A New Phenolic Diglycoside Produced in Response to Copper Toxicity and a New Flavan Dimer from the Leaves of *Viburnum ichangense* (HEMSL.) REHD.

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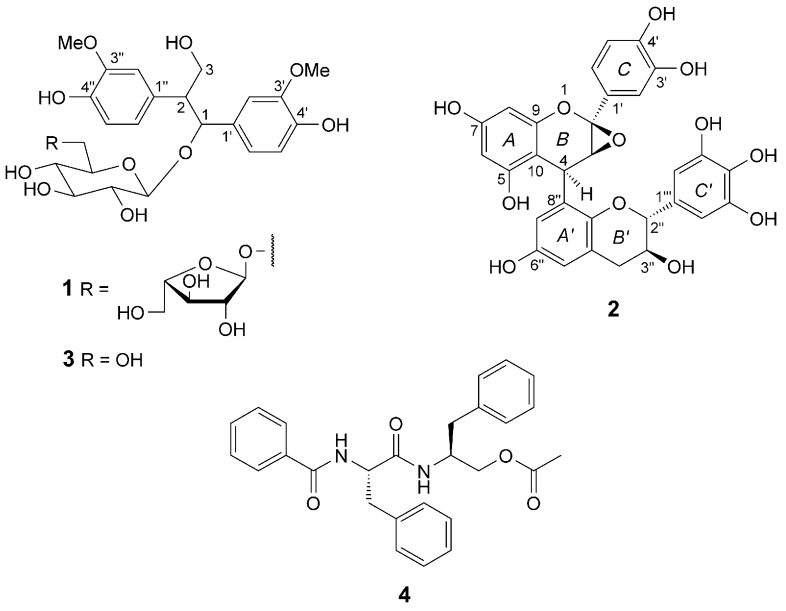
A new phenolic digycoside **1** was produced as stress metabolite in the fresh leaves of *Viburnum ichangense* (HEMSL.) REHD., in response to abiotic stress elicitation by $CuCl_2$. The stress metabolite was characterized as 1-*O*-[*α*-L-arabinofuranosyl(1 → 6)-*β*-D-glucopyranosyl]-*erythro*-1,2-bis(4-hydroxy-3-methoxyphenyl)propane-1,3-diol (**1**). A new flavan dimer, 2,3-epoxyflavan-3′,4′,5,7-tetraol-(4 → 8″)-flavan-3″,3‴,4‴,5‴,6″-pentaol (**2**), and two known compounds, hovetrichoside A (**3**) and asperglaucide (**4**), were also isolated. Their structures were established by spectroscopic means.

Introduction. – The genus *Viburnum* comprises more than 230 species mainly distributed in either the temperate or subtropical zones, from South America (Peru) to South-East Asia (Philippines, Malaysia), and the majority of them are endemic [1]. *Viburnum* species are commonly used in folk medicine for their diuretic, antispasmodic, and sedative properties, mainly as uterine excitability [2][4], and the dry powder of *V. tinus* leaves was reported as an effective molluscicidal agent [5]. The genus *Viburnum* is known to contain iridoids, iridoid glycosides [6–9], flavonoids, and biflavonoids [10], monoterpene, triterpenoids, and diterpenoids [11–15], and other constituents [16–18]. In our previous phytochemical studies on the genus *Viburnum*, phenolic glycosides, including stilbene glycoside and lignan glycosides, were isolated from *V. fordiae* [19], and salicin analog, quercetin derivatives, and quinic acid derivatives were isolated from *V. dilatatum* [20][21]. In Traditional Chinese Medicine, this genus is the resource of many medicinal herbs [22]. *V. ichangense* (HEMSL.) REHD., Chinese name '*Yichang Jiami*', is an evergreen shrub mainly distributed in south China [22]. Previously, we isolated lignan, flavan, monoterpene glycoside, and quercetin derivatives from this plant [23].

Copper is an essential trace element for all higher plants, and it has several roles in metabolic processes in plants [24]. Copper concentrations in healthy plant tissues range from 20–30 μg g^{-1} dry weight. However, excess concentrations are assumed to generate oxidative stress due to an increase in the levels of reactive oxygen species (ROS) within subcellular compartments [25]. To find stress metabolites from *V. ichangense*, a stress application on the leaves of this plant was carried out. In the present study, application of the abiotic stress agent $CuCl_2$ to the leaves of *V. ichangense* resulted in the emergence of one additional spot in the TLC of the extract of the treated

plants in comparison with that of the corresponding control extract. The new phenolic diglycoside, ichangoside (**1**), produced in response to abiotic stress treatment, a new flavan dimer, ichangol (**2**), and two known compounds, hovetrichoside A (**3**) [26] and asperglaucide (**4**) [27], were separated by preparative TLC, and purified by *Sephadex LH-20* column chromatography. Their structures and relative configurations were established by spectroscopic means.



Results and Discussion. – The AcOEt- and BuOH-soluble fractions of the MeOH extract of the leaves of copper stressed *V. ichangense* were subjected to repeated chromatography to afford new stress metabolite **1**. Compounds occurring in both treated and untreated leaves were also isolated, and identified as a new flavan dimer **2** and two known compounds, hovetrichoside A (**3**) [26] and asperglaucide (**4**) [27] by analysis of their NMR and MS data, and by comparison of their spectroscopic data with literature values.

Compound **1** was isolated as a yellow gum. The HR-FT-ICR-MS exhibited a *pseudo*-molecular-ion peak at *m*/*z* 613.2141 ($[M-H]^-$; calc. 613.2138), providing the molecular formula, $C_{28}H_{38}O_{15}$. The IR absorption maxima at 3415 and 1614 cm^{-1} suggested the presence of a OH group and an aromatic ring. The phenolic nature of the compound was also indicated by its characteristic color reactions ($FeCl_3$: purple; phosphomolybdic acid reagent: deep blue). The ^{1}H-NMR spectrum (*Table 1*) of **1** exhibited two sets of *ABX*-type signals (δ(H) 6.83 (*d*, $J = 2.1$), 6.63 (overlap), 6.55 (*d*, $J = 8.2$), and δ(H) 6.74 (*d*, $J = 2.1$), 6.63 (overlap), 6.47 (*dd*, $J = 8.2$, 2.1)) and two MeO signals (δ(H) 3.63 (*s*) and 3.66 (*s*)), revealing the presence of two 1,3,4-trisubsituted phenyl groups [28][29]. In the aliphatic region, *ABMX*-type signals (δ(H)

Table 1. *NMR Data for Compound* **1** (in (D_6)DMSO; δ in ppm, J in Hz)

Position	δ(C)[a])[b])	δ(H)[c])	^{1}H,^{1}H-COSY	HMBC[d])
1	77.9 (*d*)	5.13 (*d*, *J* = 5.5)	2	2, 3, 2′, 6′
2	54.4 (*d*)	2.88 (*ddd*, *J* = 10.5, 8.0, 5.5)	1, 3	1, 3, 1′, 1″
3	63.2 (*t*)	3.78–3.81 (*m*), 3.35–3.39 (*m*)	2	1, 2, 1″
1′	131.9 (*s*)			
2′	112.1 (*d*)	6.83 (*d*, *J* = 2.1)		1, 3′, 4′
3′	147.6 (*s*)			
4′	145.6 (*s*)			
5′	115.0 (*d*)	6.55 (*d*, *J* = 8.2)	6′	1′, 3′
6′	120.1 (*d*)	6.63 (overlap)	5′	1, 4′
1″	131.1 (*s*)			
2″	114.2 (*d*)	6.74 (*d*, *J* = 2.1)		
3″	147.3 (*s*)			
4″	145.0 (*s*)			
5″	115.0 (*d*)	6.63 (overlap)	6″	1″, 3″
6″	122.5 (*d*)	6.47 (*dd*, *J* = 8.2, 2.1)	5″	2, 2″, 4″
3′-MeO	55.8 (*q*)	3.63 (*s*)		
3″-MeO	55.9 (*q*)	3.66 (*s*)		
Glucose				
1	101.4 (*d*)	4.80 (*d*, *J* = 7.5)	Glu-2	1, Glu-3
2	73.7 (*d*)	3.02–3.07 (*m*)	Glu-3, Glu-1	Glu-5
3	77.4 (*d*)	3.10–3.15 (*m*)	Glu-2, Glu-4	Glu-1, Glu-5
4	70.9 (*d*)	3.00–3.06 (*m*)	Glu-3, Glu-5	Glu-2, Glu-6
5	75.6 (*d*)	3.20–3.25 (*m*)	Glu-4, Glu-6	Glu-3
6	67.7 (*t*)	3.78–3.82 (*m*), 3.37–3.40 (*m*)	Glu-5	Glu-4, Ara-1
Arabinose				
1	109.0 (*d*)	4.74 (*s*)	Ara-2	Glu-6
2	81.3 (*d*)	3.80–3.84 (*m*)	Ara-1, Ara-3	Ara-4
3	76.1 (*d*)	3.82–3.87 (*m*)	Ara-2, Ara-4	Ara-1, Ara-5
4	83.0 (*d*)	3.97–4.02 (*m*)	Ara-3, Ara-5	Ara-2
5	60.6 (*t*)	3.58–3.62 (*m*), 3.48–3.53 (*m*)	Ara-4	Ara-3

[a]) Recorded at 125 MHz. [b]) Multiplicities inferred from DEPT and HMQC experiments. [c]) Recorded at 500 MHz. [d]) H-Atom showing long-range correlation with indicated C-atoms.

5.13 (*d*, *J* = 5.5), 2.88 (*ddd*, *J* = 10.5, 8.0, 5.5), 3.78–3.81 (*m*), and 3.35–3.39 (*m*)) were observed. The ^{13}C-NMR spectrum displayed eleven signals for a β-glucopyranose moiety and a terminal arabinose moiety, together with the twelve signals corresponding to two aromatic rings, and three aliphatic C-atom signals, including those of one CH–O (δ(C) 77.9), one CH_2–O (δ(C) 63.2), and one benzylic CH group (δ(C) 54.4). Comparing the NMR data of **1** with those of hovetrichoside A (**3**) isolated from the same plant, the 1,2-bis(4-hydroxy-3-methoxyphenyl)propane-l,3-diol moiety was determined as the aglycone of **1**. The carbohydrate moieties were identified by comparison with authentic glucose and arabinose on TLC after acid hydrolysis, and D-glucose and L-arabinose were confirmed by GC analysis. The ^{13}C-NMR data of the arabinose unit were in good agreement with those reported for α-L-arabinofuranoside [30]. The HMBC cross-peaks from the CH–O H-atom signals at δ(H) 5.13 (*d*, *J* = 5.5,

H–C(1)) to the C-atom signal at δ(C) 101.4 (*d*, C(Glu-1)), and the anomeric H-atom signal of the glucopyranose moiety at δ(H) 4.80 (*d*, $J = 7.5$, H–C(Glu-1)) to the C-atom signal at δ(C) 77.9 (*d*, C(1)) indicated that the glucosyloxy unit was at benzylic C(1). The remaining terminal arabinose residue was at C(6) of glucose, based on the observation of long-range correlation from the anomeric H-atom signal of the arabinose moiety at δ(H) 4.74 (*s*, H–C(Ara-1)) to the downfield-shifted glucosyl C-atom signal at δ(C) 67.7 (*t*, C(Glu-6)). The configurations of glycosidic linkages in **1** were determined as β for glucose and α for arabinose units on the basis of the *J* values (δ(H) 4.80 (*d*, $J = 7.5$, H–C(Glu-1)) and 4.74 (*s*, H–C(Ara-1))) of the two anomeric H-atoms. Comparison of the coupling constant $J(1,2) = 5.5$ with published data of known 1,2-bis(4-hydroxy-3-methoxyphenyl)propane-1,3-diol isomers provided evidence for the determination of the *erythro*-configuration of the substituents at C(1) and C(2) [26][31]. Thus, compound **1** was elucidated as 1-*O*-[α-L-arabinofuranosyl($1 \rightarrow 6$)-β-D-glucopyranosyl]-*erythro*-1,2-bis(4-hydroxy-3-methoxyphenyl)propane-1,3-diol, and was named ichangoside. Ichangoside (**1**) was considered as a stress metabolite in response to copper toxicity, and the production of this new phenolic diglycoside was assumed to be an antioxidant activity-promoting transformation, which was hypothesized to play a role in the antioxidative defense system of the plant.

Compound **2** was obtained as white powder. The HR-FT-ICR-MS exhibited a molecular-ion peak at *m/z* 575.1198 ($[M-H]^-$; calc. 575.1195), corresponding to the molecular formula $C_{30}H_{24}O_{12}$. The UV spectrum showed typical benzenoid absorptions at 210, 250, and 281 nm. Analysis of the IR spectrum of **2** indicated the presence of a OH group (3459 cm^{-1}) and an aromatic ring (1617 cm^{-1}), suggesting the presence of phenol moieties, which was further confirmed by the characteristic color reactions. The ^{13}C-NMR spectrum (*Table 1*) displayed 30 signals, among which six were aliphatic C-atom signals, indicating a dimeric flavan, as confirmed further by the molecular formula $C_{30}H_{24}O_{12}$. The 2,3-dioxygenated 4-substituted flavan unit was deduced from analysis of resonances in the ^{13}C-NMR spectrum (*Table 2*) at δ(C) 100.2 (*s*), 67.7 (*d*), and 29.1 (*d*) attributable to C(2), C(3), and C(4), respectively, and confirmed by the ^{1}H,^{1}H-COSY correlation from H–C(4) to H–C(3), and the HMBC correlations from H–C(3) and H–C(4) to the dioxygenated C(2). Further analysis of the NMR data, aided by the molecular formula, evidenced the presence of an epoxide ring at C(2) and C(3). The C-atom signals at δ(C) 84.3 (*d*), 68.0 (*d*) and 28.8 (*t*) were assigned to C(2″), C(3″), and C(4″), respectively, of another flavan unit, confirmed by the ^{1}H,^{1}H-COSY correlation of H–C(2″)/H–C(3″)/CH_2(4″) and HMBC correlations H–C(3″)/C(2″) and CH_2(4″)/C(2″). The C-atom resonance of C(4) was attributed to a methine in the DEPT spectrum of **2**, indicating that C(4) in ring *B* was one of the connecting positions of the two flavans. Another linkage position in the flavan unit was deduced by analysis of the HMBC correlations. The HMBC correlations from H–C(4) at the connecting position to the oxygenated C(9″) and quaternary C(8″) indicated that the flavans units were linked at C(4) (ring *B*) and C(8″) (ring *A*′). The assignment of proposed C(8″) linkage position was supported from analysis of the ^{13}C-NMR spectrum, where the C(8″) resonance was observed at δ(C) 107.0 (*s*) [32]. Besides the dimeric flavan skeleton with an epoxide ring at C(2) and C(3), and one OH group at C(3″), there were eight phenolic OH groups in the structure of **2**. The assignment of a phenolic OH group was determined mainly from the HMBC spectrum of **2**. The signal of H–C(4) showed a

cross-peak with the C-atom resonance of the oxygenated C(5), indicating a OH group at C(5). The signals of H–C(6) and H–C(8), *meta* to each other, displayed correlations with C(10), indicating that C(7) was oxygenated. The relatively upfield signals of C(6) (δ(C) 96.5) and C(8) (δ(C) 98.1) supported this inference [33]. The HMBC correlations from the double *doublet* resonance of H–C(6′) and *doublet* resonance of H–C(2′) to the dioxygenated C-atom signal of C(2) indicated that ring *C* was 1,3,4-trisubstituted, and two phenolic OH groups were located at C(3′) and C(4′). The OH group in ring *A*′ of another flavan unit was inferred to be located at C(6″) from the HMBC correlations from H–C(5″) and H–C(7″), which were *meta* to each other, to oxygenated C(9″). The remaining three OH groups were assigned to C(3‴), C(4‴), and C(5‴) from the observation of HMBC correlation of H–C(2″) to C(2‴ and 6‴). Thus, the structure of **2** was established as shown. The complete ^{1}H- and ^{13}C-NMR spectroscopic assignments are compiled in *Table 2*. The relative configuration of **2** was

Table 2. *NMR Data for Compound* **2** (in (D_6)DMSO; δ in ppm, *J* in Hz)

Position	δ(C)[a])[b])	δ(H)[c])	^{1}H,^{1}H-COSY	HMBC[d])
2	100.2 (*s*)			
3	67.7 (*d*)	4.08 (*d*, *J* = 3.2)	4	2, 4, 10, 1′, 8″
4	29.1 (*d*)	4.24 (*d*, *J* = 3.2)	3	2, 3, 5, 9, 10, 7″, 8″, 9″
5	154.1 (*s*)			
6	96.5 (*d*)	6.08 (*d*, *J* = 2.5)		5, 7, 8, 10
7	158.0 (*s*)			
8	98.1 (*d*)	5.97 (*d*, *J* = 2.5)		6, 7, 9, 10
9	156.6 (*s*)			
10	104.0 (*s*)			
1′	132.2 (*s*)			
2′	115.6 (*d*)	7.14 (*d*, *J* = 2.5)		2, 1′, 3′, 4′, 6′
3′	146.2 (*s*)			
4′	145.5 (*s*)			
5′	120.6 (*d*)	6.80 (overlap)	6′	1′ , 3′, 4′, 6′
6′	119.8 (*d*)	7.03 (*dd*, *J* = 8.0, 2.5)	5′	2, 1′, 2′, 4′, 5′
2″	84.3 (*d*)	4.75 (*d*, *J* = 9.0)	3″	3″, 4″, 9″, 1‴, 2‴, 6‴
3″	68.0 (*d*)	4.13–4.17 (*m*)	2″, 4″	2″, 4″, 10″, 1‴
4″	28.8 (*t*)	2.94 (*dd*, *J* = 16.2, 5.2, H_α), 2.59 (*dd*, *J* = 16.2, 8.5, H_β)	3″	2″, 3″, 5″, 9″, 10″
5″	96.5 (*d*)	6.09 (*d*, *J* = 2.5)		4″, 6″, 7″, 9″, 10″
6″	156.0 (*s*)			
7″	115.7 (*s*)	6.91 (*d*, *J* = 2.5)		5″, 6″, 8″, 9″
8″	107.0 (*s*)			
9″	152.0 (*s*)			
10″	103.0 (*s*)			
1‴	130.5 (*s*)			
2‴ (6‴)	116.3 (*s*)	6.80 (overlap)		2″, 1‴, 3‴ (5‴), 4‴
3‴ (5‴)	146.6 (*s*)			
4‴	151.3 (*s*)			

[a]) Recorded at 125 MHz. [b]) Multiplicities inferred from DEPT and HMQC experiments. [c]) Recorded at 500 MHz. [d]) H-Atom showing long-range correlation with indicated C-atoms.

determined by analysis of H-atom coupling patterns. The coupling constant observed for H–C(2″) is in close agreement with those reported in the literature [34][35] for the 2,3-*trans*-configuration. The epoxide ring and the flavan unit at C(4) were established to be on the same face as depicted, which was deduced from coupling constant observed for H–C(3) (δ(H) 4.08 (d, $J = 3.2$)) and H–C(4) (δ(H) 4.24 (d, $J = 3.2$)) [36]. From the above information, compound **2** was deduced to be a new flavan dimer, 2,3-epoxyflavan-3′,4′,5,7-tetraol-(4 → 8″)-flavan-3″,3‴,4‴,5‴,6″-pentaol, and was assigned the trivial name ichangol. Ichangol was also been detected in the roots and leaves of other species of the same genus, *V. chinshanense* and *V. dilatatum*.

Experimental Part

General: Merck precoated plates (silica gel *60 F_{254}*) of 0.25-mm thickness. Prep. HPLC: *Agilent 1100* with a *Shim-pack PREP-ODS* (250 × 20 mm) column. Column chromatography (CC): *Sephadex LH-20* (*Amersham*). M.p.: *Reichert* apparatus; uncorrected. UV Spectra: *Jasco UV-2200* spectrophotometer; λ (log ε) in nm. Optical rotations: *Perkin-Elmer-341* polarimeter. IR Spectra: *Nicolet AVTAR-360* FT-IR spectrometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H- (500 MHz) and ^{13}C-NMR (125 MHz) spectra: *Bruker Avance DMX 500* NMR spectrometer, with TMS as internal standard, at 25°, δ in ppm, J in Hz. HR-FT-ICR-MS: *Bruker Apex III* spectrometer; ESI-MS: *Bruker Esquire-3000 ^{plus}* spectrometer; m/z.

Plant Material and Stress Applications. Viburnum ichangense (HEMSL.) REHD. were collected in Linan County, Zhejiang Province, P. R. China, in June, 2010, and identified by Prof. *Changxi Zhang* (Jinhua Medical College, Jinhua, P. R. China.). A voucher specimen (Vs121) has been deposited with the Jinhua Medical College, Jinhua, P. R. China. The stress applications were carried out on ten plants according to our previous method [37][38]. All the plants were separated into control (5 plants) and stressed groups (5 plants). To elicit the stress, plants were sprayed with 2% aq. soln. of $CuCl_2$. After 48 h, leaves of the control and sprayed plants were collected and dried at 60°, and finely powdered in an electronic blender and kept in separate containers for extraction.

Extraction and Isolation. The dried, powdered $CuCl_2$-treated leaves (1.1 kg) of *V. ichangense* and untreated leaves (1.3 kg) were extracted at r.t. with MeOH (3 × 5 l), resp. The extracts were evaporated *in vacuo* to afford a gummy residue (114 g) for treated and a gummy residue (122 g) for the corresponding control. The residues were partitioned in H_2O (500 ml), and extracted with AcOEt (4 × 500 ml) and BuOH (4 × 500 ml), successively. The AcOEt and BuOH extracts of treated and the corresponding control were subjected to TLC on aluminium sheets pre-coated with silica gel *60 F_{254}* (*Merck*). The spots were applied in as equal amounts as possible. The plates were developed in the following developing solvent systems: benzene/acetone 6:1, benzene/AcOEt 5:1, petroleum ether/AcOEt 5:1 for the AcOEt extract; $CHCl_3$/MeOH 3:1, CH_2Cl_2/MeOH 4:1, and benzene/$CHCl_3$/MeOH 1:3:1 for the BuOH extract. After development, the plates were examined under UV light (250 nm) to locate any additional spots of the different extracts of the treated leaves in comparison with that of the corresponding control extracts. The spots on the plates were also visualized by spraying with an EtOH/H_2SO_4 soln. Several prep.-TLC plates were prepared, and the compounds were separated by prep. TLC in different solvent systems. The crude compounds were applied to a *Sephadex LH-20* column (1 × 80 cm, 38 g; *Amersham*) and eluted with MeOH to yield pure compounds **1** (2.6 mg), **2** (3.1 mg), **3** (2.4 mg), and **4** (2.5 mg). The extract of untreated leaves were separated by the same method to afford **2** (1.7 mg), **3** (3.1 mg), and **4** (2.7 mg).

Ichangoside (= *3-Hydroxy-1,2-bis(4-hydroxy-3-methoxyphenyl)propyl 6*-O-*α*-L-*Arabinofuranosyl-β*-D-*glucopyranoside*; **1**). Yellow gum. UV (MeOH): 210 (4.43), 260 (3.87), 280 (4.12). $[\alpha]_D^{20} = -15$ (c = 0.15, MeOH). IR (KBr): 3415, 1614, 1460, 1455, 1230. ^{1}H- and ^{13}C-NMR: see *Table 1*. ESI-MS: 613 ($[M-H]^-$). HR-FT-ICR-MS: 613.2141 ($[M-H]^-$, $C_{28}H_{37}O_{15}^-$; calc. 613.2138).

Ichangol (= rel-*5-[(2*R,*3*S*)-8-[(1a*R,*7*S,*7a*S*)-1a-(3,4-dihydroxyphenyl)-1a,7a-dihydro-4,6-dihydroxy-7*H-*oxireno[*b*][1]benzopyran-7-yl]-3,4-dihydro-3,6-dihydroxy-2*H-*1-benzopyran-2-yl]-1,2,3-benzenetriol*; **2**). White powder. M.p. 231–233°. UV (MeOH): 210 (4.10), 250 (4.02), 281 (4.18). $[\alpha]_D^{20} = -36$

($c = 0.23$, MeOH). IR (KBr): 3459, 2922, 1617, 1499, 1302, 1144, 1055. ^{1}H- and ^{13}C-NMR: see *Table 2*. ESI-MS: 575 ($[M-H]^-$). HR-FT-ICR-MS: 575.1198 ($[M-H]^-$, $C_{30}H_{23}O_{12}^-$; calc. 575.1195).

This work was supported by the *NSFC* (No. 30801430) and the *Science Foundations of Zhejiang Province* (No. Y2110527 and Y4090121).

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Received March 18, 2011