JOC The Journal of Organic Chemistry

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Structure Revision of Four Classes of Prenylated Aromatic Natural Products Based on a Rule for Diagnostic ^{13}C NMR Chemical Shifts

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Cite This: https://dx.doi.org/10.1021/acs.joc.0c02409 Read Online

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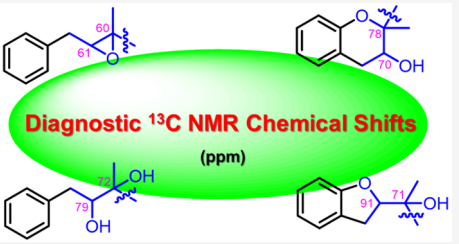
ABSTRACT: Errors in elucidating the structures of four natural classes of prenylated aromatic compounds with 2,3-epoxy, 2,3-dihydroxy, and cyclization with an *ortho*-phenolic hydroxyl to give a pyran or furan ring moiety are frequent and inevitable. Based on rigorous literature research and a series of chemical transformation experiments, a rule for the rapid determination of these four classes of prenylated derivates based on ^{13}C NMR data was formulated, and 57 corrections featuring these fragments were accordingly reported.



INTRODUCTION

Natural products represent a rich source of molecular diversity in compound libraries and, as an important part of our achievement in scientific research, have greatly promoted the development of medicine, synthetic chemistry, and system ecology.[1,2] The major challenges associated with natural products are mainly isolation, purification, and structure elucidation. Structure elucidation is generally considered a vital task in natural product chemistry research.[3] In particular, the structure elucidation of novel compounds is the most complicated task, and errors can never be completely ruled out due to the reliance on the experience of the structure appraiser and the deductive or indirect nature of NMR techniques.[4,5]

Aromatic secondary metabolites containing prenyl side chains represent a rare class of natural products that have been recognized as interesting and valuable biologically active phytochemicals for decades.[6] Simple modifications by biological or chemical approaches, such as oxidation or cyclization, typically produce four classes (class-A: 2,3-epoxy; class-B: 2,3-dihydroxy; class-C: 3,3-dimethyl-2-hydroxypyrano ring; class-D: 2-(1-hydroxy-1-methylethyl)dihydrofuran) of prenylated aromatic compounds (Figure 1). However, errors in elucidating the structures of the above four classes of prenylated aromatic compounds inevitably occur from time to time because of the similarities of the modification position. Herein, we report a rule for the rapid determination of these four classes of prenylated derivates based on ^{13}C NMR data and structure revision of 57 prenylated aromatic natural products, including 30 new structures.

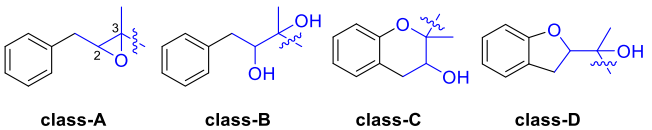


Figure 1. Four classes of prenylated aromatic compounds.

RESULTS AND DISCUSSION

To resolve the above-mentioned dilemma, we attempted to find a reliable and convenient strategy to distinguish among these four classes. ^{1}H NMR signals are more susceptible to spatial effects than ^{13}C NMR values, such as shielding/deshielding effects, chelation of the H atom, etc., because hydrogen atoms are generally located at the edges of molecules, and this often leads to a unique range of chemical shifts in different chemical groups.[7,8] So, it is difficult and complicated to distinguish the four classes of prenylated aromatic compounds mentioned above by ^{1}H NMR.

2D NMR spectroscopy is an indispensable tool for determining natural products, the most important of which is heteronuclear multiple bond correlation (HMBC) spectroscopy. But specific to these four classes of prenylated aromatic compounds, similar HMBC correlations (Figure 2) might be one of the main reasons for the confusion frequently occurring

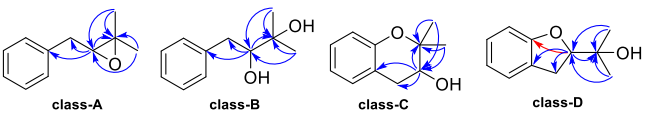
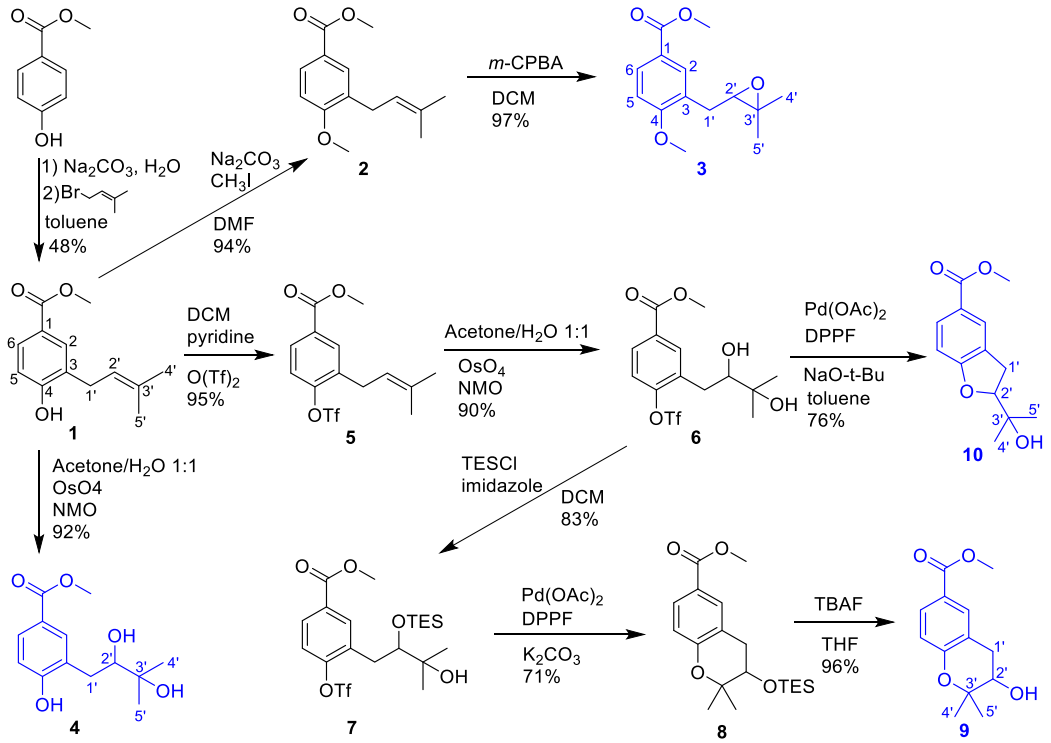


Figure 2. HMBC correlations of the four classes of prenylated aromatic compounds.

Special Issue: Natural Products: An Era of Discovery in Organic Chemistry

Received: October 11, 2020

Scheme 1. Synthetic Routes of Four Classes of Prenylated Aromatic Compounds



in structure elucidation. An important HMBC correlation (red arrow in Figure 2) in class-D is a key signal to elucidate a correct structure; however, this very weak correlation is often ignored or cannot be obtained through HMBC experiments due to the existence of two carbon−oxygen bonds.[9,10] As a result, 2D NMR played a limited role in the discrimination of the four classes of prenylated aromatic compounds.

During thorough investigations on the above-mentioned four classes of prenylated aromatic natural products, ∼670 structures were found (class-A: ∼40; class-B: ∼70; class-C: ∼260; class-D: ∼300), including flavonoids, chalcones, xanthones, coumarins, pterocarpans, chromenes, and so on. We carefully studied the literature related to the conversion among different isopentene groups via chemical or biological methods and the isolation and structure elucidation of these four classes of prenylated aromatic compounds. By examining the ^{13}C NMR spectroscopic data, we formulated a rule for easily and rapidly distinguishing these four classes of prenylated derivates. Specifically, the C-2 and C-3 carbon shifts of the compounds with an epoxy moiety (class-A) are approximately 62 and 59 ppm, respectively.[11,12] When the epoxy ring is opened to form a dihydroxy structure (class-B), the chemical shifts of C-2 and C-3 move by approximately 16 and 13 ppm downfield, respectively, due to the introduction of a new oxygen atom. The chemical shift of the C-2 position is then approximately 78 ppm, and the chemical shift of C-3 is approximately 72 ppm.[13,14] On the other hand, cyclization between the dihydroxy form and an *ortho* aromatic hydroxyl group leads to a pyran ring or a furan ring. Because of different rings and different etherification shifts depending on the aromatic group, the chemical shifts of C-2 and C-3 of the pyran ring (class-C) are approximately 70 and 78 ppm,[15,16] respectively, whereas C-2 of the furan ring (class-D) appears at 91 ppm and C-3 appears at 71 ppm.[17,18]

To corroborate the rule that we have formulated above, a series of experiments related to the transformation of the four classes of isopentene via chemical methods were performed, as it turns out that the rule provides an accurate and simple method to distinguish these four classes of fragments. Our synthesis started with the *ortho*-alkylation of metal phenolate from commercially available methyl 4-hydroxybenzoate to provide methyl 4-hydroxy-3-prenylbenzoate (**1**).[19] Epoxidation of substrate **1** using *m*-CPBA could yield the epoxide. Nevertheless, the epoxide could not be obtained upon purification using column chromatography; instead, a mixture of compounds **4**, **9**, and **10** was observed with a ratio of 1:2:7.[20] It is necessary to protect the hydroxyl group with a methyl group to produce substrate **2**, and compound **3** was obtained from **2** using *m*-CPBA.[21] The dihydroxy form, compound **4**, was obtained by the oxidation of substrate **1** using osmium tetroxide.[22] Esterification of methyl 4-hydroxy-3-prenylbenzoate (**1**) by trifluoromethanesulfonic anhydride afforded substrate **5**, and subsequent oxidation with osmium tetroxide provided dihydroxy substrate **6**. To construct a pyran ring, the secondary hydroxyl group of **6** was protected with a TES group. Cyclization of the monoprotected substrate **7** yielded substrate **8** using $Pd(OAc)_2$, DPPF, and K_2CO_3. The pyran ring product (±)-methyl 3-hydroxy-2,2-dimethylchromane-6-carboxylate (**9**) was obtained after removal of the TES group. With the use of $Pd(OAc)_2$, DPPF, and NaO-*t*-Bu, the furan ring product (±)-methyl anodendroate (**10**) was obtained from substrate **6** exclusively (Scheme 1).[23]

To further confirm the synthesized structures and verify the above rule, we calculated the chemical shifts of the synthesized compounds **3**, **4**, **9**, and **10** at the mPW1PW91/6-311+G-(2d,p) level using the gauge-including atomic orbitals (GIAO) method. The calculated chemical shifts of **3**, **4**, **9**, and **10** were in significantly better agreement with the experimental data, as indicated by linear regression analysis (Figure 3). The ^{13}C

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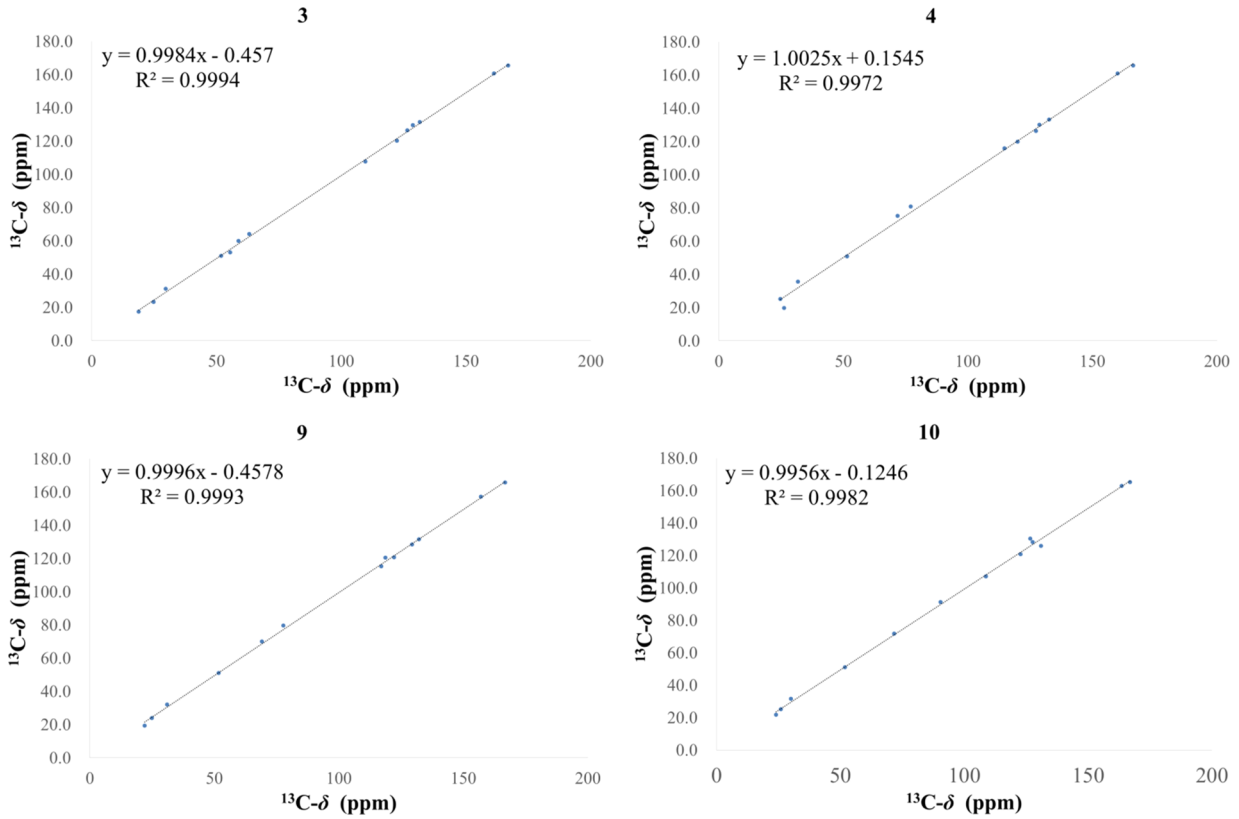

Figure 3. Linear regression analysis between the experimental and calculated NMR chemical shifts of compounds **3**, **4**, **9**, and **10**.

Table 1. ^{13}C NMR Data of Compounds 3, 4, 9, and 10

	2,3-epoxy		2,3-dihydroxy		pyran ring		furan ring	
position	3[a]	3 (calcd)	4[b]	4 (calcd)	9[a]	9 (calcd)	10[a]	10 (calcd)
1	122.4	120.3	120.0	119.7	118.8	120.3	122.8	120.9
2	131.5	131.4	132.7	133.1	132.2	131.5	131.0	126.1
3	126.5	126.4	127.4	126.1	122.3	120.6	127.6	128.3
4	161.2	160.7	160.2	160.9	157.1	157.0	163.6	163.0
5	109.7	107.6	114.8	115.8	117.1	115.1	108.8	107.2
6	130.2	129.6	128.8	130.0	129.5	128.4	126.7	130.5
1′	29.7	31.1	31.8	35.6	31.1	32.0	30.0	31.7
2′ (CH)	**63.2**	**64.2**	**77.1**	**80.8**	**69.2**	**69.9**	**90.4**	**91.2**
3′ (C)	**58.8**	**59.9**	**71.8**	**75.1**	**77.8**	**79.6**	**71.7**	**71.8**
4′	18.9	17.5	26.2	25.2	25.0	23.9	26.0	25.3
5′	24.8	23.2	24.7	19.7	22.0	19.3	24.0	21.8
COOCH$_3$	166.9	165.5	166.4	165.6	166.9	165.7	166.9	165.4
COO*CH*$_3$	51.9	51.0	51.5	50.7	51.8	51.1	51.8	51.0
4-OCH$_3$	55.5	53.0						

[a]Measured in $CDCl_3$ (δ_C 77.0 ppm). [b]Measured in DMSO-d_6 (δ_C 39.5 ppm).

NMR data of the side chain moieties of synthesized compounds **3**, **4**, **9**, and **10** together with the calculated data are listed in Table 1.

Due to the higher energy and instability of an epoxy moiety, the number of natural aromatic compounds bearing a 2,3-epoxy-3-methylbutyl side chain (class-A) is relatively small, no more than 40.[12] Correspondingly, many such structures were unfortunately assigned incorrectly and should be revised to reflect a more stable form. As a result, 21 natural products were subsequently revised to a pyran or furan class, generating 14 new structures (Figure 4, Table S1). The NMR data of all revised known structures were consistent with literature data.

Two structures belong to class-A that must be illustrated were **26a** ((±)-6,7-*cis*-epoxycannabigerol, (±)-6,7-*trans*-epoxycannabigerol) and **27a** ((±)-6,7-*trans*-epoxycannabigerolic acid, (±)-6,7-*cis*-epoxycannabigerolic acid), four constituents isolated from *Cannabis sativa*,[24] displaying a 6,7-epoxy-geranyl moiety at C-6′ and two hydroxy groups at C-1′ and C-5′. The carbon resonances at 67.3 (d, C-7) and 81.4 (s, C-6), 68.3 (d, C-7) and 78.4 (s, C-6), δ_c 66.9 (d, C-7) and 78.9 (s, C-6), together with 67.2 (d, C-7) and 81.9 (s, C-6), indicated a pyran ring (class-C) based on the rule we formulated; problems for the revisions arise from the pyran ring formed via C-2′ or C-6′. For epoxycannabigerols (**26a**), the pyran ring

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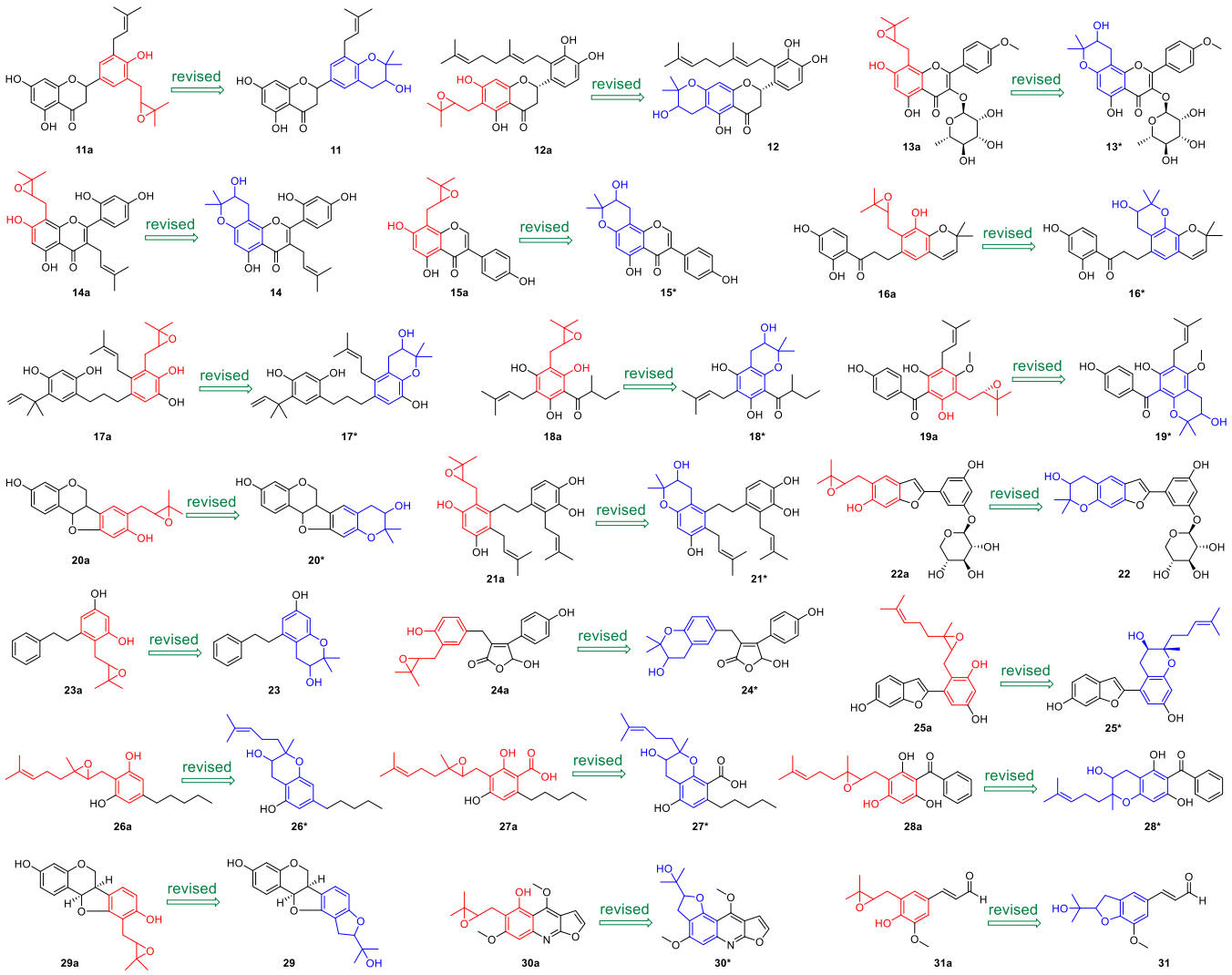

Figure 4. Reassignments of compounds originally misassigned as having moiety A. (*New compound.)

formed via C-2′ or C-6′ achieved the same structure **26** due to the symmetry. A careful comparison was conducted between epoxycannabigerolic acids (**27a**) and radstrictin C/D[25] for the similiality of their chromene moiety (Table S2). As a result, epoxycannabigerolic acids (**27a**) should be revised as **27**.

The moiety of the 2,3-dihydroxy-3-methylbutyl group (class-B) is more stable in the natural state than 2,3-epoxy-3-methylbutyl (class-A). There are more than 70 compounds bearing this moiety, and 15 compounds, including two new structures, should be revised (Figure 5, Table S3). The class-B structures have an added molecule of water compared with the other classes, and it would be helpful to identify class-B compounds. However, it is worth mentioning that mistakes often occur as that the correct molecular ion peak was mistakenly designated as a dehydration peak, because vicinal diol compounds are very prone to dehydration peaks.[26] For example, for macasiamenene R (**36a**), the molecular formula $C_{24}H_{28}O_4$ elucidated on the basis of the atmospheric pressure chemical ionization time-of-flight mass spectrometry (APCI-TOF MS) was consistent not with the original structure but with the revised structure (**36**). For gigasol (**38a**), the molecular formula tends to be wrong due to the complicated mass spectrum mentioned in the original paper; the mass spectral peak of high abundance at 505 (*m*/*z*, 35) would be the correct molecular weight, which displayed consistency with the revised structure (**38**). For myricoidiol (**39a**), the highest ion in the electron ionization mass spectrometry (EIMS) observed at *m*/*z* 358 corresponding to a molecular formula of $C_{22}H_{30}O_4$ was perfectly consistent with the revised structure **39**, but the *m*/*z* 358 ion was incorrectly assigned as an $[M^+ - H_2O]$ peak for a diol in the original paper. For dulcisxanthone G (**43a**), the fast atom bombardment mass spectrometry (FABMS) [*m*/*z* (% rel. int): 444 (2), 428 (100)] suggests the molecular weight should be 428, consistent with the revised structure **43**. MS of floribol C (**46a**) exihibited a molecular formula of $C_{36}H_{58}O_8Na$, which would give a peak at *m*/*z* 641 as opposed to 623; in fact, the high resolution electrospray ionization mass spectrometry (HRESIMS) *m*/*z* 623.3927 shown in the original text was most likely to be a $C_{36}H_{56}O_6K$ peak, which showed high consistency with the revision structure (**46**). As a result, we can infer from the above-mentioned mass spectrometry that it is inaccurate to judge dihydroxy or the cyclization fragments based on the mass spectrometry alone.

The 3,3-dimethyl-2-hydroxy-pyran ring (class-C) is a frequent result of the derivatization of a prenyl group with an *ortho*-hydroxy for an aromatic natural compound. There are almost 260 aromatic compounds exhibiting "moiety C", including coumarins, flavonoids, isoflavonoids, xanthones,

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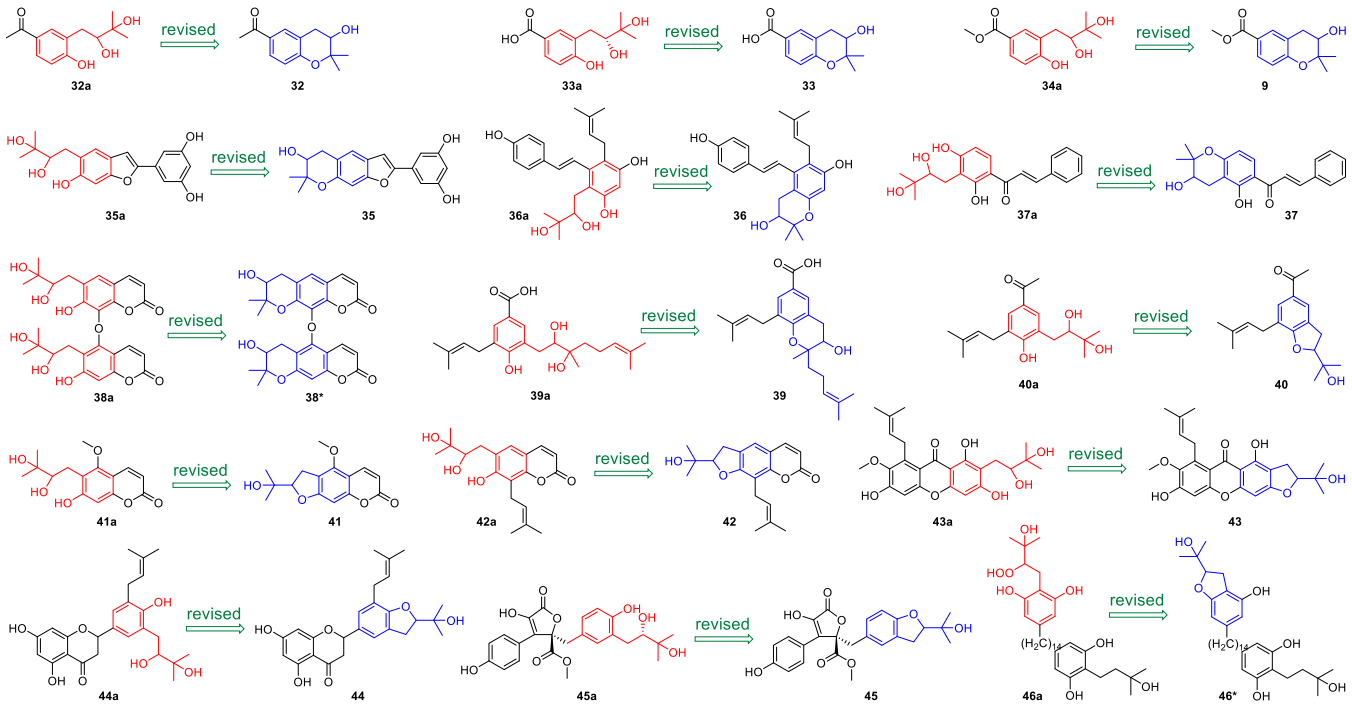

Figure 5. Reassignments of compounds originally misassigned as having moiety B.

chalcones, stilbenes, chromones, alkaloids, and so on. In total, 19 compounds should be revised (Figure 6, Table S4). Many of them were revised to be the furan form (class-D) according to the diagnostic carbon signals of C-2 (~91 ppm) and C-3 (~71 ppm), whereas four of them should be revised to be the 2,3-dihydroxy form according to the ^{13}C NMR data (C-2: ~79 ppm, C-3: ~72 ppm).

2-(1-Hydroxy-1-methylethyl)dihydrofuran (class-D), a very stable moiety that easily forms via the oxidative cyclization of prenyl and *ortho*-hydroxy groups, represents a large proportion of the prenyl modification family, ~300 compounds including chromones, flavonoids, isoflavonoids, xanthones, chalcones, coumarins, stilbenes, alkaloids, and so on. Possibly because the chemical shift of the C-2 site is much lower (90 ppm) than that of the generally oxidized tertiary carbon NMR signal (72−83 ppm) in natural products, only two compounds, including a new structure, were wrongly assigned and should be revised to be the pyran form (Figure 7, Table S5).

The NMR data of the prenyl moiety of all revised compounds were reassigned and listed in Tables S6−S8, respectively. Because there are only four compounds actually bearing moiety B, it is not suitable for regression analysis. Subsequently, linear regression analysis between compounds **9** and **10** together with all revised structures bearing moieties C and D were done, respectively (Figure 8). The high R^2 values of 0.9999 and 0.9999 indicate very little random error occurred in classes C and D structures, respectively. And the slopes of 1.0021 and 1.0058 indicate that the rule we formulated exhibits little systematic error.

CONCLUSIONS

In summary, all of the incorrect structures bearing the above four classes of prenylated aromatic natural products were revised according to the rule we formulated. This rule provides a quick and convenient method for the future study of these four kinds of prenylated aromatic compounds, and this approach might be further extended to other classes of natural compounds. This may speed up the process of discovering new prenylated compounds with high added value or various biological activities for drug discovery or industrial applications.

EXPERIMENTAL SECTION

General Information. All reactions were performed with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF) was distilled over sodium. Dichloromethane (DCM) was distilled over calcium hydride. *N*,*N*-Dimethylformamide (DMF) and pyridine were dried with a 4A molecular sieve without distillation. Reagents were used as received without further purification, unless otherwise stated. An oil bath was used as the heat resource for reactions that require heating. NMR spectra were carried out on a Bruker Avance III 400 (Bruker BioSpin GmbH, Rheinstetten, Germany) spectrometer with deuterated solvent signals used as internal standards. IR spectra (KBr) were obtained on a Bruker Tensor-27 infrared spectrophotometer. Electrospray ionization mass spectrometry (ESIMS) and HRESIMS were performed on an Agilent G6230 time-of-flight mass spectrometer, whereas EIMS and high resolution electron ionization mass spectrometry (HREIMS) were collected on a Waters AutoSpec Premier P776. Column chromatography (CC) was performed on silica gel (100−200 mesh and 200−300 mesh, Qingdao Marine Chemical Co., Ltd., Qingdao, China). Fractions were monitored by TLC plates (Si gel G and GF_{254}, Qingdao Haiyang Chemical Co., Ltd., Qingdao, China).

Methyl 4-Hydroxy-3-prenylbenzoate (1). Na_2CO_3 (4.66 g, 44 mmol, 1.1 equiv) was added to a solution of methyl 4-hydroxybenzoate (6.08 g, 40 mmol, 1.0 equiv) in 20 mL of H_2O and stirred for 2 h at 25 °C. Then, the solvent was evaporated in vacuo, and to the mixture was added 40 mL of toluene. After the suspension was stirred for 5 min, 1-bromo-3-methyl-2-butene (8.52 g, 48 mmol, 1.2 equiv) was added dropwise. The suspension was stirred for 20 h at 30 °C, and then, the reaction mixture was quenched with aqueous NH_4Cl solution. The mixture was extracted with EtOAc (3 × 100 mL) and washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 2.5:1) to give **1** (4.22 g, 48% yield) as a white solid.[27] ^1H NMR

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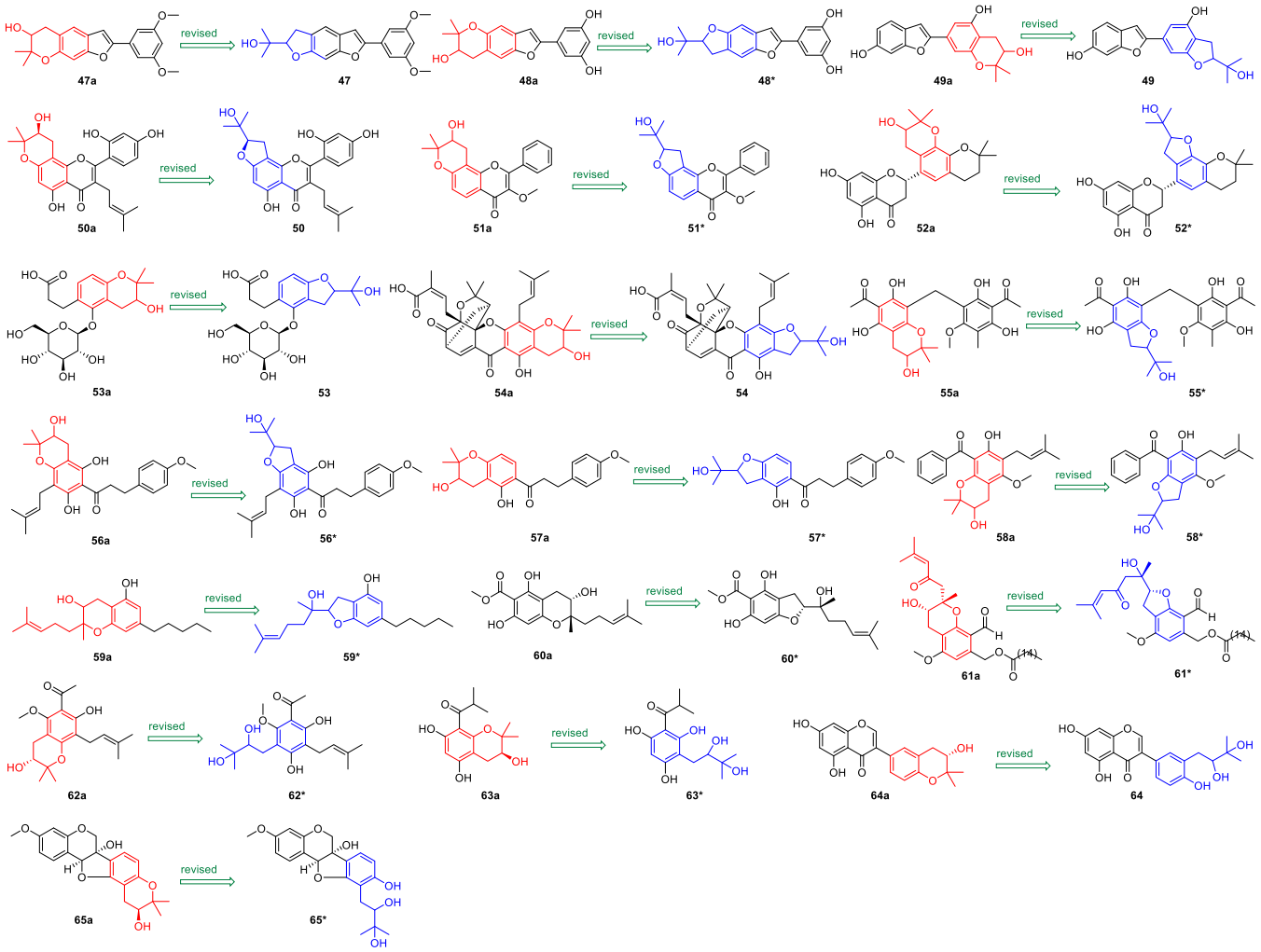

Figure 6. Reassignments of compounds originally misassigned as having moiety C.

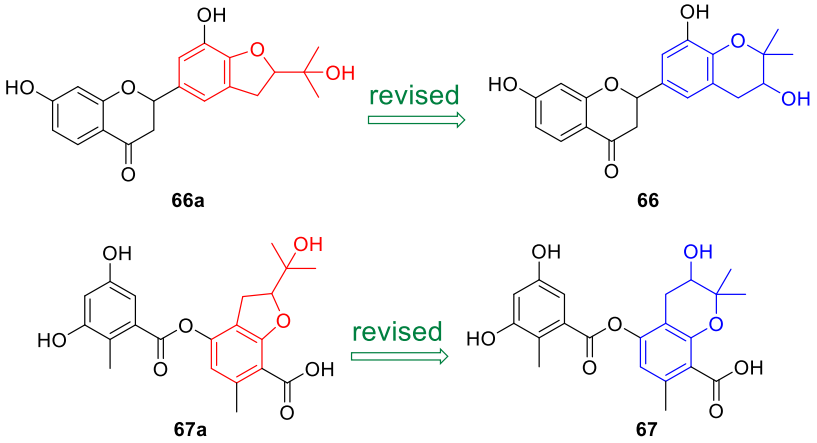

Figure 7. Reassignments of compounds originally misassigned as having moiety D.

($CDCl_3$, 400 MHz) δ_H 7.83 (1H, d, J = 2.2 Hz, H-2), 7.80 (1H, dd, J = 8.3, 2.2 Hz, H-6), 7.02 (1H, s, OH-4), 6.87 (1H, d, J = 8.3 Hz, H-5), 5.32 (1H, t, J = 7.3 Hz, H-2′), 3.89 (3H, s, H−COOCH_3), 3.37 (2H, d, J = 7.3 Hz, H-1′), 1.75 (3H, s), 1.74 (3H, s); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ_C 167.9, 159.0, 134.5, 131.7, 129.5, 127.5, 121.7, 121.2, 115.2, 52.0, 28.9, 25.7, 17.8.

*Methyl 4-Methoxy-3-prenylbenzoate (**2**).* To a solution of methyl 4-hydroxy-3-prenylbenzoate **1** (220 mg, 1 mmol, 1.0 equiv) in DMF (4 mL) was added sodium carbonate (117 mg, 1.1 mmol, 1.1 equiv) and iodomethane (170 mg, 1.2 mmol, 1.2 equiv), and the mixture was stirred at 25 °C for 4 h. The reaction was quenched by saturated NH_4Cl aqueous solution (40 mL). The organic solvent was removed by rotary evaporation, extracted with EtOAc (3 × 40 mL), washed with brine (50 mL), dried over anhydrous Na_2SO_4, and filtered. After removal of the solvent under vacuum, the residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 50:1) to provide **2** (221 mg, 94% yield) as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.89 (1H, dd, J = 8.5, 2.2 Hz, H-6), 7.82 (1H,

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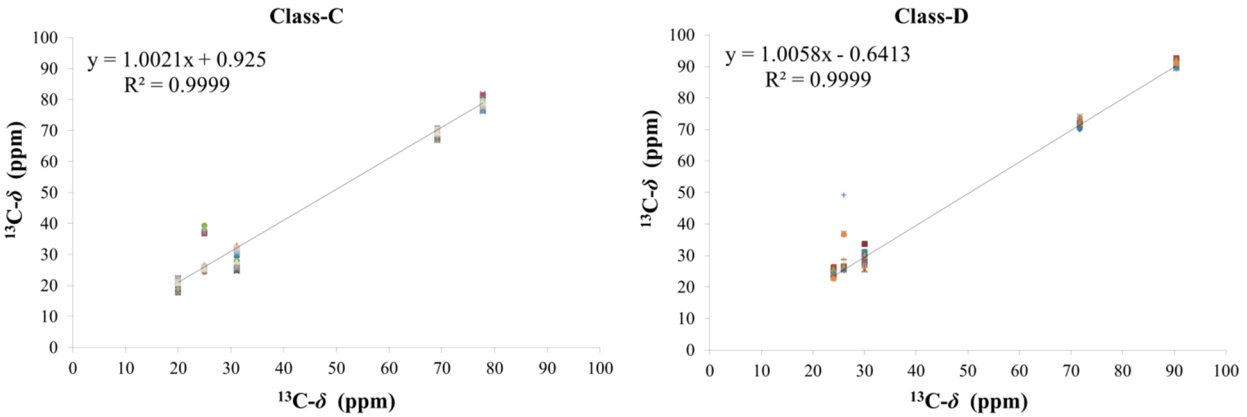

Figure 8. Linear regression analysis of compounds actually bearing moieties C and D.

d, J = 2.2 Hz, H-2), 6.84 (1H, d, J = 8.5 Hz, H-5), 5.29 (1H, t, J = 7.3 Hz, H-2′), 3.88 (3H, s), 3.87 (3H, s), 3.32 (2H, d, J = 7.3 Hz, H-1′), 1.74 (3H, s), 1.71 (3H, s); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 167.1, 161.1, 133.0, 130.7, 130.1, 129.3, 122.1, 121.7, 109.4, 55.5, 51.7, 28.4, 25.8, 17.7; IR (KBr) ν_{max} 2982, 2952, 1715, 1697, 1604, 1501, 1463, 1437, 1333, 1318, 1270, 1192, 1132, 1020, 971, 792 cm^{-1}; HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1259.

*Methyl 3-((3,3-Dimethyloxiran-2-yl)methyl)-4-methoxybenzoate (**3**).* To a solution of **2** (117 mg, 0.5 mmol, 1.0 equiv) in DCM (2 mL) was added 3-chloroperbenzoic acid (*m*-CPBA) (129 mg, 0.75 mmol, 1.5 equiv). The mixture was stirred for 2 h at r.t. After completion of the reaction, the solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 40:1) to provide **3** (221 mg, 97% yield) as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.95 (1H, dd, J = 8.6, 2.2 Hz, H-6), 7.88 (1H, d, J = 2.2 Hz, H-2), 6.88 (1H, d, J = 8.6 Hz, H-5), 3.89 (3H, s), 3.88 (3H, s), 3.00 (1H, dd, J = 6.6, 5.7 Hz, H-2′), 2.91 (1H, dd, J = 14.7, 5.7 Hz, H-1′a), 2.85 (1H, dd, J = 14.7, 6.6 Hz, H-1′b), 1.39 (3H, s), 1.32 (3H, s); $^{13}C\{^1H\}$ NMR data, see Table 1. IR (KBr) ν_{max} 2955, 1717, 1608, 1503, 1460, 1438, 1378, 1326, 1303, 1268, 1199, 1172, 1149, 1130, 1027, 793 cm^{-1}; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{14}H_{18}NaO_4$ 273.1103, found 273.1105.

*Methyl 3-(2,3-Dihydroxy-3-methylbutyl)-4-hydroxybenzoate (**4**).* **1** (110 mg, 0.50 mmol, 1.0 equiv) was dissolved in 2 mL of acetone, and to this, H_2O (2 mL), 4-methylmorpholine *N*-oxide (NMO) (87 mg, 0.75 mmol, 1.5 equiv), and 1% (w/v) osmium tetroxide solution (500 μL) in *t*-BuOH were added dropwise at 0 °C. The mixture was warmed to r.t. and stirred at that temperature for 12 h until completion (monitored by TLC analysis). The organic solvent was removed by rotary evaporation, and the resulting aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with brine (80 mL), dried over anhydrous Na_2SO_4, and filtered. After removal of the solvent under vacuum, the residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 40:1) to provide **4** (117 mg, 92% yield) as a white amorphous powder.[28] ^1H NMR (DMSO-d_6, 400 MHz) δ_H 10.17 (1H, br. s, OH-4), 7.79 (1H, d, J = 2.3 Hz, H-2), 7.65 (1H, dd, J = 8.4, 2.3 Hz, H-6), 6.84 (1H, d, J = 8.4 Hz, H-5), 4.60 (1H, s, OH-2′), 4.23 (1H, s, OH-3′), 3.77 (3H, s, H−COOCH_3), 3.40 (1H, dd, J = 10.3, 1.9 Hz, H-2′), 2.94 (1H, dd, J = 14.0, 1.9 Hz, H-1′a), 2.34 (1H, dd, J = 14.0, 10.3 Hz, H-1′b), 1.11 (3H, s, H-4′), 1.09 (3H, s, H-5′); $^{13}C\{^1H\}$ NMR data, see Table 1.

*Methyl 3-Prenyl-4-(trifluoromethylsulfonyloxy)benzoate (**5**).* To a solution of methyl 4-hydroxy-3-prenylbenzoate **1** (3.2 g, 14.5 mmol, 1.0 equiv) in DCM (20 mL) was added pyridine (1.2 mL, 3.0 equiv) and trifluoromethanesulfonic anhydride (4.9 g, 17.4 mmol, 1.2 equiv). The reaction mixture was stirred at r.t. for 1 h before it was quenched by saturated NH_4Cl aqueous solution (50 mL), and the resulting aqueous layer was extracted with EtOAc (4 × 50 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4, and filtered. After removal of the solvent under vacuum, the residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 50:1) to provide **5** (4.85 g, 95% yield) as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.99 (1H, d, J = 2.2 Hz, H-2), 7.94 (1H, dd, J = 8.5, 2.2 Hz, H-6), 7.32 (1H, d, J = 8.6 Hz, H-5), 5.25 (1H, t, J = 7.3 Hz, H-2′), 3.93 (3H, s, H−COOCH_3), 3.45 (2H, d, J = 7.3 Hz, H-1′), 1.77 (3H, s), 1.72 (3H, s); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 165.8, 150.9, 135.3, 134.9, 132.5, 130.1, 129.1, 121.2, 119.6, 118.5 (q, J = 320.1 Hz, C-OTf), 52.5, 28.3, 25.7, 17.9; IR (KBr) ν_{max} 2980, 2957, 1731, 1612, 1487, 1428, 1298, 1249, 1217, 1141, 1117, 1081, 984, 910, 871, 771, 613 cm^{-1}; HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{15}O_5F_3S$ 352.0592, found 352.0597.

*Methyl 3-(2,3-Dihydroxy-3-methylbutyl)-4-(trifluoromethylsulfonyloxy)benzoate (**6**).* According to the reaction method of **1** to **4**, **6** (1.52 g) was obtained as a colorless oil from **5** (1.54 g) with a yield of 90%. ^1H NMR ($CDCl_3$, 400 MHz) δ_H 8.12 (1H, d, J = 2.2 Hz, H-2), 7.97 (1H, dd, J = 8.6, 2.2 Hz, H-6), 7.33 (1H, d, J = 8.6 Hz, H-5), 3.91 (3H, s, H−COOCH_3), 3.64 (1H, dd, J = 10.9, 2.2 Hz, H-2′), 3.00 (1H, dd, J = 14.2, 2.2 Hz, H-1′a), 2.73 (1H, dd, J = 14.2, 10.9 Hz, H-1′b), 1.30 (3H, s), 1.27 (3H, s); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 165.7, 151.3, 134.0, 132.8, 129.9, 129.7, 121.3, 118.4 (q, J = 320.5 Hz, C-OTf), 77.4, 72.9, 52.5, 32.2, 26.4, 23.6; IR (KBr) ν_{max} 2984, 2970, 1728, 1441, 1418, 1291, 1263, 1248, 1228, 1208, 1186, 1157, 1136, 1114, 1082, 916, 872, 863, 772, 614 cm^{-1}; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{14}H_{17}F_3NaO_7S$ 409.0545, found 409.0538.

*Methyl 3-(3-Hydroxy-3-methyl-2-triethylsilyloxybutyl)-4-(trifluoromethylsulfonyloxy)benzoate (**7**).* **6** (820 mg, 2.12 mmol, 1.0 equiv) was dissolved in 10 mL of DCM, and to this, imidazole (318 mg, 0.45 mmol, 2.2 equiv) and 392 μL of triethylchlorosilane (TESCl) (352 mg, 2.33 mmol, 1.1 equiv) were added slowly at 0 °C. The reaction mixture was warmed to r.t. and stirred at that temperature for 2 h before it was quenched with saturated NH_4Cl aqueous solution (80 mL). The resulting aqueous layer was extracted with EtOAc (3 × 80 mL), and the combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4, and filtered. After removal of the solvent under vacuum, the residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 30:1) to provide **7** (881 mg, 83% yield) as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ_H 8.05 (1H, d, J = 2.2 Hz, H-2), 8.00 (1H, dd, J = 8.6, 2.2 Hz, H-6), 7.36 (1H, d, J = 8.6 Hz, H-5), 3.94 (3H, s, H−COOCH_3), 3.81 (1H, dd, J = 10.1, 2.6 Hz, H-2′), 3.06 (1H, dd, J = 13.9, 2.6 Hz, H-1′a), 2.73 (1H, dd, J = 13.9, 10.1 Hz, H-1′b), 1.25 (3H, s), 1.24 (3H, s), 0.78 (9H, t, J = 8.0 Hz, H−CH_2CH_3), 0.25 (6H, m, H-CH_2CH$_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 165.5, 151.5, 134.9, 133.0, 129.8, 129.7, 121.3, 118.5 (q, J = 320.2 Hz, C-OTf), 79.4, 73.0, 52.5, 33.9, 26.3, 24.2, 6.8, 4.9; IR (KBr) ν_{max} 2955, 2912, 2908, 1726, 1608, 1589, 1489, 1458, 1449, 1436, 1415, 1377, 1358, 1290, 1240, 1205, 1106, 1005, 767, 744 cm^{-1};

https://dx.doi.org/10.1021/acs.joc.0c02409
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HRMS (EI) m/z: $[M]^+$ calcd for $C_{20}H_{31}O_7F_3SiS$ 500.1512, found 500.1503.

*Methyl 2,2-Dimethyl-3-triethylsilyloxychromane-6-carboxylate (**8**).* To a solution of **7** (447 mg, 0.89 mmol, 1.0 equiv) in toluene (5 mL) was added $Pd(OAc)_2$ (20 mg, 0.089 mmol, 0.1 equiv), 1,1′-bis(diphenyphosphino)ferrocene (DPPF) (99 mg, 0.18 mmol, 0.2 equiv), and K_2CO_3 (370 mg, 2.68 mmol, 3.0 equiv) under N_2 protection. The reaction mixture was stirred at 90 °C for 10 h before it was quenched by saturated NH_4Cl aqueous solution (50 mL), and the resulting aqueous layer was extracted with EtOAc (3 × 50 mL). After removal of the solvent under vacuum, the residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 50:1) to provide **8** (222 mg, 71% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.77 (1H, dd, J = 8.4, 2.2 Hz, H-6), 7.76 (1H, d, J = 2.2 Hz, H-2), 6.79 (1H, d, J = 8.4 Hz, H-5), 3.86 (3H, s, H−COOCH_3), 3.82 (1H, dd, J = 9.0, 5.5 Hz, H-2′), 2.93 (1H, dd, J = 16.4, 5.5 Hz, H-1′a), 2.74 (1H, dd, J = 16.4, 9.0 Hz, H-1′b), 1.38 (3H, s), 1.21 (3H, s), 0.96 (9H, t, J = 7.9 Hz, H−CH_2CH_3), 0.63 (6H, q, J = 7.9 Hz, H-CH_2CH_3); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 167.0, 157.3, 131.7, 129.3, 121.9, 120.1, 116.9, 78.4, 70.2, 51.7, 32.1, 26.2, 19.7, 6.8, 5.0; IR (KBr) ν_{max} 2955, 2912, 2878, 1720, 1615, 1585, 1495, 1459, 1438, 1320, 1304, 1280, 1265, 1193, 1178, 1155, 1145, 1114, 1015, 846, 770, 746 cm^{-1}; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{19}H_{30}NaO_4Si$ 373.1811, found 373.1807.

*Methyl 3-Hydroxy-2,2-dimethylchromane-6-carboxylate (**9**).* Tetrabutylammonium fluoride (TBAF) (187 mg, 0.72 mmol, 2.0 equiv) was added to a stirred mixture of **8** (125 mg, 0.36 mmol, 1.0 equiv) in THF (3 mL). The reaction mixture was stirred at r.t. for 20 min until completion (monitored by TLC analysis). The organic solvent was removed by rotary evaporation, and then, the residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 20:1) to provide **9** (121 mg, 96% yield) as a colorless oil.[28] ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.78 (1H, dd, J = 9.0, 2.0 Hz, H-6), 7.77 (1H, d, J = 2.0 Hz, H-2), 6.82 (1H, d, J = 9.0 Hz, H-5), 3.86 (3H, s, H−COOCH_3), 3.83 (1H, dd, J = 5.8, 4.9 Hz, H-2′), 3.07 (1H, dd, J = 16.8, 4.9 Hz, H-1′a), 2.79 (1H, dd, J = 16.8, 5.8 Hz, H-1′b), 1.36 (3H, s), 1.33 (3H, s); ^{13}C{^{1}H} NMR data, see Table 1.

*Methyl 2-(2-Hydroxypropan-2-yl)-2,3-dihydrobenzofuran-5-carboxylate (**10**).* To a solution of **6** (102 mg, 0.26 mmol, 1.0 equiv) in toluene (2.5 mL) was added $Pd(OAc)_2$ (5.9 mg, 0.026 mmol, 0.1 equiv), 1,1′-bis(diphenyphosphino)ferrocene (DPPF) (29.3 mg, 0.052 mmol, 0.2 equiv), and 792 μL of 1 M *t*-BuONa (79 mg, 0.79 mmol, 3.0 equiv) under N_2 protection. The reaction mixture was stirred at 90 °C for 12 h. The reaction was quenched by saturated NH_4Cl aqueous solution (20 mL), and the resulting aqueous layer was extracted with EtOAc (3 × 20 mL). After removal of the solvent under vacuum, the residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 20:1) to provide **10** (47 mg, 76% yield) as a colorless oil.[28] ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.85 (1H, dd, J = 8.7, 1.9 Hz, H-6), 7.84 (1H, d, J = 1.9 Hz, overlapped, H-2), 6.77 (1H, d, J = 8.7 Hz, H-5), 4.68 (1H, t, J = 9.0 Hz, H-2′), 3.86 (3H, s, H−COOCH_3), 3.17 (2H, d like, H-1′), 1.34 (3H, s), 1.21 (3H, s); ^{13}C{^{1}H} NMR data, see Table 1.

NMR Calculations. Conformational analysis was performed by using the MMFF94 molecular mechanics force field. The molecules of **3**, **4**, **9**, and **10** showed 14, 26, 6, and 7 conformers within an energy window of 3.0 kcal/mol, respectively. NMR calculations were carried out by Gaussian 09 following the protocol adapted from Tantillo.[29] The theoretical calculation of NMR was conducted using the GIAO method at the mPW1PW91/6-311+G(2d,p) level. Finally, the calculated NMR chemical shift values were averaged according to a Boltzmann distribution for each conformer and fit to the experimental values by linear regression.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02409.

Additional tables and spectra for compounds **1**−**10** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the Yunnan Provincial Science and Technology Department (No. 2017ZF003-04).

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