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**NEW ASPIDOFRACTININE, ASPIDOSPERMATAN AND AKUAMILINE  
INDOLE ALKALOIDS FROM THE ROOTS OF *KOPSIA  
SINGAPURENSIS* RIDL.**

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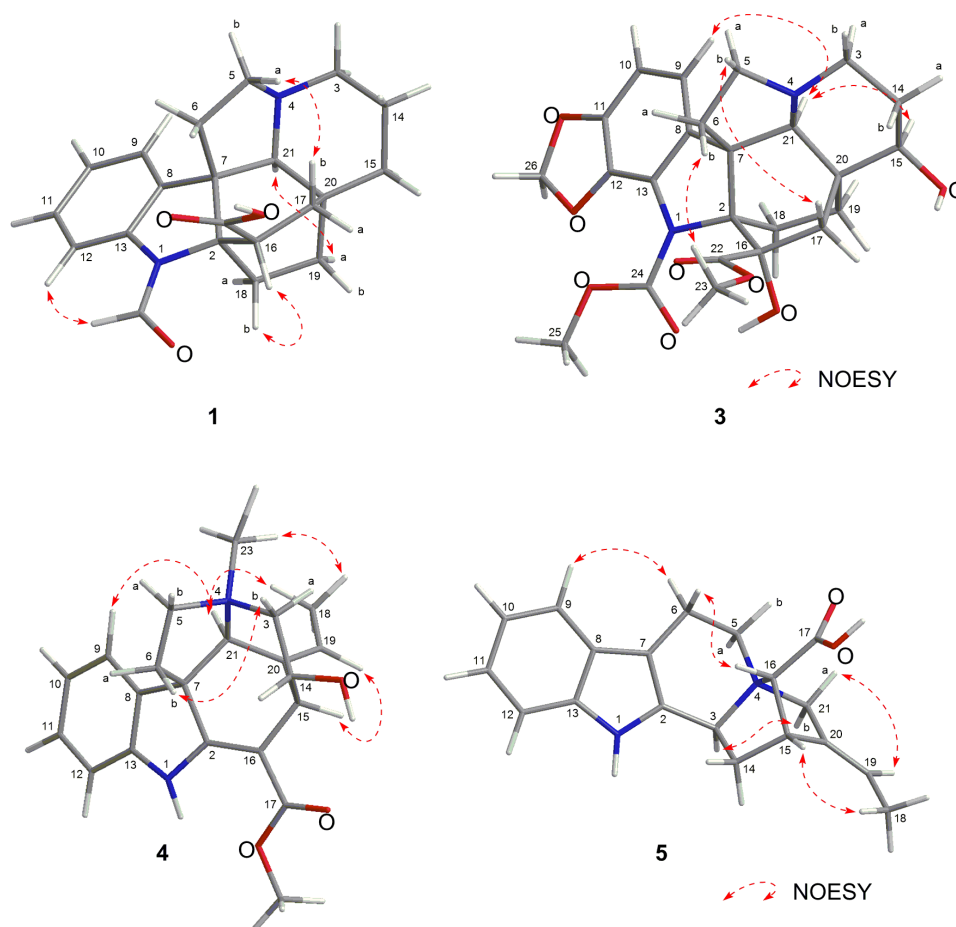
**Abstract** – Three new aspidofractinines; *N*(1)-formylkopsininic acid (**1**),  
*N*(1)-formylkopsininic acid-*N*(4)-oxide (**2**), 15-hydroxykopsamine (**3**), a new  
aspidospermatan; 14 $\alpha$ -hydroxy-*N*(4)-methylcondylocarpine (**4**) and a new  
akuamiline; singaporentinidine (**5**) type indole alkaloids were isolated from the  
roots of *Kopsia singapurensis*. Their structures were determined on the basis of  
the 2D NMR and chemical correlations.

In Malay Peninsula, *Kopsia singapurensis* Ridl. (Apocynaceae) is one of the 18 *Kopsia* species that are distributed from Negeri Sembilan southward to Singapore and common in lowland swampy forest.<sup>1,2</sup> The species which is locally known as ‘selada’ and also known as white kopsia, is a small evergreen tree with a conical crown up to 25 ft high. This plant too has been discovered to show interesting biological activities with peculiar skeleton of indoles.<sup>3-8</sup> Previous chemical investigation on this plant afforded several skeletal types of indoles such as aspidofractinine type; singaporentine A,<sup>8</sup> singapurensines A-D,<sup>7</sup> and kopsilosines A-F,<sup>5</sup> aspidosperma type; rhazinilam and rhazinal,<sup>5</sup> vincorine type; vincophylline<sup>5</sup> and akuammiline type; 16-epideacetylakuammiline.<sup>5</sup> Our continuous study on the roots of *Kopsia singapurensis* Ridl., have afforded five new indole alkaloids; *N*(1)-formylkopsininic acid (**1**), *N*(1)-formylkopsininic acid-*N*(4)-oxide (**2**), 15-hydroxykopsamine (**3**), 14 $\alpha$ -hydroxy-*N*(4)-methylcondylocarpine (**4**) and singaporentinidine (**5**) and their structures were elucidated by using spectroscopic techniques such as 1D and 2D NMR and chemical correlations.

<sup>†</sup>Dedicated to Professor Ei-ichi Negishi, Purdue University, on the occasion of his 77<sup>th</sup> birthday.



(Figure 2), and the presence of a hydroxylcarbonyl connected to C-16 was deduced from the HMBC correlations of H<sub>2</sub>-17 to C-22.



**Figure 2.** Selected NOESY correlations for **1**, **3**, **4** and **5**.

The relative configuration of **1** was deduced by NOESY correlations as shown in the computer-generated 3D drawing (Figure 2). The NOESY correlations of H-5a/H-17b and H-19a/H-21 established the relative configuration of C-2, C-7, C-20 and C-21. The orientation of H-16 was deduced to be  $\alpha$  from the NOESY correlations of H-16/H-18b. Therefore, the relative configuration of **1** was assigned to be as depicted in Figure 2.

*N*(1)-Formylkopsinic acid-*N*(4)-oxide, **2**: [ $\alpha$ ]<sub>D</sub><sup>26</sup> -93 (*c* 0.25, MeOH)}, showed the pseudo-molecular ion peak at *m/z* 369.17966 ([M + H]<sup>+</sup>,  $\Delta$  -1.77 mmu), which is consistent to the molecular formula C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>, differing from **1** by addition of one oxygen atom. The similar IR and UV spectra to **1** were observed for **2**. Comparison of the <sup>1</sup>H and <sup>13</sup>C NMR data of **2** with **1** (Table 1 & Table 2) suggested that **2** is closely related to **1** except for the characteristic downfield chemical shifts involving protons and carbons at position 3 ( $\delta_{\text{H}}$  3.93 and 4.17,  $\delta_{\text{C}}$  63.2), 5 ( $\delta_{\text{H}}$  3.80 and 3.96,  $\delta_{\text{C}}$  63.8) and 21 ( $\delta_{\text{H}}$  4.01,  $\delta_{\text{C}}$  83.1), indicating the presence of *N*(4)-oxide. Reduction of *N*(1)-formylkopsinic acid-*N*(4)-oxide (**2**) with

sodium sulfite afforded **1**, whose spectral data and the  $[\alpha]_D$  value were identical with those of **1**. Thus, **2** was concluded to be the *N*-oxide of **1**.

15-Hydroxykopsamine **3**:  $[\alpha]_D^{26} -19$  (*c* 0.12, MeOH) showed a molecular formula  $C_{24}H_{28}N_2O_8$ , which was determined by HRESITOFMS [ $m/z$  473.1934 ( $M + H$ )<sup>+</sup>,  $\Delta$  +1.0 mmu]. The IR absorption at  $3450\text{ cm}^{-1}$  was characteristic of amino or hydroxy group and the band at  $1710\text{ cm}^{-1}$  indicated the presence of a carbonyl group. The UV spectrum showed the maximum absorption at 203, 226 and 290 nm which were characteristic of a indoline chromophore.<sup>9,10</sup> The NMR data for **3** resembled those of kopsamine which was isolated from the leaves extract of *K. pauciflora* Hook f.<sup>17</sup> The significant difference was the presence of an oxymethine signal ( $\delta_H$  3.80, *s*;  $\delta_C$  76.2) in place of the  $CH_2$ -15 signal of kopsamine. Thus, **3** was assumed to be a 15-hydroxy derivative of kopsamine, and this assumption was further confirmed by the HMBC correlations of H-15 with C-3 and C-21 (Figure 1). The relative configuration of **3** was established by NOESY correlations (Figure 2) to be similar to kopsamine, with the NOESY correlation of H-15/H-21 indicated that H-15 took an  $\alpha$ -orientation. Finally, C-15 was determined to have the *R*-configuration by employing the advanced Mosher's method.

14 $\alpha$ -Hydroxy-*N*(4)-methylcondylocarpine **4**:  $[\alpha]_D^{26} +386$  (*c* 0.25, MeOH) showed the molecular ion peak at  $m/z$  353.18396 ( $[M]^+$ ,  $\Delta$  -2.56 mmu), which was consistent to the molecular formula  $C_{21}H_{25}N_2O_3$ . Its UV absorption maxima at 224, 290, and 327 nm suggested the presence of an anilinoacrylate chromophore.<sup>11,12</sup> The IR spectrum showed absorption band at  $3460\text{ cm}^{-1}$  and  $1700\text{ cm}^{-1}$  indicating the presence of an amine and/or a hydroxy and an ester carbonyl groups, respectively. The <sup>1</sup>H and <sup>13</sup>C NMR data (Table 1 and Table 2) were reminiscent of those of 14 $\alpha$ -hydroxycondylocarpine<sup>13</sup> except for the additional methyl signal ( $\delta_H$  3.81,  $\delta_C$  51.7) and the downfield chemical shifts of protons and carbons at position 3 ( $\delta_H$  3.47 and 3.85,  $\delta_C$  61.5), 5 ( $\delta_H$  3.70 and 3.74,  $\delta_C$  64.5) and 21 ( $\delta_H$  5.37,  $\delta_C$  72.1), suggesting the presence of an *N*(4)-methyl. The position of the additional methyl was verified by HMBC correlations from H<sub>3</sub>-23 to C-3, C-5, and C-21 (Figure 1) and the relative configuration of **4** was deduced by NOESY correlations to be the same as 14 $\alpha$ -hydroxycondylocarpine (Figure 2). Thus, compound **4** was concluded to be 14 $\alpha$ -hydroxy-*N*(4)-methylcondylocarpine.

Singaporentinidine **5**:  $[\alpha]_D^{26} -2$  (*c* 0.175, MeOH) showed a molecular formula  $C_{19}H_{21}N_2O_2$ , which was determined by HRESITOFMS [ $m/z$  309.1577 ( $M$ )<sup>+</sup>,  $\Delta$  -2.1 mmu]. The IR absorption at  $3440\text{ cm}^{-1}$  was indicating the presence of amino or hydroxyl group and the band at  $1730\text{ cm}^{-1}$  indicated the presence of a carbonyl group. The UV spectrum revealed the maximum absorption at 200, 220, 280 and 327 nm which were characteristic of an indole chromophore.<sup>9,10</sup> Analysis of the 1D and 2D NMR data of **5** (Figure 1) revealed a planar structure which is related to excelsinidine<sup>14</sup> isolated from *Aspidosperma*

*excelsum*, and the difference was the presence of a proton at C-16 in **5** instead of a hydroxymethyl in *excelsinidine*. Analysis of the NOESY data (Figure 2) established the relative configuration of **5**. The *E* configuration of C-19 double bond was deduced from the NOESY correlations of H-15/H<sub>3</sub>-18 and H-19/H-21a. The  $\alpha$ -orientation of C-3 was suggested by NOESY cross-peaks between H-3/H-21b and the orientation of H-16 was deduced from the NOESY correlation of H-6/H-16. Thus, the relative configuration of **5** was assigned to be as depicted in Figure 2.

**Table 1.** <sup>1</sup>H NMR [400 MHz,  $\delta_{\text{H}}$  (*J*, Hz)] of **1-5** in CDCl<sub>3</sub>

Position	1	2	3	4	5
3a	3.20 ( <i>m</i> )	3.93 ( <i>d</i> , 11 Hz)	3.01 ( <i>m</i> )	3.47 ( <i>m</i> )	4.97 ( <i>br s</i> )
3b	3.27 ( <i>m</i> )	4.17 ( <i>d</i> , 11 Hz)	3.10 ( <i>m</i> )	3.85 ( <i>m</i> )	
5a	3.39 ( <i>t</i> , 10 Hz)	3.80 ( <i>d</i> , 10 Hz)	3.00 ( <i>m</i> )	3.70 ( <i>m</i> )	3.59 ( <i>m</i> )
5b	3.52 ( <i>t</i> , 10 Hz)	3.96 ( <i>d</i> , 10 Hz)	3.05 ( <i>m</i> )	3.74 ( <i>m</i> )	4.86 ( <i>m</i> )
6a	1.74 ( <i>m</i> )	1.99 ( <i>m</i> )	1.66 ( <i>m</i> )	2.23 ( <i>m</i> )	3.09( <i>m</i> )
6b	2.80 ( <i>m</i> )	2.98 ( <i>m</i> )	2.12 ( <i>m</i> )	3.13 ( <i>m</i> )	
9	7.50 ( <i>d</i> , 8 Hz)	7.68 ( <i>d</i> , 8 Hz)	6.77 ( <i>d</i> , 8 Hz)	7.59 ( <i>d</i> , 7 Hz)	7.46 ( <i>d</i> , 8 Hz)
10	6.71 ( <i>t</i> , 8 Hz)	6.77 ( <i>t</i> , 8 Hz)	6.52 ( <i>d</i> , 8 Hz)	6.97 ( <i>t</i> , 7 Hz)	7.08 ( <i>t</i> , 8 Hz)
11	6.96 ( <i>t</i> , 8 Hz)	7.00 ( <i>t</i> , 8 Hz)		7.21 ( <i>t</i> , 7 Hz)	7.17 ( <i>t</i> , 8 Hz)
12	6.68 ( <i>d</i> , 8 Hz)	6.66 ( <i>d</i> , 8 Hz)		6.98 ( <i>d</i> , 7 Hz)	7.34 ( <i>d</i> , 8 Hz)
14a	1.64 ( <i>m</i> )	1.88 ( <i>m</i> )	1.53 ( <i>m</i> )	4.18 ( <i>br, s</i> )	2.34 ( <i>d</i> , 7 Hz)
14b	1.89 ( <i>m</i> )	1.93 ( <i>m</i> )	1.79 ( <i>m</i> )		
15a	1.37 ( <i>m</i> )	1.42 ( <i>m</i> )	3.45 ( <i>dd</i> , 4, 12 Hz)	3.61 ( <i>br, s</i> )	3.80 ( <i>s</i> )
15b	1.62 ( <i>m</i> )	1.85 ( <i>m</i> )			
16	2.85 ( <i>m</i> )	2.93 ( <i>m</i> )			4.08 ( <i>s</i> )
17a	1.60 ( <i>m</i> )	1.53 ( <i>m</i> )	1.89 ( <i>d</i> , 15 Hz)		
17b	2.56 ( <i>m</i> )	2.63 ( <i>m</i> )	2.58 ( <i>dd</i> , 2, 15 Hz)		
18a	1.39 ( <i>m</i> )	1.36 ( <i>m</i> )	1.51 ( <i>m</i> )	1.75 ( <i>d</i> , 7 Hz)	1.73 ( <i>d</i> , 7 Hz)
18b	1.84 ( <i>m</i> )	1.65 ( <i>m</i> )	2.38 ( <i>t</i> , 11 Hz)		
19a	1.35 ( <i>m</i> )	1.51 ( <i>m</i> )	1.12 ( <i>t</i> , 11 Hz)	5.95 ( <i>q</i> , 7 Hz)	5.49 ( <i>q</i> , 7 Hz)
19b	1.57 ( <i>m</i> )	1.59 ( <i>m</i> )	2.17 ( <i>m</i> )		
21a	3.60 ( <i>s</i> )	4.01 ( <i>s</i> )	2.89 ( <i>s</i> )	5.37 ( <i>br, s</i> )	3.97 ( <i>d</i> , 14 Hz)
21b					4.88 ( <i>m</i> )
22				3.81 ( <i>s</i> )	
23	8.40 ( <i>s</i> )	8.43 ( <i>s</i> )	3.76 ( <i>s</i> )	3.51 ( <i>s</i> )	
25			3.89 ( <i>s</i> )		
26			5.90 ( <i>d</i> , 1 Hz)		
NH				8.52 ( <i>br, s</i> )	
16-OH			6.92 ( <i>br s</i> )		

Biogenetically, the skeleton of **1-5** can be derived from the corynantheine skeleton. C-16 ~ N-4 cyclization of a corynantheine skeleton would yield an akuammiline skeleton as in **5**. Rearrangements of a corynantheine skeleton may yield a stemmadenine skeleton, of which the aspidofractinine (**1-3**) and aspidospermatan (**4**) skeleton can be derived.

**Table 2.**  $^{13}\text{C}$  NMR [100 MHz,  $\delta_{\text{C}}$ ] of **1-5** in  $\text{CDCl}_3$

Position	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
2	65.2	65.1	74.8	167.8	129.8
3	46.6	63.2	45.9	61.5	70.1
5	49.9	63.8	50.3	64.5	51.7
6	33.6	32.4	37.3	41.5	18.5
7	58.2	58.8	57.6	58.3	104.9
8	137.4	137.4	123.3	133.3	125.9
9	122.7	124.3	114.5	121.0	118.8
10	122.3	121.5	103.9	122.8	120.4
11	127.9	128.1	148.4	130.3	123.3
12	113.1	112.7	134.2	112.0	112.1
13	147.1	148.3	135.7	145.9	138.0
14	15.1	19.3	26.4	67.1	34.8
15	33.3	31.9	76.2	44.4	42.6
16	42.1	42.8	74.6	101.0	72.3
17	32.8	31.8	34.5	168.0	168.0
18	31.6	34.3	23.5	13.3	14.4
19	33.8	33.0	28.2	130.8	119.3
20	30.9	34.0	38.9	125.9	132.7
21	66.8	83.1	67.8	72.1	66.2
22	177.0	177.1	172.9	52.0	
23	167.6	167.3	52.5	51.7	
24			156.1		
25			53.3		
26			100.3		

## EXPERIMENTAL

**General Experimental Procedures.** Spectra were recorded on the following instruments. Optical rotations were taken on Jasco DIP-1000 Digital polarimeter at 25 °C. UV spectra were recorded on a Shimadzu UVmini-1240 spectrophotometer and IR spectra on a Perkin Elmer 1600 spectrophotometer. CD spectra were recorded on a JASCO J-820 polarimeter. Mass spectra were obtained using LC-EIMS,

Waters Micromass ZQ and a LTQ Orbitrap XL (Thermo Scientific) spectrometer. NMR spectra were recorded on a Bruker Avance 600 spectrometer and chemical shifts were reported using residual CD<sub>3</sub>OD ( $\delta_{\text{H}}$  3.31 and  $\delta_{\text{C}}$  49.0) as internal standards. HPLC was performed on a C18 MG-II ( $\phi$  10 mm I.D x 250 mm).

**Plant Material.** The roots of *Kopsia singaporensis* were collected in Kluang, Johor, Malaysia in 2010. Identification was made by Mr. Teo Leong Eng, University of Malaya. Voucher specimens (KL 5724) were deposited at Herbarium of the Department of Chemistry, University of Malaya, Kuala Lumpur, Malaysia.

**Extraction and Isolation.** The dried roots (1 kg) of *Kopsia singaporensis* were ground and extracted exhaustively with MeOH to give 35 g of MeOH crude extract. The MeOH crude extract (20 g) were further extracted with EtOAc/3% tartaric acid (pH 2), CHCl<sub>3</sub>/saturated Na<sub>2</sub>CO<sub>3</sub> (pH 10) to yielded EtOAc crude extract (15.0 g) and alkaloid crude extract (4.0 g) respectively. The alkaloidal fraction (2.59 g) was subjected to a Sephadex LH-20 column with solvent system CHCl<sub>3</sub>/MeOH (1:1) to give 20 series of fractions. Each series of fractions was then treated separately by extensive column chromatography. Fractions I and J (190.0 mg) was further purified by an ODS column (MeOH/H<sub>2</sub>O + 0.1% formic acid, 2:8 → 1:0) to afford *N*(1)-formylkopsininic acid (**1**, 18.8 mg) and *N*(1)-formylkopsininic acid-*N*(4)-oxide (**2**, 6.6 mg) together with kopsamine *N*(4)-oxide (11.5 mg). Further purification on fractions eluted by the ODS column with an ODS HPLC (MeCN/H<sub>2</sub>O + 0.1% formic acid, 2:8, flow rate 2mL/min; UV detection at 220 nm,  $t_{\text{R}}$  15.0 min, 17.0 min and 21.0 min) to give 14 $\alpha$ -hydroxy-*N*(4)-methylcondylocarpine (**4**, 5.3 mg) together with 16-epiakuumiline (2.4 mg), *N*-methylpleiocarpamine (7.6 mg) and aspidodasycarpine (81.1 mg). The work-up procedure on fractions M and N (680.0 mg) with normal silica and followed by ODS column with an ODS HPLC (MeCN/H<sub>2</sub>O + 0.1% formic acid, 2:8, flow rate 2mL/min; UV detection at 220 nm,  $t_{\text{R}}$  18.0 min and 23.0 min) to give 15-hydroxykopsamine (**3**, 2.4 mg) and singaporentinidine (**5**, 3.5 mg) together with kopsamine (5.2 mg), kopsinine (14.8 mg) and kopsininic acid (2.0 mg).

***N*(1)-Formylkopsininic acid (1):** yellowish amorphous, with  $[\alpha]_{\text{D}}^{26}$  -304 ( $c$  0.25, MeOH); UV (MeOH)  $\lambda_{\text{max}}$  200, 240, and 290 nm; IR (liquid film)  $\lambda_{\text{max}}$  3400 (OH), 1730 and 1710 (C=O), and 1616 cm<sup>-1</sup>; HRESIMS  $m/z$  353.18391 ( $[\text{M} + \text{H}]^+$ ; calcd. for C<sub>21</sub>H<sub>25</sub>N<sub>2</sub>O<sub>3</sub>, 353.18652). <sup>1</sup>H-NMR and <sup>13</sup>C-NMR see Table 1 and Table 2.

***N*(1)-Formylkopsininic acid-*N*(4)-oxide (2):** light yellowish amorphous, with  $[\alpha]_{\text{D}}^{26}$  -93 ( $c$  0.25, MeOH); UV (MeOH)  $\lambda_{\text{max}}$  200, 240 and 290 nm; IR (liquid film)  $\lambda_{\text{max}}$  3450 (OH), 1720 (C=O) and 1614 cm<sup>-1</sup>; HRESIMS  $m/z$  369.17966 ( $[\text{M} + \text{H}]^+$ ; calcd. for C<sub>21</sub>H<sub>25</sub>N<sub>2</sub>O<sub>4</sub>, 369.18143). <sup>1</sup>H-NMR and <sup>13</sup>C-NMR see Table 1 and Table 2.

**15-Hydroxykopsamine (3):** yellowish amorphous, with  $[\alpha]_D^{26}$  -19 (*c* 0.12, MeOH); UV (MeOH)  $\lambda_{\max}$  203, 226 and 290 nm; IR (liquid film)  $\lambda_{\max}$  3450 (OH) and 1710 (C=O)  $\text{cm}^{-1}$ ; HRESIMS *m/z* 473.1934 ( $[\text{M} + \text{H}]^+$ ; calcd. for  $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_8$ , 473.1924).  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  see Table 1 and Table 2.

**14 $\alpha$ -Hydroxy-*N*(4)-methylcondylocarpine (4):** light yellowish amorphous, with  $[\alpha]_D^{26}$  +386 (*c* 0.25, MeOH); UV (MeOH)  $\lambda_{\max}$  200, 224, 290 and 327 nm; IR (liquid film)  $\lambda_{\max}$  3460 (NH/OH) and 1700 (C=O)  $\text{cm}^{-1}$ ; HRESIMS *m/z* 353.18396 ( $[\text{M} + \text{H}]^+$ ; calcd. for  $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_3$ , 353.18652).  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  see Table 1 and Table 2.

**Singaporentinidine (5):** light yellowish amorphous, with  $[\alpha]_D^{26}$  -2 (*c* 0.175 MeOH); UV (MeOH)  $\lambda_{\max}$  200, 220, 280 and 327 nm; IR (liquid film)  $\lambda_{\max}$  3440 (NH/OH) and 1730 (C=O)  $\text{cm}^{-1}$ ; HRESIMS *m/z* 309.1577 ( $[\text{M}]^+$ ; calcd. for  $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_2$ , 309.1598).  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  see Table 1 and Table 2.

**Reduction of *N*(1)-formylkopsininic acid-*N*(4)-oxide (2).** To a stirred solution of *N*(1)-formylkopsininic acid-*N*(4)-oxide (2) (1.0 mg, 2.72  $\mu\text{mol}$ ) in MeOH (1.0 mL) was added sodium sulphite anhydrous (2 equiv.) at room temperature. The mixture was allowed to stir at room temperature for 1 h. When starting material was consumed (based on the TLC), an aqueous solution of  $\text{NH}_4\text{Cl}$  (25 mL) was added. The mixture was transferred to a separating funnel and extracted with EtOAc (3x25 mL). The organic layer was then washed with distilled water and dried over  $\text{Na}_2\text{SO}_4$  to yield *N*(1)-formylkopsininic acid (1) (0.9 mg, 94 %) as a light yellowish oil.

**Reaction of 15-hydroxykopsamine (3) with (*R*)- and (*S*)-MTPA.** The solution of 15-hydroxykopsamine (3, 0.3 mg, 0.636  $\mu\text{mol}$ ) in dry  $\text{CHCl}_3$  (1 mL),  $\text{Et}_3\text{N}$  (1.3  $\mu\text{L}$ , 9.54  $\mu\text{mol}$ ) and 4-(dimethylamino)pyridine (as a catalyst) were added and the mixture were treated with (+)-*S*-MTPA and (-)-*R*-MTPA (2  $\mu\text{L}$ ) at room temperature for 3 h, respectively. When starting material was consumed (based on the TLC), evaporation of the organic solvent and chromatographic purification ( $\text{SiO}_2$ ,  $\text{CHCl}_3/\text{MeOH}$ , 1:0 – 1:1) of the crude products afforded (*R*)- and (*S*)-MTPA analogous of (3) 0.3 mg each.

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