 3761–3763

Shiori Oshimi, Yuichiro Tomizawa, Yusuke Hirasawa, Toshio Honda, Wiwied Ekasari, Aty Widyawaruyanti, Marcellino Rudyanto, Gunawan Indrayanto, Noor Cholies Zaini, Hiroshi Morita*

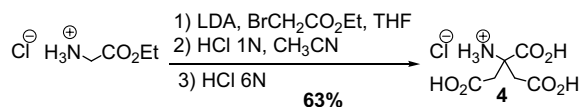


A new bischromone, chrobisiamone A (1) with an antiplasmodial activity has been isolated from the leaves of *Cassia siamea* and the structure was elucidated by 2D NMR analysis. Cyclization of 5-acetonyl-7-hydroxy-2-methylchromone (2) in the presence of ammonium acetate resulted in generation of cassiarin A (3) with an unprecedented tricyclic skeleton, supporting a biogenetic pathway proposed for 3.

2-Aminopropane-1,2,3-tricarboxylic acid: Synthesis and co-crystallization with the class A β -lactamase BS3 of *Bacillus licheniformis*

pp 3764–3768

Joséphine Beck, Eric Sauvage, Paulette Charlier, Jacqueline Marchand-Brynaert*

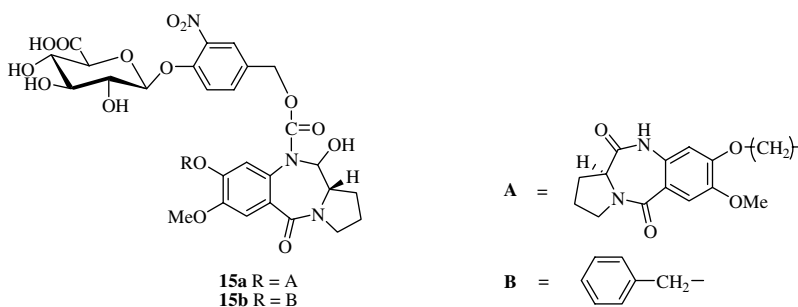


Synthesis and biochemical evaluation against β -lactamases of amino analog of citric acid are presented. The structure of the complex aminocitrate-BS3 has been analyzed by X-ray diffraction and compared to ones with citrate and isocitrate.


Pyrrrolo[2,1-c][1,4]benzodiazepine- β -glucuronide prodrugs with a potential for selective therapy of solid tumors by PMT and ADEPT strategies

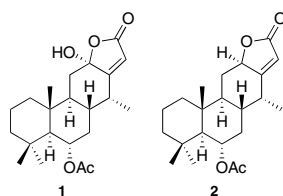
pp 3769–3773

Ahmed Kamal*, Venkatesh Tekumalla, P. Raju, V. G. M. Naidu, Prakash V. Diwan, Ramakrishna Sistla


Sucutiniranes A and B, new cassane-type diterpenes from *Bowdichia nitida*

pp 3774–3777

Yusuke Matsuno, Jun Deguchi, Yusuke Hirasawa, Kunio Ohyama, Hiroo Toyoda, Chieko Hirobe, Wiwied Ekasari, Aty Widyawaruyanti, Noor Cholies Zaini, Hiroshi Morita*

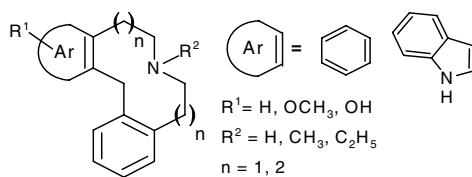


Two new diterpenes, sucutiniranes A (1) and B (2), have been isolated from *Bowdichia nitida*. Sucutinirane A (1) and 6 α -acetoxyvouacapane (3) showed a moderate cytotoxicity and 6 α ,7 β -diacetoxyvouacapane (4) showed in vitro antiplasmodial activity against parasite *Plasmodium falciparum* 3D7.

**Dopamine/serotonin receptor ligands. Part 17: A cross-target SAR approach:
Affinities of azecine-styled ligands for 5-HT_{2A} versus D₁ and D₂ receptors**

pp 3809–3813

Christoph Enzensperger, Tilo Görnemann, Heinz H. Pertz, Jochen Lehmann*



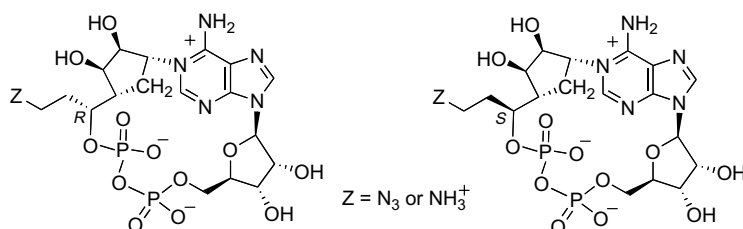
pK_i for D₁: 6.79 to 9.45; for D₂: 6.41 to 8.45; pA_2 for 5-HT_{2A}: 7.21 to 9.97

A cross-target SAR was conducted with 13 azecine-styled compounds on D₁, D₂ and 5-HT_{2A} receptors. Surprisingly, molecular modifications affect the affinity for the D₁ receptor in the same manner as the 5-HT_{2A} receptor. The protein–ligand interactions were discussed with respect to the different binding pockets.

**Synthesis of 5''-branched derivatives of cyclic ADP-carbocyclic-ribose, a potent Ca²⁺-mobilizing agent:
The first antagonists modified at the N1-ribose moiety**

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Sucutiniranes A and B, new cassane-type diterpenes from *Bowdichia nitida*

Yosuke Matsuno^a, Jun Deguchi^a, Yusuke Hirasawa^a, Kunio Ohyama^b, Hiroo Toyoda^b, Chieko Hirobe^c, Wiwied Ekasari^d, Aty Widnyaruyanti^d, Noor Cholies Zaini^d, Hiroshi Morita^{a,*}

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ABSTRACT

Two new cassane-type diterpenes, sucutiniranes A (**1**) and B (**2**), have been isolated from the seeds of *Bowdichia nitida* together with 6 α -acetoxyvouacapane (**3**) and 6 α ,7 β -diacetoxyvouacapane (**4**), and the structures of **1** and **2** were elucidated by using 2D NMR data and chemical correlations. Sucutinirane A (**1**) and **3** showed a moderate cytotoxicity against human colon carcinoma COLO201 cells, and 6 α ,7 β -diacetoxyvouacapane (**4**) showed in vitro antiplasmodial activity against parasite *Plasmodium falciparum* 3D7.

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Bowdichia nitida Spruce ex Benth., common name ‘sucupira’, is distributed in the Brazilian Amazon, and the seeds of this plant are used for rheumatic, antipyretic, and gouty agents.¹ So far, alkaloids, triterpenes, isoflavonoids, benzofuranes, and benzopyranes have been isolated from the genus *Bowdichia*.^{2–4}

Our efforts on identifying new natural products from the seeds of *B. nitida* resulted in the isolation of two new cassane-type diterpenes, sucutiniranes A (**1**) and B (**2**). This Letter describes the structure elucidation of **1** and **2** on the basis of spectroscopic data and chemical correlations as well as cytotoxicity against human colon carcinoma COLO201 cells and antiplasmodial activity.

Structures of sucutiniranes A (1) and B (2). The seeds of *Bowdichia nitida* were extracted with MeOH, and the extract was partitioned between EtOAc and 3% tartaric acid. EtOAc-soluble materials were subjected to a silica gel column (hexane/EtOAc and CHCl₃/MeOH) and an ODS column (MeOH/H₂O) followed by HPLC (MeOH/H₂O) to afford sucutiniranes A (**1**, 0.0002% yield) and B (**2**, 0.00006%) together with 6 α -acetoxyvouacapane (**3**, 0.02%)⁵ and 6 α ,7 β -diacetoxyvouacapane (**4**, 0.0008%).⁶

Sucutinirane A (**1**, $[\alpha]_D^{22} -24$ (c, 1.0, CHCl₃)) was revealed to have the molecular formula C₂₂H₃₂O₅, by HRESITOFMS [*m/z* 399.2142 (M+Na)⁺, $\Delta -0.5$ mmu]. IR absorptions implied the presence of hydroxyl (3480 cm⁻¹) and carbonyl (1740 cm⁻¹) groups. The ¹H

and ¹³C NMR data (Table 1) suggested the presence of two carbonyl carbons, one sp² methine, one sp² quaternary carbon, five sp³ methylenes, five sp³ methines, three sp³ quaternary carbons, and five methyl groups. The presence of the α , β -unsaturated γ -lactone moiety was substantiated by the signals of one sp² methine (δ_C 114.2), one sp² quaternary carbon (δ_C 175.0), one sp³ quaternary carbon with two oxygen atoms (δ_C 107.6), and one carbonyl carbon (δ_C 173.4).

Partial structures **a** (C-1 to C-3) and **b** (C-5 to C-9, C-11, C-14, and C-17) were deduced from a detailed analysis of 2D NMR data of **1** (Fig. 1). The HMBC cross-peaks of H₃-19 to C-3, C-4, C-5, and C-18 indicated the connection among C-3, C-5, C-18, and C-19 through C-4. HMBC correlations for H₃-20 to C-1, C-5, C-9, and C-10 indicated connection among C-1, C-5, C-9, and C-20 through C-10. On the other hand, HMBC correlations for H-14 to C-12 and C-15, H₃-17 to C-13, and H-15 to C-12 and C-16 supported the location of the methyl group at C-14, and the α , β -unsaturated γ -lactone moiety at C-12 and C-13. Furthermore, the presence of an acetoxy group at C-6 was elucidated by the HMBC correlation for H-6 and H₃-22 to C-21. Thus, the gross structure of sucutinirane A was assigned to be **1** with a cassane-type skeleton⁷ with the methyl group at C-14 and the α , β -unsaturated γ -lactone moiety at C-12 and C-13. The existence of cassane butenolides is rare as compared to that of cassane furanoditerpenes.

To assign the relative stereochemistry at the hemiketal C-12 position, **1** was acetylated with acetic anhydride in pyridine at

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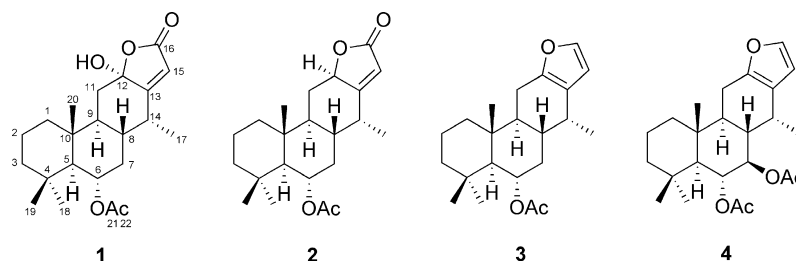


Table 1
 ^1H [δ_{H} (J, Hz)] and ^{13}C [δ_{C}] NMR Data of sucutiniranes A (**1**) and B (**2**)

	1^a		2^b	
	^1H	^{13}C	^1H	^{13}C
1a	1.10 (1H, m)	40.7	1.02 (1H, m)	39.7
1b	1.74 (1H, m)		1.71 (1H, m)	
2a	1.48 (1H, m)	19.5	1.47 (1H, m)	18.4
2b	1.59 (1H, m)		1.52 (1H, m)	
3a	1.29 (1H, m)	44.6	1.24 (1H, m)	43.4
3b	1.38 (1H, m)		1.39 (1H, m)	
4		34.1		33.1
5	1.31 (1H, d, 11.0)	58.4	1.22 (1H, m)	57.2
6	5.12 (1H, ddd, 11.0, 11.0, 4.1)	73.5	5.07 (1H, ddd, 11.1, 11.1, 4.3)	72.0
7a	1.49 (1H, m)	38.0	1.41 (1H, m)	36.7
7b	1.84 (1H, m)		1.88 (1H, m)	
8	1.84 (1H, m)	40.9	1.82 (1H, m)	38.7
9	1.54 (1H, m)	45.6	1.25 (1H, m)	44.4
10		39.5		38.7
11a	1.25 (1H, m)	38.9	0.99 (1H, m)	33.7
11b	2.38 (1H, dd, 12.9, 3.3)		2.50 (1H, ddd, 11.8, 6.4, 3.0)	
12		107.6	4.84 (1H, dd, 11.4, 6.4)	79.1
13		175.0		176.1
14	2.96 (1H, m)	37.3	2.95 (1H, m)	35.7
15	5.74 (1H, s)	114.2	5.68 (1H, s)	110.9
16		173.4		173.4
17	1.17 (3H, d, 7.3)	12.9	1.08 (3H, d, 7.3)	13.9
18	1.10 (3H, s)	37.2	1.06 (3H, s)	36.5
19	0.91 (3H, s)	23.0	0.89 (3H, s)	22.5
20	0.91 (3H, s)	15.8	0.88 (3H, s)	15.3
21		172.2		170.3
22	2.04 (3H, s)	21.9	2.06 (3H, s)	21.9

^a In CD_3OD .

^b In CDCl_3 .

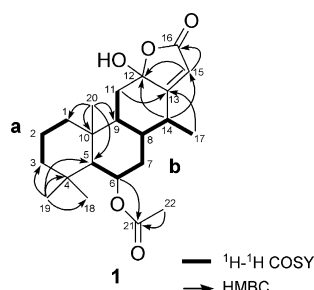


Figure 1. Selected 2D NMR correlations for sucutinirane A (**1**).

room temperature to afford the monoacetylated product **1a**. The relative stereostructure of **1a** as shown in computer-generated 3D drawing (Fig. 2) was deduced from cross-peaks observed in the NOESY spectrum and 3J coupling constants. The NOESY correlation of H_3 -17/ H_3 -24 indicated to be α -orientation for CH_3 -17 and CH_3 -24. Antiperiplanar conformation between H-5 and H-6 was preferred because of the coupling constant, $^3J_{\text{H5/H6}} = 11.0\text{ Hz}$. The β -configuration of H-6, CH_3 -19, and CH_3 -20 was

supported by the NOESY cross-peaks among H-6, H_3 -19, and H_3 -20, while the α -configuration of both H-5 and H-9 was supported by the NOESY cross-peak between H-5 and H-9. Furthermore, oxidation of the furan ring of 6 α -acetoxyvouacapane (**3**) with *m*CPBA gave sucutinirane A (**1**) as shown in Scheme 1. Thus, the structure of sucutinirane A including relative stereochemistry was assigned as shown in Figure 2.

Sucutinirane B (**2**, $[\alpha]_{\text{D}}^{22} -33$ (c, 0.2, CHCl_3)) was revealed to have the molecular formula $\text{C}_{22}\text{H}_{32}\text{O}_4$, by HRESITOFMS [m/z 361.2389 ($\text{M}+\text{H}$)⁺, $\Delta +2.1$ mmu]. IR absorptions implied the presence of carbonyl (1735 cm^{-1}) group. The ^1H and ^{13}C NMR data (Table 1), and 2D NMR correlations (Fig. 3) suggested that **2** had the same cassane-type skeleton as that of **1**, except for the presence of an oxymethine at C-12 (δ_{H} 4.84, δ_{C} 79.1). The relative stereochemistry of sucutinirane B (**2**) was deduced by NOESY spectrum (Fig. 4) and 3J coupling constants. The configuration of β -oriented H-6, H-8, CH_3 -19, and CH_3 -20 was supported by the NOESY correlations of H-6/H-8, H-6/ H_3 -19, and H-8/ H_3 -20. The coupling constant, $^3J_{\text{H5/H6}} = 11.1\text{ Hz}$ indicated antiperiplanar conformation between H-5 and H-6. The α -configuration of H-5, H-9, H-12, and CH_3 -17 was supported by the NOESY cross-peaks of H-5/H-9 and H-12/H-9 and H_3 -17. Thus, the structure of **2** was assigned as 12-deoxy-sucutinirane A.

The absolute stereochemistry of sucutiniranes A (**1**) and B (**2**) was deduced by applying CD curves for γ -lactone chromophore.⁸ The sign of the CD curve in MeOH [**1**: λ_{max} 222 nm ($\Delta\epsilon -0.8$) and 244 nm ($\Delta\epsilon -0.6$), **2**: λ_{max} 218 nm ($\Delta\epsilon -1.1$)] was negative, indicating that the chirality at C-12 of **1** and **2** was as shown in Figures 3 and 4.

To confirm the proposed structure for **2**, treatment of 6 α -acetoxyvouacapane (**3**) with *m*CPBA in the presence of 1 drop 12 N HCl in CHCl_3 afforded sucutinirane B (**2**) together with two byproducts, compounds **5** and **6**, which was elucidated by 2D NMR correlations as shown in Figure 5. Stereochemistry of

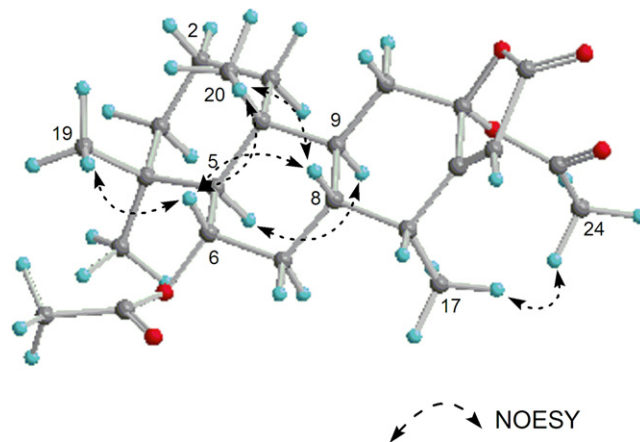
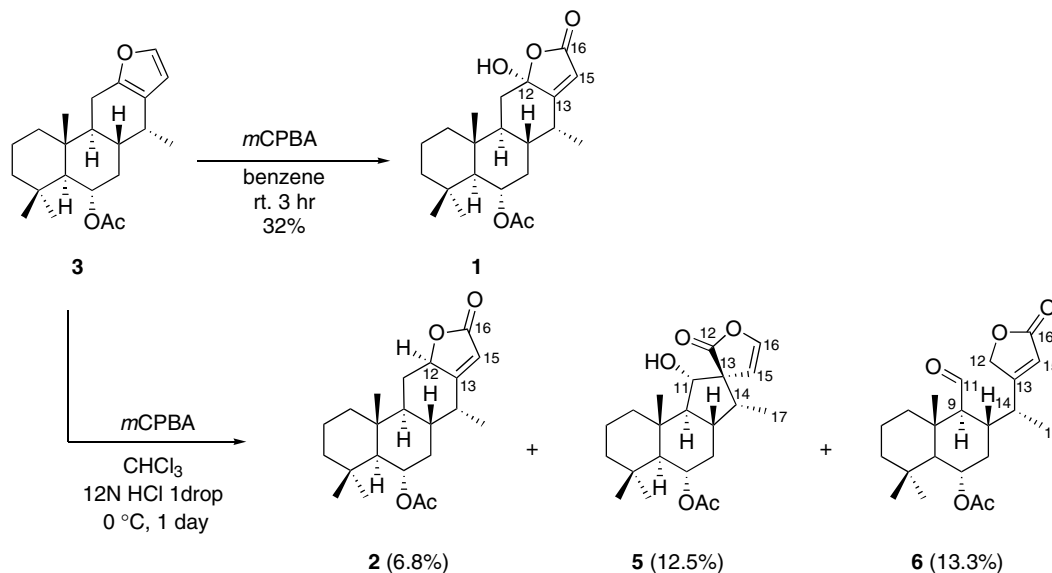


Figure 2. Selected NOESY correlations and relative stereochemistry of compound **1a**.



Scheme 1. Oxidation of 6 α -acetoxyvouacapanone (**3**) by mCPBA.

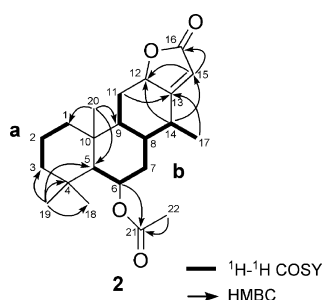


Figure 3. Selected 2D NMR correlations for sucutinirane B (**2**).

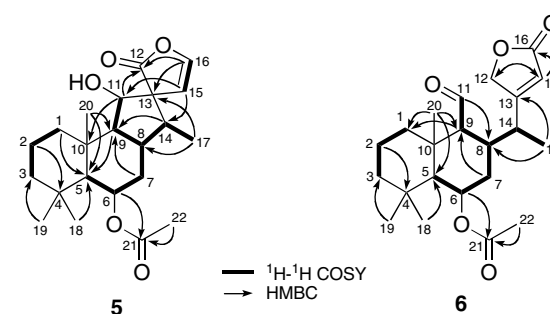


Figure 5. Selected 2D NMR correlations for **5** and **6**.

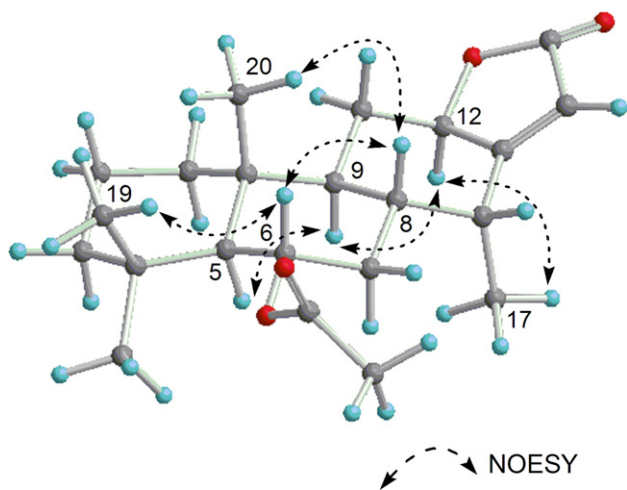


Figure 4. Selected NOESY correlations and relative stereochemistry of sucutinirane B (**2**).

a hydroxyl at C-11 and spiro carbon at C-13 for **5** was assigned by NOESY data of H-8/H-11 and H-15/H₃-17. Compound **5**, which was derived from oxidative intermediate at C-11 followed by epoxidation at Δ^{12} and Pinacol-type rearrangement, possesses a spirojoined β , γ -unsaturated γ -lactone, and cyclopentane bicycles with a hydroxyl group at C-11. On the other

hand, compound **6**, which was produced from oxidative intermediate at C-11 followed by epoxidation at Δ^{15} and cleavage between C-11 and C-12 bond accompanied with cleavage of the epoxide, contains an aldehyde moiety at C-11 and an α , β -unsaturated γ -lactone moiety at C-14 (Scheme 1). These structures of **5** and **6** were also supported by HMBC (Fig. 5) and NOESY correlations.

Sucutinirane A (**1**) and 6 α -acetoxyvouacapanone (**3**) showed a moderate cytotoxicity against human colon carcinoma COLO201 cells with IC₅₀ 37.3 and 86.6 μ g/mL, respectively, while sucutinirane B (**2**), 6 α ,7 β -diacetoxyvouacapanone (**4**), and compounds **5** and **6** were inactive (IC₅₀ > 100 μ g/mL).

Each compound was also tested for its ability to inhibit *Plasmodium falciparum* growth.⁹ 6 α ,7 β -diacetoxyvouacapanone (**4**) showed promising in vitro antiplasmodial activity against parasite *P. falciparum* 3D7 (IC₅₀ 0.39 μ g/mL) and a good selectivity index with regard to the cytotoxicity on COLO201 cells (IC₅₀ > 100 μ g/mL), whereas other compounds were inactive at a concentration of 1 μ g/mL (Chloroquine: IC₅₀ 0.006 μ g/mL).

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