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An ingenious method for the determination of the relative and absolute configurations of compounds containing aryl-glycerol fragments by ^{1}H NMR spectroscopy†

Xu Zhang, Kai-Zhou Lu, Hai-Wei Yan, Zi-Ming Feng, Ya-Nan Yang, Jian-Shuang Jiang and Pei-Cheng Zhang *

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A concise method was established to determine the relative and absolute configurations of aryl-glycerols that depend on the chemical shift differences ($\Delta\delta$) of the diastereotopic methylene protons (H-3) by ^{1}H NMR spectroscopy. When using DMSO-d_6 as the preferred solvent, the *threo* configuration corresponded to a larger $\Delta\delta_{H3a-H3b}$ value (>0.15 ppm), whereas the *erythro* configuration (<0.07 ppm) corresponded to a smaller value. Furthermore, the absolute configurations were determined with the aid of a simple acylation reaction through camphanoyl chloride. In the *threo* enantiomers, the $\Delta\delta$ value of the 1*R*,2*R* configuration was <0.15 ppm, and that of the 1*S*,2*S* configuration was >0.20 ppm. In the *erythro* enantiomers, the $\Delta\delta$ value of 1*R*,2*S* was >0.09 ppm, and that of 1*S*,2*R* was <0.05 ppm. Remarkably, this empirical rule is invalid in $CDCl_3$. In addition, this method was also verified by a quantum ^{1}H NMR calculation.

Introduction

Chiral alcohols, such as chiral secondary alcohols, *prim*,*sec*-diols, *sec*,*sec*-diols and 1,2,3-*prim*,*sec*,*sec*-triols, are ubiquitous in natural products and synthetic products. The assignment of their relative and absolute configurations is always a challenging task. Because of the difficulty of growing crystals of these compounds and the lack of distinct Cotton effects in their electronic circular dichroism (ECD) spectra, NMR spectroscopy is suitable for this purpose and is readily available compared with other methods. For instance, the absolute configurations of chiral secondary alcohols were determined using Mosher's method by ^{1}H NMR spectroscopy;[1] the relative configurations of some *sec*,*sec*-diols were assigned using a JBCA (*J*-based configuration analysis) method[2] or by comparison of their ^{13}C-$\Delta\delta$ behaviors in a chiral bidentate NMR solvent.[3] We have also developed two approaches to (1) discriminate the *threo* and *erythro* configurations of vicinal diol in polyacetylene glycosides by the $^3J_{HH}$ value using acetic acid-d_4/D_2O as the solvent;[4] and (2) determine the absolute configurations of 2-hydroxy phenylethanoid glycosides (*prim*,*sec*-diol derivatives) by the chemical shift differences ($\Delta\delta$) of the diastereotopic methylene protons.[5]

Aryl-glycerols (AGs), a kind of 1,2,3-*prim*,*sec*,*sec*-triols, are frequent in natural products such as phenylpropanoids and lignans[6–15] and are important intermediates in many chemical syntheses.[16–21] Due to the conformational flexibility of the triol chain in AGs, determining the relative and absolute configurations is significantly challenging. Recently, Mosher's method was developed to assign the absolute configuration of AGs by comparing the ^{1}H NMR data of the tris-(*R*)- and the tris-(*S*)-MPA ester derivatives with those of the AGs.[22,23] However, the inability to prepare tris-MPA ester derivatives for trace compounds and the complex rules governing the comparison of the $\Delta\delta^{RS}$(H-1) and $|\Delta\delta^{RS}_{H(2)} - \Delta\delta^{RS}_{H(1)}|$ of AGs, to some extent, have limited the application of this method. For some naturally occurring AGs, the regular $\Delta\delta_{C1-C2}$ parameters have been used to differentiate only the *threo* and *erythro* relative

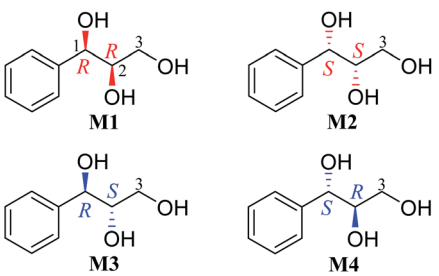

Fig. 1 Structures of compounds M1–M4.

State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing 100050, People's Republic of China. E-mail: pczhang@imm.ac.cn

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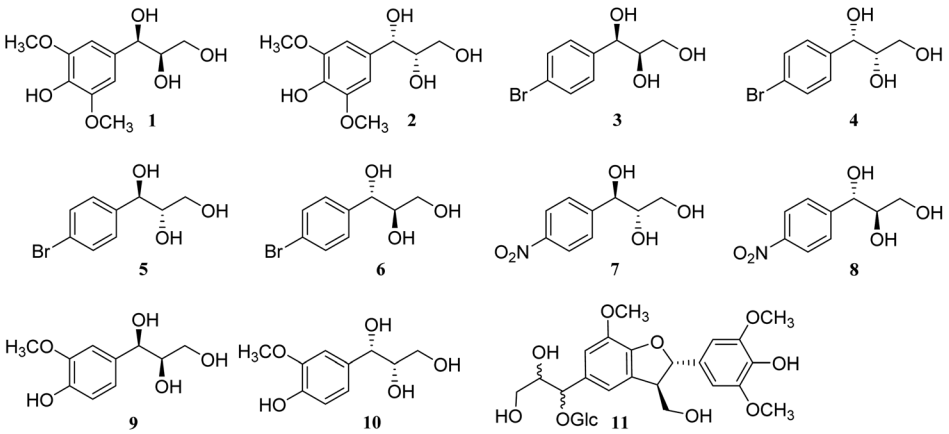


Fig. 2 Structures of compounds **1–11**.

configurations.[9,15] However, we found that this rule is not applicable to AGs without substituent groups on the benzene ring. Therefore, a new reliable method to determine the relative and absolute configurations of AGs is a worthwhile task.

Results and discussion

Our recent study found that the *threo* and *erythro* configurations of H-7 and H-8 in 8,4′-oxyneolignans can be discriminated by the values of $\Delta\delta_{H9a-H9b}$ of methylene protons in ^{1}H NMR spectroscopy.[24] When we determined the configurations of a pair of *threo* syringylglycerol enantiomers (**1** and **2**) obtained from the *Arnebia euchroma*, a careful comparison of the ^{1}H NMR spectroscopic data of **1** in methanol-d_4 with the corresponding data in *erythro* syringylglycerol in the literature showed that there were significant differences.[9] The value of $\Delta\delta_{H3a-H3b}$ of methylene protons in **1** is 0.13 ppm, while the value is only 0.07 ppm in *erythro* syringylglycerol. Surprisingly, this result is similar to the rule in 8,4′-oxyneolignans. For AGs without large steric hindrance groups, can the $\Delta\delta_{H3a-H3b}$ values of the methylene groups reflect their relative stereochemistry? To explore and summarize this phenomenon, two pairs of 1-phenylpropane-1,2,3-triol enantiomers were prepared (**M1–M4**) through the hydrolysis of (2*R*,3*R*)-3-phenyl-2-oxiranemethanol and (2*S*,3*S*)-3-phenyl-2-oxiranemethanol (Fig. 1). The ^{1}H NMR spectra of compounds **M1** and **M4** in methanol-d_4 were recorded. Obviously, the $\Delta\delta_{H3a-H3b}$ (0.14 ppm) value of methylene protons in the *threo* configuration was remarkably larger than the corresponding value (0.06 ppm) in the *erythro* configuration (Fig. 3). Considering that deuterated solvents have a major impact on the chemical shifts of methylene protons, the ^{1}H NMR spectra of compounds **M1** and **M4** were recorded in other deuterated solvents, acetone-d_6, pyridine-d_5, DMSO-d_6, and $CDCl_3$, as shown in Fig. 3. Similarly, in the *threo* configurations, the $\Delta\delta_{H3a-H3b}$ values of methylene protons were 0.12 in acetone-d_6, 0.15 in pyridine-d_5, and 0.21 in DMSO-d_6. In the *erythro* configurations, the $\Delta\delta_{H3a-H3b}$ values of methylene protons were 0.00 in acetone-d_6, 0.00 in pyridine-d_5, and 0.06 in DMSO-d_6. Remarkably, there was no obvious difference in $CDCl_3$ (*threo*:

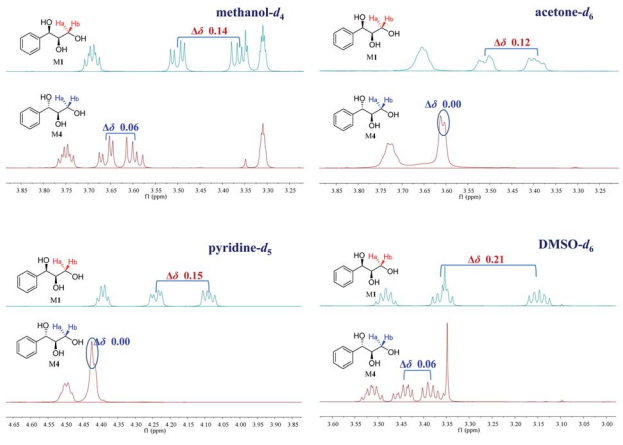
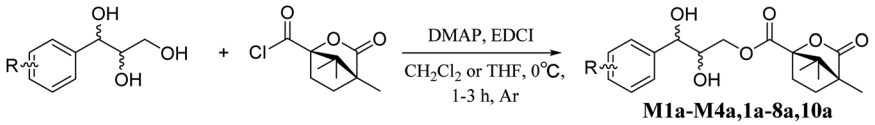


Fig. 3 Influence of different deuterated solvents on the $\Delta\delta_{H3a-H3b}$ values of **M1** and **M4** (^{1}H NMR 500 MHz).

Table 1 $\Delta\delta_{H3a-H3b}$ values (ppm) of the AGs **1–11** in different solvents (^{1}H NMR 500 MHz)

No.	δ_{H3a}	δ_{H3b}	$\Delta\delta_{H3a-H3b}$	Solvent	Relative conf.
1 & **2**	3.50	3.37	0.13	Methanol-d_4	*Threo*
	3.49	3.40	0.09	Acetone-d_6	
3 & **4**	3.55	3.39	0.16	Methanol-d_4	*Threo*
	3.56	3.42	0.14	Acetone-d_6	
	4.27	4.09	0.18	Pyridine-d_5	
	3.39	3.15	0.24	DMSO-d_6	
5 & **6**	3.64	3.59	0.05	Methanol-d_4	*Erythro*
	3.61	3.61	0.00	Acetone-d_6	
	4.39	4.39	0.00	Pyridine-d_5	
	3.42	3.37	0.05	DMSO-d_6	
7 & **8**	3.68	3.65	0.03	Methanol-d_4	*Erythro*
	3.67	3.63	0.04	Acetone-d_6	
	3.42	3.42	0.00	DMSO-d_6	
9 & **10**	3.47	3.34	0.13	Methanol-d_4	*Threo*
	3.31	3.14	0.17	DMSO-d_6	
11	3.52	3.38	0.14	Methanol-d_4	*Threo*
	3.35	3.18	0.17	DMSO-d_6	



Scheme 1 The acylation reaction.

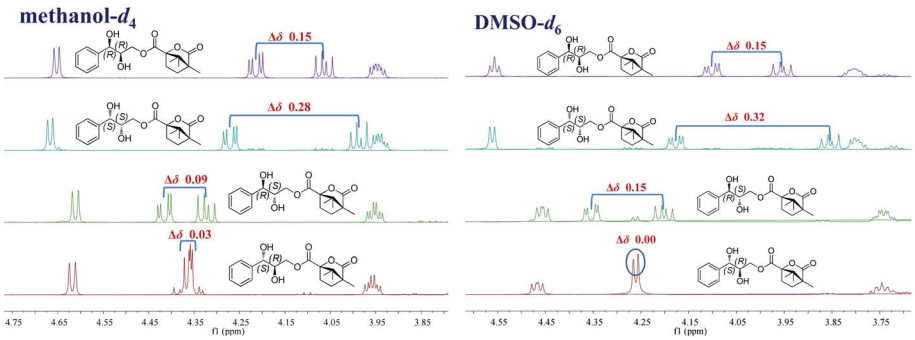


Fig. 4 Influence of different deuterated solvents on the $\Delta\delta_{H3a-H3b}$ values of **M1a–M4a** (^{1}H NMR 500 MHz).

0.09 ppm; *erythro*: 0.07 ppm). In addition, the chemical shift values of methylene protons in the *erythro* configuration were obviously larger than those in the *threo* configuration.

To further confirm the accuracy and reliability of the method and investigate the influence of different substitution groups on the benzene ring, 1-(4-bromophenyl)propane-1,2,3-triol (**3–6**) and 1-(4-nitrophenyl)propane-1,2,3-triol (**7** and **8**) were synthesized through the Sharpless asymmetric epoxidation and hydrolysis reaction (Fig. 2).[25] As expected, larger $\Delta\delta_{H3a-H3b}$ values of methylene protons appeared in the *threo* configurations (**3–4**), and smaller $\Delta\delta_{H3a-H3b}$ values of methylene protons appeared in the *erythro* configurations (**5–8**). Additionally, three natural products, *threo*-1-*C*-guaiacylglycerol (**9** and **10**), obtained from bamboo juice, and compound **11**, obtained from *Cortex Lycii*, were also in accordance with the general trends in methanol-d_4 and DMSO-d_6 (Fig. 2). Thus, the relative configuration of AGs can be determined from the $\Delta\delta_{H3a-H3b}$ values of methylene protons of the ^{1}H NMR spectra in methanol-d_4, acetone-d_6, pyridine-d_5, and DMSO-d_6; DMSO-d_6 is the preferred solvent (Table 1).

Then, a more challenging task is how to determine the absolute configurations of a pair of enantiomers. Considering the conformational flexibility of the triol chain in AGs, the introduction of a chiral auxiliary agent bearing a larger steric hindrance group may be an efficient approach. Camphanoyl chloride, a acylating agent containing two special stereogenic centers, is frequently utilized to determine enantiomeric purity in organic synthesis and its derivatives was also used to assign absolute configurations of chiral alcohols by NMR.[26,27] It made molecules more rigid due to its steric hindrance in conformational studies. These features inspired us to thoroughly investigate the relationship between the chemical shift differences of methylene protons and the absolute configurations of monocamphanoyl AGs.

Accordingly, acylation reactions (Scheme 1) were carried out using (−)-1*S*,4*R*-camphanoyl chloride and two pairs of 1-phenyl glycerol enantiomers **M1–M4** as raw materials, and four products (**M1a–M4a**) were successfully obtained. Their ^{1}H NMR spectra were measured in several deuterated solvents, including methanol-d_4, DMSO-d_6, acetone-d_6, pyridine-d_5, and $CDCl_3$. To our delight, in methanol-d_4 and DMSO-d_6, the $\Delta\delta_{H3a-H3b}$ values

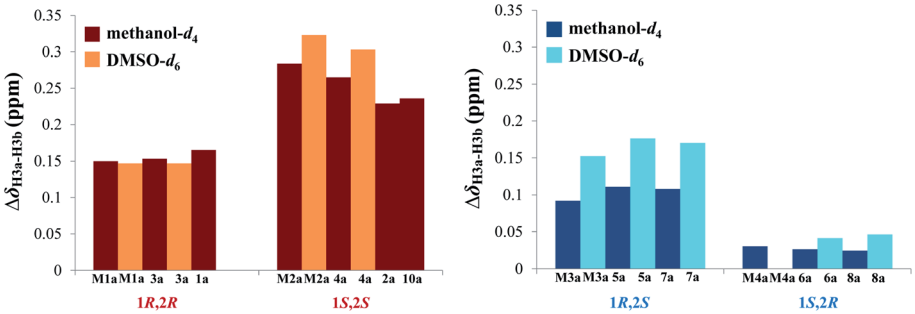


Fig. 5 $\Delta\delta_{H3a-H3b}$ values (ppm) of the acylation products.

of methylene protons showed obvious differences in the *threo* and *erythro* configurations. In the *threo* enantiomers, the $\Delta\delta_{H3a-H3b}$ values of methylene protons in **M1a** (1*R*,2*R*) were 0.15 and 0.15, respectively, while the $\Delta\delta_{H3a-H3b}$ values in **M2a** (1*S*,2*S*) were 0.28 and 0.32, respectively (Fig. 4). In the *erythro* system, the $\Delta\delta_{H3a-H3b}$ values of methylene protons in **M3a** (1*R*,2*S*) were 0.09 and 0.15, respectively, while the $\Delta\delta_{H3a-H3b}$ values in **M4a** (1*S*,2*R*) were 0.03 and 0.00, respectively. The chemical shift differences were high enough to discriminate the absolute configuration, especially when using DMSO-d_6 as the solvent. However, in the other three deuterated solvents, acetone-d_6, $CDCl_3$, and pyridine-d_5, the $\Delta\delta_{H3a-H3b}$ values were irregular. These results suggested that the anisotropic effect of camphanoyl could be efficiently and selectively space oriented toward the methylene protons of mono-camphanoyl AGs in methanol-d_4 and DMSO-d_6. To further verify the reliability of the method, derivatives **1a–8a,** and **10a** were also successfully synthesized. As expected, the rule still applies in methanol-d_4 and DMSO-d_6 (Fig. 5). Furthermore, the theoretical ^{1}H NMR calculation of **M1a–M4a** was carried out by GIAO NMR calculation method in DMSO (the detailed procedure see ESI†).[28] The calculated results were better match with the experimental data ($R^2 \geq 0.995$) (Fig. 6). The calculated $\Delta\delta_{H3a-H3b}$ values were **M1a:** 0.08, **M2a:** 0.37, **M3a:** 0.72, and **M4a:** 0.06, respectively. This result verified our method was also reliable by quantum chemical calculation. These results confirmed that camphanoyl chloride is a suitable pure chiral derivatizing agent to assign the absolute configuration of AGs.

Experimental section

General experimental procedures

The optical rotations were recorded with a RUDOLPH automatic V polarimeter (RUDOLPH, Hackettstown, NJ, USA). The NMR spectra were recorded with a Bruker 500 MHz (Bruker-Biospin, Billerica, MA, USA). HRESIMS reports were obtained from an Agilent 6520 HPLC-Q-TOF (Agilent Technologies, Waldbronn, Germany) and Q Exactive Focus LCMSMS (Thermo Scientific, MA, USA). Preparative HPLC separations were performed using a Shimadzu LC-10AT with an ODS-A column (250 mm × 10 mm, 5 μm; YMC Corp., Kyoto, Japan). An Agilent 1200 series system with an Apollo C 18 column (250 mm × 4.6 mm, 5 μm; Alltech Corp., KY, USA) was used for HPLC-DAD analysis. All reactions were magnetically stirred with a DF-101S magnetic stirrer (Hengfengchangwei Technology Co. Ltd, Beijing, China). Commercially available reagents were used without further purification unless otherwise stated. All reactions were monitored by TLC with silica gel pre-coated GF254 plates and HPLC-DAD.

Structure characterization and synthesis procedures

(2*S*,3*S*)-3-Phenyl-2-oxiranemethanol and (2*R*,3*R*)-3-phenyl-2-oxiranemethanol. The asymmetric epoxidation was carried out according to the Sharpless asymmetric Epoxidation. Colorless oil; the specific rotations were $[\alpha]_D^{20}$ −47 (*c* 0.1 methanol) and $[\alpha]_D^{20}$ +70 (*c* 0.1 methanol), respectively; ^{1}H-NMR (500 MHz, methanol-d_4): δ 7.27–7.35 (5H, one mono-substituted benzene ring system), 3.87 (1H, dd, J = 12.5, 3.0 Hz), 3.83 (1H, d, J = 2.0 Hz), 3.67 (1H, dd, J = 12.5, 5.5 Hz), 3.15 (1H, m); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 136.8, 128.7, 128.7, 128.5, 125.9, 125.9, 62.5, 61.3, 55.7; HRESIMS *m*/*z* 151.0754 $[M + H]^+$ (calcd for $C_9H_{11}O_2$ 151.0753).

A solution of (2*R*,3*R*)-3-phenyl-2-oxiranemethanol (100 mg, 0.6 mmol) and acetic acid (0.5 ml) in acetonitrile was stirred by rotary evaporator at 55 °C until the solution was dry. Through the analysis of HPLC, the (2*R*,3*R*)-3-phenyl-2-oxiranemethanol was completely hydrolyzed. The residue was separated by preparative HPLC (MeOH/H_2O, 25 : 75, v\v, HOAc, 0.1%) to

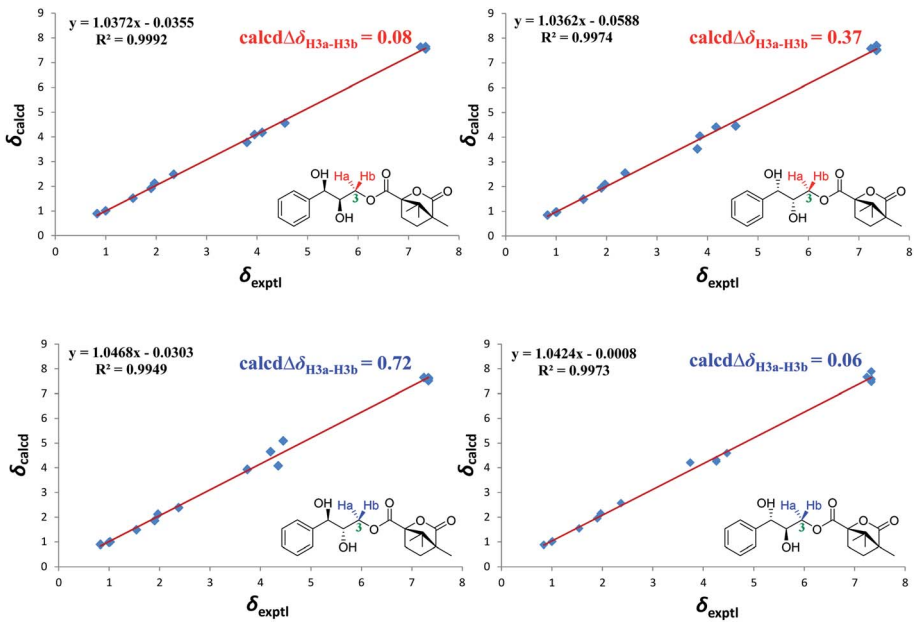


Fig. 6 Linear correlation plots of predicted *versus* experimental ^{1}H NMR chemical shifts.

afford **M1** (45 mg) and **M4** (50 mg). The hydrolysis procedure of (2*S*,3*S*)-3-phenyl-2-oxiranemethanol was same as the above. The residue was separated by preparative HPLC (MeOH/H_2O, 25 : 75, v\v, HOAc, 0.1%) to afford **M2** and **M3**. Compounds **M1–M4** are known compounds and they were identified by comparing their spectral data with those of the known compounds.[22]

(1*R*,2*R*)-1-Phenylpropane-1,2,3-triol and (1*S*,2*S*)-1-phenylpropane-1,2,3-triol (M1 and M2). Colorless oil; the specific rotations were $[\alpha]_D^{20}$ −39 (*c* 0.1 methanol) and $[\alpha]_D^{20}$ +33 (*c* 0.1 methanol), respectively. ^{1}H-NMR (500 MHz, methanol-d_4): *δ* 7.25–7.40 (5H, one mono-substituted benzene ring system), 4.63 (1H, d, J = 5.5 Hz), 3.69 (1H, m), 3.50 (1H, dd, J = 11.5, 4.0 Hz), 3.36 (1H, dd, J = 11.5, 6.0 Hz). ^{1}H-NMR (500 MHz, acetone-d_6): *δ* 7.23–7.41 (5H, one mono-substituted benzene ring system), 4.68 (1H, d, J = 5.5 Hz), 3.65 (1H, m), 3.51 (1H, dd, J = 11.0, 3.5 Hz), 3.39 (1H, dd, J = 11.5, 5.5 Hz). ^{1}H-NMR (500 MHz, pyridine-d_5): *δ* 7.84 (2H, d, J = 7.5 Hz), 7.40 (2H, t, J = 7.5 Hz), 7.30 (1H, t, J = 7.5 Hz), 5.39 (1H, d, J = 5.5 Hz), 4.39 (1H, m), 4.24 (1H, dd, J = 11.0, 4.5 Hz), 4.09 (1H, dd, J = 11.0, 6.0 Hz). ^{1}H-NMR (500 MHz, DMSO-d_6): *δ* 7.19–7.34 (5H, one mono-substituted benzene ring system), 4.53 (1H, t, J = 5.0 Hz), 3.48 (1H, m), 3.36 (1H, m), 3.15 (1H, m). ^{1}H-NMR (500 MHz, $CDCl_3$): *δ* 7.28–7.33 (5H, one mono-substituted benzene ring system), 4.66 (1H, d, J = 5.5 Hz), 3.76 (1H, brs), 3.54 (1H, brd, J = 11.0 Hz), 3.46 (1H, brd, J = 11.0 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$): *δ* 140.6, 128.6, 128.6, 128.2, 126.8, 126.8, 76.2, 74.8, 63.2; HRESIMS refer to compounds **M3** and **M4**.

(1*R*,2*S*)-1-Phenylpropane-1,2,3-triol and (1*S*,2*R*)-1-phenylpropane-1,2,3-triol (M3 and M4). Colorless oil; the specific rotations were $[\alpha]_D^{20}$ −47 (*c* 0.1 methanol) and $[\alpha]_D^{20}$ +27 (*c* 0.1 methanol), respectively. ^{1}H-NMR (500 MHz, methanol-d_4): *δ* 7.24–7.41 (5H, one mono-substituted benzene ring system), 4.61 (1H, d, J = 6.5 Hz), 3.75 (1H, m), 3.66 (1H, dd, J = 11.5, 3.5 Hz), 3.60 (1H, dd, J = 11.5, 6.5 Hz); ^{1}H-NMR (500 MHz, acetone-d_6): *δ* 7.21–7.41 (5H, one mono-substituted benzene ring system), 4.67 (1H, d, J = 4.0 Hz), 3.73 (1H, m), 3.61 (2H, overlap). ^{1}H-NMR (500 MHz, pyridine-d_5): *δ* 7.88 (2H, d, J = 8.0 Hz), 7.40 (2H, t, J = 8.0 Hz), 7.30 (1H, t, J = 8.0 Hz), 5.35 (1H, d, J = 6.0 Hz), 4.50 (1H, m), 4.42 (2H, overlap). ^{1}H-NMR (500 MHz, DMSO-d_6): *δ* 7.19–7.34 (5H, one mono-substituted benzene ring system), 4.42 (1H, overlap), 3.51 (1H, m), 3.44 (1H, m), 3.38 (1H, m). ^{1}H-NMR (500 MHz, $CDCl_3$): *δ* 7.30–7.39 (5H, one mono-substituted benzene ring system), 4.89 (1H, d, J = 5.0 Hz), 3.85 (1H, m), 3.74 (1H, dd, J = 11.0, 5.5 Hz), 3.67 (1H, dd, J = 11.0, 3.5 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$): *δ* 140.4, 128.8, 128.8, 128.3, 126.3, 126.3, 76.1, 74.6, 63.1; HRESIMS m/z 191.0679 $[M + Na]^+$ (calcd for $C_9H_{12}O_3Na$ 191.0679).

(2*R*,3*R*)-2,3-Dihydroxy-3-phenylpropyl(1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (M1a). Compound **M1** (10 mg, 0.06 mmol) solution in dry CH_2Cl_2 or THF was added to a solution of camphanic acid chloride (13 mg, 0.06 mmol), EDCI (11.4 mg, 0.06 mmol) and DMAP (3.6 mg, 0.03 mmol) at 0 °C with the protection of argon gas. The reaction was stirred at 0 °C for 1 h and was detected by TLC. Then, the reaction was quenched by dropwise addition of H_2O. The suspension was extracted with CH_2Cl_2. Removal of the solvent under reduced pressure and purification of the residue by preparative HPLC, eluting with 40% acetonitrile/H_2O, gave the **M1a** 8.7 mg. Colorless oil; ^{1}H-NMR (500 MHz, methanol-d_4): *δ* 7.27–7.42 (5H, one mono-substituted benzene ring system), 4.65 (1H, d, J = 5.5 Hz), 4.21 (1H, dd, J = 11.5, 3.5 Hz), 4.06 (1H, dd, J = 11.5, 7.0 Hz), 3.95 (1H, m), 2.47 (1H, m), 2.03 (1H, m), 1.96 (1H, m), 1.62 (1H, m), 1.09 (3H, s), 1.09 (3H, s), 0.94 (3H, s). ^{1}H-NMR (500 MHz, DMSO-d_6): *δ* 7.23–7.38 (5H, one mono-substituted benzene ring system), 4.56 (1H, t, J = 5.0 Hz), 4.10 (1H, dd, J = 11.0, 3.5 Hz), 3.95 (1H, dd, J = 11.0, 7.5 Hz), 3.80 (1H, m), 2.35 (1H, m), 1.97 (1H, m), 1.90 (1H, m), 1.54 (1H, m), 1.01 (3H, s), 1.00 (3H, s), 0.83 (3H, s). ^{1}H-NMR (500 MHz, acetone-d_6): *δ* 7.26–7.45 (5H, one mono-substituted benzene ring system), 4.73 (1H, t, J = 5.0 Hz), 4.24 (1H, dd, J = 11.5, 3.5 Hz), 4.11 (1H, dd, J = 11.5, 7.0 Hz), 3.98 (1H, m), 2.46 (1H, m), 2.01 (1H, m), 1.95 (1H, m), 1.60 (1H, m), 1.09 (3H, s), 1.05 (3H, s), 0.92 (3H, s). ^{1}H-NMR (500 MHz, pyridine-d_5): *δ* 7.80 (2H, d, J = 7.5 Hz), 7.42 (2H, d, J = 7.5 Hz), 7.32 (1H, t, J = 7.5 Hz), 5.22 (1H, d, J = 5.0 Hz), 4.75 (1H, dd, J = 11.0, 7.5 Hz), 4.70 (1H, dd, J = 11.0, 4.0 Hz), 4.52 (1H, m), 2.47 (1H, m), 1.99 (1H, m), 1.82 (1H, m), 1.57 (1H, m), 1.06 (3H, s), 1.05 (3H, s), 1.02 (3H, s). ^{1}H-NMR (500 MHz, $CDCl_3$): *δ* 7.30–7.37 (5H, one mono-substituted benzene ring system), 4.68 (1H, d, J = 7.0 Hz), 4.25 (1H, dd, J = 11.5, 3.5 Hz), 4.11 (1H, dd, J = 11.5, 6.5 Hz), 3.98 (1H, m), 2.41 (1H, m), 2.02 (1H, m), 1.92 (1H, m), 1.69 (1H, m), 1.11 (3H, s), 1.05 (3H, s), 0.96 (3H, s). ^{13}C-NMR (125 MHz, methanol-d_4): *δ* 180.3, 168.7, 142.9, 129.3, 129.3, 128.8, 127.9, 127.9, 92.9, 75.6, 74.5, 67.6, 56.0, 55.4, 31.5, 29.9, 17.1, 17.0, 9.9; HRESIMS m/z 371.1465 $[M + Na]^+$ (calcd for $C_{19}H_{24}O_6Na$ 371.1458).

(2*S*,3*S*)-2,3-Dihydroxy-3-phenylpropyl(1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (M2a). The synthesis procedure of **M2a** was same with the **M1a**. Colorless oil; ^{1}H-NMR (500 MHz, methanol-d_4): *δ* 7.27–7.41 (5H, one mono-substituted benzene ring system), 4.67 (1H, d, J = 6.0 Hz), 4.27 (1H, dd, J = 11.0, 3.5 Hz), 3.99 (1H, dd, J = 11.0, 6.5 Hz), 3.94 (1H, m), 2.49 (1H, m), 2.04 (1H, m), 1.97 (1H, m), 1.63 (1H, m), 1.11 (3H, s), 1.09 (3H, s), 0.94 (3H, s). ^{1}H-NMR (500 MHz, DMSO-d_6): *δ* 7.23–7.37 (5H, one mono-substituted benzene ring system), 4.56 (1H, d, J = 5.0 Hz), 4.18 (1H, dd, J = 11.0, 3.5 Hz), 3.85 (1H, dd, J = 11.0, 7.0 Hz), 3.80 (1H, m), 2.38 (1H, m), 1.97 (1H, m), 1.90 (1H, m), 1.54 (1H, m), 1.01 (3H, s), 1.00 (3H, s), 0.83 (3H, s). ^{1}H-NMR (500 MHz, acetone-d_6): *δ* 7.25–7.45 (5H, one mono-substituted benzene ring system), 4.73 (1H, d, J = 5.5 Hz), 4.29 (1H, dd, J = 11.0, 4.0 Hz), 4.03 (1H, dd, J = 11.0, 6.5 Hz), 3.97 (1H, m), 2.49 (1H, m), 2.02 (1H, m), 1.96 (1H, m), 1.60 (1H, m), 1.10 (3H, s), 1.05 (3H, s), 0.92 (3H, s). ^{1}H-NMR (500 MHz, pyridine-d_5): *δ* 7.80 (2H, d, J = 8.0 Hz), 7.42 (2H, d, J = 8.0 Hz), 7.32 (1H, t, J = 8.0 Hz), 5.24 (1H, d, J = 5.0 Hz), 4.80 (1H, dd, J = 11.0, 3.0 Hz), 4.62 (1H, dd, J = 11.0, 7.0 Hz), 4.53 (1H, m), 2.50 (1H, m), 2.01 (1H, m), 1.84 (1H, m), 1.58 (1H, m), 1.06 (3H, s), 1.06 (3H, s), 1.02 (3H, s). ^{1}H-NMR (500 MHz, $CDCl_3$): *δ* 7.30–7.38 (5H, one mono-substituted benzene ring system), 4.68 (1H, d, J = 6.5 Hz), 4.25 (1H, dd, J = 11.5, 3.5 Hz), 4.08 (1H, dd, J = 11.5, 6.5 Hz), 3.98 (1H, m), 2.42 (1H, m), 2.02 (1H, m), 1.92 (1H, m), 1.68 (1H, m), 1.11 (3H, s), 1.06 (3H, s), 0.97 (3H, s). ^{13}C-NMR (125 MHz, methanol-d_4): *δ* 180.3, 168.8, 142.8, 129.3, 129.3,

128.8, 127.9, 127.9, 92.9, 75.6, 74.5, 67.6, 56.0, 55.4, 31.5, 30.0, 17.1, 17.0, 9.9; HRESIMS refer to compound **M1a**.

(2*S*,3*R*)-2,3-Dihydroxy-3-phenylpropyl(1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (M3a). The synthesis procedure of **M3a** was same with the **M1a**. Colorless oil; ^{1}H-NMR (500 MHz, methanol-d_4): δ 7.26–7.42 (5H, one mono-substituted benzene ring system), 4.61 (1H, d, $J = 6.5$ Hz), 4.42 (1H, dd, $J = 11.5$, 3.0 Hz), 4.32 (1H, dd, $J = 11.5$, 7.0 Hz), 3.95 (1H, m), 2.49 (1H, m), 2.04 (1H, m), 1.97 (1H, m), 1.62 (1H, m), 1.10 (3H, s), 1.09 (3H, s), 0.94 (3H, s). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 7.23–7.37 (5H, one mono-substituted benzene ring system), 4.46 (1H, dd, $J = 6.5$, 4.5 Hz), 4.35 (1H, dd, $J = 11.5$, 3.0 Hz), 4.20 (1H, dd, $J = 11.5$, 7.0 Hz), 3.74 (1H, m), 2.39 (1H, m), 1.98 (1H, m), 1.90 (1H, m), 1.55 (1H, m), 1.03 (3H, s), 1.00 (3H, s), 0.83 (3H, s). ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.24–7.44 (5H, one mono-substituted benzene ring system), 4.72 (1H, dd, $J = 6.5$, 4.5 Hz), 4.39 (1H, dd, $J = 11.5$, 3.0 Hz), 4.33 (1H, dd, $J = 11.5$, 7.0 Hz), 4.01 (1H, m), 2.48 (1H, m), 2.00 (1H, m), 1.94 (1H, m), 1.59 (1H, m), 1.09 (3H, s), 1.05 (3H, s), 0.92 (3H, s). ^{1}H-NMR (500 MHz, pyridine-d_5): δ 7.82 (2H, d, $J = 7.5$ Hz), 7.41 (2H, d, $J = 7.5$ Hz), 7.31 (1H, t, $J = 7.5$ Hz), 5.22 (1H, d, $J = 6.5$ Hz), 5.06 (1H, dd, $J = 11.5$, 3.0 Hz), 4.98 (1H, dd, $J = 11.5$, 7.0 Hz), 4.55 (1H, m), 2.49 (1H, m), 1.99 (1H, m), 1.82 (1H, m), 1.57 (1H, m), 1.07 (3H, s), 1.06 (3H, s), 1.05 (3H, s). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.29–7.38 (5H, one mono-substituted benzene ring system), 4.83 (1H, d, $J = 5.5$ Hz), 4.34 (1H, dd, $J = 11.5$, 7.5 Hz), 4.25 (1H, dd, $J = 11.5$, 3.0 Hz), 4.09 (1H, m), 2.40 (1H, m), 2.00 (1H, m), 1.92 (1H, m), 1.67 (1H, m), 1.10 (3H, s), 1.04 (3H, s), 0.95 (3H, s). ^{13}C-NMR (125 MHz, methanol-d_4): δ 180.3, 168.9, 143.2, 129.2, 129.2, 128.6, 128.1, 128.1, 93.0, 75.8, 74.1, 67.8, 56.0, 55.4, 31.5, 30.0, 17.1, 17.0, 9.9; HRESIMS refer to compound **M1a**.

(2*R*,3*S*)-2,3-Dihydroxy-3-phenylpropyl(1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (M4a). The synthesis procedure of **M4a** was same with the **M1a**. Colorless oil; ^{1}H-NMR (500 MHz, methanol-d_4): δ 7.26–7.42 (5H, one mono-substituted benzene ring system), 4.62 (1H, d, $J = 7.0$ Hz), 4.38 (1H, dd, $J = 11.5$, 6.5 Hz), 4.35 (1H, dd, $J = 11.5$, 3.5 Hz), 3.96 (1H, m), 2.49 (1H, m), 2.03 (1H, m), 1.97 (1H, m), 1.62 (1H, m), 1.10 (3H, s), 1.09 (3H, s), 0.94 (3H, s). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 7.22–7.36 (5H, one mono-substituted benzene ring system), 4.47 (1H, dd, $J = 6.5$, 4.5 Hz), 4.26 (2H, overlap), 3.75 (1H, m), 2.38 (1H, m), 1.97 (1H, m), 1.90 (1H, m), 1.54 (1H, m), 1.01 (3H, s), 1.00 (3H, s), 0.84 (3H, s). ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.24–7.44 (5H, one mono-substituted benzene ring system), 4.72 (1H, dd, $J = 6.0$, 4.5 Hz), 4.38 (1H, dd, $J = 11.5$, 7.0 Hz), 4.33 (1H, dd, $J = 11.5$, 3.5 Hz), 4.01 (1H, m), 2.47 (1H, m), 2.00 (1H, m), 1.94 (1H, m), 1.59 (1H, m), 1.09 (3H, s), 1.05 (3H, s), 0.92 (3H, s). ^{1}H-NMR (500 MHz, pyridine-d_5): δ 7.82 (2H, d, $J = 7.5$ Hz), 7.41 (2H, d, $J = 7.5$ Hz), 7.31 (1H, t, $J = 7.5$ Hz), 5.22 (1H, d, $J = 7.0$ Hz), 5.06 (1H, dd, $J = 11.5$, 7.0 Hz), 4.98 (1H, dd, $J = 11.5$, 3.0 Hz), 4.55 (1H, m), 2.50 (1H, m), 1.99 (1H, m), 1.83 (1H, m), 1.57 (1H, m), 1.07 (3H, s), 1.06 (3H, s), 1.04 (3H, s). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.30–7.38 (5H, one mono-substituted benzene ring system), 4.84 (1H, d, $J = 5.5$ Hz), 4.38 (1H, dd, $J = 11.5$, 7.5 Hz), 4.24 (1H, dd, $J = 11.5$, 3.0 Hz), 4.08 (1H, m), 2.41 (1H, m), 2.01 (1H, m), 1.92 (1H, m), 1.68 (1H, m), 1.11 (3H, s), 1.04 (3H, s), 0.95 (3H, s). ^{13}C-NMR (125 MHz, methanol-d_4): δ 180.3, 168.9, 143.2, 129.2, 129.2, 128.6, 128.1, 128.1, 93.0, 75.8, 74.2, 67.8, 56.0, 55.4, 31.5, 30.0, 17.1, 17.0, 9.9; HRESIMS refer to compound **M1a**.

(1*R*,2*R*)-1-(4-Hydroxy-3,5-dimethoxyphenyl)propane-1,2,3-triol and (1*S*,2*S*)-1-(4-hydroxy-3,5-dimethoxyphenyl)propane-1,2,3-triol (1 and 2). Colorless oil; the specific rotations were $[\alpha]_D^{20}$ −100 (*c* 0.1 methanol) and $[\alpha]_D^{20}$ +70 (*c* 0.1 methanol), respectively. ^{1}H-NMR (500 MHz, methanol-d_4): δ 6.68 (2H, brs), 4.53 (1H, d, $J = 6.0$ Hz), 3.67 (1H, m), 3.50 (1H, dd, $J = 11.5$, 4.0 Hz), 3.37 (1H, dd, $J = 11.5$, 6.5 Hz). ^{1}H-NMR (500 MHz, acetone-*d*6): δ 6.69 (2H, brs), 4.56 (1H, d, $J = 6.0$ Hz), 3.62 (1H, m), 3.49 (1H, dd, $J = 11.0$, 4.0 Hz), 3.40 (1H, dd, $J = 11.0$, 6.0 Hz). ^{13}C-NMR (125 MHz, methanol-d_4): δ 149.1, 149.1, 135.9, 134.1, 105.0, 105.0, 77.6, 75.6, 64.2, 56.7, 56.7; HRESIMS *m*/*z* 267.0839 $[M + Na]^+$ (calcd for $C_{11}H_{16}O_6Na$ 267.0837). Compounds **1** and **2** are known compounds and they were identified by comparing their spectral data with those of the known compounds.[8]

4-((1*R*,2*R*)-1,2-Dihydroxy-3-(((1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carbonyl)oxy)propyl)-2,6-dimethoxyphenyl(1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (1a). Compound **1** (6 mg, 0.02 mmol) solution in dry CH_2Cl_2 or THF was added to a solution of camphanic acid chloride (9 mg, 0.04 mmol), EDCI (7.6 mg, 0.04 mmol) and DMAP (2.4 mg, 0.02 mmol) at 0 °C with the protection of argon gas. The reaction was stirred at 0 °C for 1 h and was detected by TLC. Then, the reaction was quenched by dropwise addition of H_2O. The suspension was extracted with CH_2Cl_2. Removal of the solvent under reduced pressure and purification of the residue by preparative HPLC, eluting with 40% acetonitrile/H_2O, gave the **1a** 2.9 mg. Colorless oil; ^{1}H-NMR (500 MHz, methanol-d_4): δ 6.84 (2H, brs), 4.68 (1H, d, $J = 5.0$ Hz), 4.33 (1H, dd, $J = 11.5$, 4.0 Hz), 4.16 (1H, dd, $J = 11.5$, 6.5 Hz), 3.97 (1H, m), 2.67 (1H, m), 2.48 (1H, m), 2.12 (2H, overlap), 2.04 (1H, m), 1.97 (1H, m), 1.70 (1H, m), 1.63 (1H, m), 1.22 (3H, s), 1.14 (3H, s), 1.10 (3H, s), 1.09 (3H, s), 1.08 (3H, s), 0.97 (3H, s); HRESIMS *m*/*z* 605.2593 $[M + H]^+$ (calcd for $C_{31}H_{41}O_{12}$ 605.2593).

4-((1*S*,2*S*)-1,2-Dihydroxy-3-(((1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carbonyl)oxy)propyl)-2,6-dimethoxyphenyl(1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (2a). Compound **2** (4.4 mg, 0.018 mmol) solution in dry CH_2Cl_2 or THF was added to a solution of camphanic acid chloride (7.8 mg, 0.036 mmol), EDCI (6.8 mg, 0.036 mmol) and DMAP (2.2 mg, 0.018 mmol) at 0 °C with the protection of argon gas. The reaction was stirred at 0 °C for 1 h and was detected by TLC. Then, the reaction was quenched by dropwise addition of H_2O. The suspension was extracted with CH_2Cl_2. Removal of the solvent under reduced pressure and purification of the residue by preparative HPLC, eluting with 55% methanol/H_2O, gave the **2a** 2.0 mg. Colorless oil; ^{1}H-NMR (500 MHz, methanol-d_4): δ 6.82 (2H, brs), 4.69 (1H, d, $J = 5.0$ Hz), 4.36 (1H, dd, $J = 11.5$, 4.0 Hz), 4.13 (1H, dd, $J = 11.5$, 6.5 Hz), 3.97 (1H, m), 2.67 (1H, m), 2.49 (1H, m), 2.12 (2H, overlap), 2.02 (2H, overlap), 1.70 (1H, m), 1.63 (1H, m), 1.22 (3H, s), 1.14 (3H, s), 1.11 (3H, s), 1.09 (3H, s), 1.08 (3H, s), 0.94 (3H, s); HRESIMS *m*/*z* 605.2593 $[M + H]^+$ (calcd for $C_{31}H_{41}O_{12}$ 605.2600).

((2*R*,3*R*)-3-(4-Bromophenyl)oxiran-2-yl)methanol and ((2*S*,3*S*)-3-(4-bromophenyl)oxiran-2-yl)methanol. The asymmetric epoxidation was also carried out according to the Sharpless asymmetric Epoxidation. Colorless oil; the specific rotations were $[\alpha]_D^{20}$ +45 (*c* 0.1 methanol) and $[\alpha]_D^{20}$ −25 (*c* 0.1 methanol), respectively. ^{1}H-NMR (500 MHz, methanol-d_4): δ 7.49 (2H, d, J = 8.5 Hz), 7.22 (2H, d, J = 8.5 Hz), 3.85 (1H, dd, J = 12.5, 3.0 Hz), 3.83 (1H, d, J = 1.5 Hz), 3.67 (1H, dd, J = 12.5, 4.5 Hz), 3.13 (1H, m); ^{13}C-NMR (125 MHz, methanol-d_4): δ 138.2, 132.6, 132.6, 128.7, 128.7, 122.8, 63.9, 62.6, 56.2; HRESIMS *m*/*z* 228.9859 $[M + H]^+$ (calcd for $C_9H_{10}O_2Br$ 228.9858).

A solution of ((2*R*,3*R*)-3-(4-bromophenyl)oxiran-2-yl) methanol (65 mg, 0.3 mmol) and acetic acid (0.5 ml) in acetonitrile was stirred by rotary evaporator at 55 °C until the solution was dry. Through the analysis of HPLC, the ((2*R*,3*R*)-3-(4-bromophenyl)oxiran-2-yl)methanol was completely hydrolyzed. The residue was separated by preparative HPLC (MeOH/H_2O, 45 : 55, v\v) to afford **3** (27 mg) and **6** (38 mg). The hydrolysis procedure of ((2*S*,3*S*)-3-(4-bromophenyl)oxiran-2-yl)methanol was same as the above. The residue was separated by preparative HPLC (MeOH/H_2O, 45 : 55, v\v) to afford **4** and **5**. Compounds **3–6** are known compounds and their absolute configurations were identified by comparing the optical rotations of **M1–M4**.

(1*R*,2*R*)-1-(4-Bromophenyl)propane-1,2,3-triol and (1*S*,2*S*)-1-(4-bromophenyl)propane-1,2,3-triol (3 and 4). Colorless oil; the specific rotations were $[\alpha]_D^{20}$ −20 (*c* 0.1 methanol) and $[\alpha]_D^{20}$ +16 (*c* 0.1 methanol), respectively. ^{1}H-NMR (500 MHz, methanol-d_4): δ 7.48 (2H, d, J = 8.5 Hz), 7.33 (2H, d, J = 8.5 Hz), 4.65 (1H, d, J = 5.0 Hz), 3.65 (1H, m), 3.55 (1H, dd, J = 11.5, 4.5 Hz), 3.39 (1H, dd, J = 11.5, 6.5 Hz). ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.49 (2H, d, J = 8.5 Hz), 7.37 (2H, d, J = 8.5 Hz), 4.72 (1H, t, J = 4.5 Hz), 3.64 (1H, m), 3.56 (1H, m), 3.42 (1H, m). ^{1}H-NMR (500 MHz, pyridine-d_5): δ 7.71 (2H, d, J = 8.5 Hz), 7.55 (2H, d, J = 8.5 Hz), 5.38 (1H, d, J = 5.0 Hz), 4.35 (1H, m), 4.28 (1H, dd, J = 11.0, 4.5 Hz), 4.09 (1H, dd, J = 11.0, 6.0 Hz). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 7.48 (2H, d, J = 8.5 Hz), 7.29 (2H, d, J = 8.5 Hz), 4.55 (1H, t, J = 5.0 Hz), 3.46 (1H, m), 3.39 (1H, m), 3.15 (1H, m). ^{13}C-NMR (125 MHz, methanol-d_4): δ 143.0, 132.2, 132.2, 129.8, 129.8, 122.0, 77.1, 74.4, 64.1; HRESIMS *m*/*z* 268.9784 $[M + Na]^+$ (calcd for $C_9H_{11}O_3BrNa$ 268.9778).

(1*R*,2*S*)-1-(4-Bromophenyl)propane-1,2,3-triol and (1*S*,2*R*)-1-(4-bromophenyl)propane-1,2,3-triol (5 and 6). Colorless oil; the specific rotations were $[\alpha]_D^{20}$ −8 (*c* 0.1 methanol) and $[\alpha]_D^{20}$ +12 (*c* 0.1 methanol), respectively. ^{1}H-NMR (500 MHz, methanol-d_4): δ 7.48 (2H, d, J = 8.5 Hz), 7.33 (2H, d, J = 8.5 Hz), 4.58 (1H, d, J = 6.5 Hz), 3.70 (1H, m), 3.64 (1H, dd, J = 11.5, 4.0 Hz), 3.59 (1H, dd, J = 11.5, 6.5 Hz). ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.48 (2H, d, J = 8.5 Hz), 7.37 (2H, d, J = 8.5 Hz), 4.65 (1H, d, J = 6.5 Hz), 3.69 (1H, m), 3.62 (2H, overlap). ^{1}H-NMR (500 MHz, pyridine-d_5): δ 7.74 (2H, d, J = 8.5 Hz), 7.55 (2H, d, J = 8.5 Hz), 5.30 (1H, dd, J = 5.5, 3.0 Hz), 4.42 (1H, m), 4.39 (2H, overlap). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 7.47 (2H, d, J = 8.5 Hz), 7.28 (2H, d, J = 8.5 Hz), 4.41 (1H, t, J = 5.0 Hz), 3.47 (1H, m), 3.42 (1H, m), 3.37 (1H, m). ^{13}C-NMR (125 MHz, methanol-d_4): δ 142.9, 132.0, 130.3, 130.3, 122.0, 76.5, 75.3, 64.3; HRESIMS refer to compounds **3** and **4**.

(2*R*,3*R*)-3-(4-Bromophenyl)-2,3-dihydroxypropyl(1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (3a). The synthesis procedure of **3a** was same with the **M1a**. Colorless oil; ^{1}H-NMR (500 MHz, methanol-d_4): δ 7.50 (2H, d, J = 8.5 Hz), 7.35 (2H, d, J = 8.5 Hz), 4.66 (1H, d, J = 5.0 Hz), 4.26 (1H, dd, J = 11.5, 4.0 Hz), 4.11 (1H, dd, J = 11.5, 7.0 Hz), 3.92 (1H, m), 2.46 (1H, m), 2.03 (1H, m), 1.97 (1H, m), 1.63 (1H, m), 1.09 (6H, overlap), 0.94 (3H, s). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 7.51 (2H, d, J = 8.5 Hz), 7.31 (2H, d, J = 8.5 Hz), 4.56 (1H, d, J = 3.5 Hz), 4.12 (1H, dd, J = 11.0, 3.5 Hz), 3.97 (1H, dd, J = 11.0, 8.0 Hz), 3.79 (1H, m), 2.35 (1H, m), 1.97 (1H, m), 1.90 (1H, m), 1.54 (1H, m), 1.00 (6H, overlap), 0.82 (3H, s). ^{13}C-NMR (125 MHz, methanol-d_4): δ 180.3, 168.7, 142.4, 132.3, 132.3, 129.9, 129.9, 122.3, 92.9, 74.7, 74.2, 67.6, 56.1, 55.4, 31.5, 29.9, 17.1, 17.0, 9.9; HRESIMS *m*/*z* 449.0570 $[M + Na]^+$ (calcd for $C_{19}H_{23}O_6BrNa$ 449.0562).

(2*S*,3*S*)-3-(4-Bromophenyl)-2,3-dihydroxypropyl(1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (4a). The synthesis procedure of **4a** was same with the **M1a**. Colorless oil; ^{1}H-NMR (500 MHz, methanol-d_4): δ 7.50 (2H, d, J = 8.5 Hz), 7.34 (2H, d, J = 8.5 Hz), 4.67 (1H, d, J = 5.0 Hz), 4.31 (1H, dd, J = 11.5, 4.0 Hz), 4.04 (1H, dd, J = 11.5, 7.0 Hz), 3.91 (1H, m), 2.48 (1H, m), 2.04 (1H, m), 1.98 (1H, m), 1.63 (1H, m), 1.10 (3H, s), 1.09 (3H, s), 0.93 (3H, s). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 7.51 (2H, d, J = 8.0 Hz), 7.31 (2H, d, J = 8.0 Hz), 4.56 (1H, d, J = 3.5 Hz), 4.19 (1H, dd, J = 11.5, 3.5 Hz), 3.88 (1H, dd, J = 11.5, 7.0 Hz), 3.79 (1H, m), 2.36 (1H, m), 1.97 (1H, m), 1.90 (1H, m), 1.54 (1H, m), 1.00 (6H, overlap), 0.82 (3H, s). ^{13}C-NMR (125 MHz, methanol-d_4): δ 180.3, 168.7, 142.4, 132.3, 132.3, 129.9, 129.9, 122.3, 92.9, 74.7, 74.1, 67.5, 56.0, 55.4, 31.5, 30.0, 17.1, 17.0, 9.9; HRESIMS refer to compounds **3a**.

(2*S*,3*R*)-3-(4-Bromophenyl)-2,3-dihydroxypropyl(1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (5a). The synthesis procedure of **5a** was same with the **M1a**. Colorless oil; ^{1}H-NMR (500 MHz, methanol-d_4): δ 7.50 (2H, d, J = 8.5 Hz), 7.34 (2H, d, J = 8.5 Hz), 4.57 (1H, d, J = 7.0 Hz), 4.42 (1H, dd, J = 11.5, 3.5 Hz), 4.31 (1H, dd, J = 11.5, 7.0 Hz), 3.89 (1H, m), 2.48 (1H, m), 2.03 (1H, m), 1.98 (1H, m), 1.63 (1H, m), 1.10 (3H, s), 1.09 (3H, s), 0.94 (3H, s). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 7.51 (2H, d, J = 8.5 Hz), 7.30 (2H, d, J = 8.5 Hz), 4.42 (1H, d, J = 6.0 Hz), 4.36 (1H, dd, J = 11.0, 3.0 Hz), 4.18 (1H, dd, J = 11.0, 6.5 Hz), 3.69 (1H, m), 2.38 (1H, m), 1.98 (1H, m), 1.91 (1H, m), 1.55 (1H, m), 1.02 (3H, s), 1.00 (3H, s), 0.83 (3H, s). ^{13}C-NMR (125 MHz, methanol-d_4): δ 180.3, 168.9, 142.7, 132.2, 132.2, 130.2, 130.2, 122.3, 93.0, 75.0, 74.0, 67.7, 56.0, 55.4, 31.5, 30.0, 17.1, 17.0, 9.9; HRESIMS refer to compounds **3a**.

(2*R*,3*S*)-3-(4-Bromophenyl)-2,3-dihydroxypropyl(1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (6a). The synthesis procedure of **6a** was same with the **M1a**. Colorless oil; ^{1}H-NMR (500 MHz, methanol-d_4): δ 7.50 (2H, d, J = 8.5 Hz), 7.34 (2H, d, J = 8.5 Hz), 4.57 (1H, d, J = 6.5 Hz), 4.37 (1H, dd, J = 11.5, 4.0 Hz), 4.35 (1H, dd, J = 11.5, 6.0 Hz), 3.90 (1H, m), 2.48 (1H, m), 2.03 (1H, m), 1.97 (1H, m), 1.62 (1H, m), 1.10 (3H, s), 1.09 (3H, s), 0.94 (3H, s). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 7.51 (2H, d, J = 8.5 Hz), 7.30 (2H, d, J = 8.5 Hz), 4.43 (1H, d, J = 6.5

Hz), 4.28 (1H, dd, J = 11.5, 3.5 Hz), 4.23 (1H, dd, J = 11.5, 6.5 Hz), 3.69 (1H, m), 2.37 (1H, m), 1.97 (1H, m), 1.91 (1H, m), 1.54 (1H, m), 1.00 (6H, overlap), 0.84 (3H, s). ^{13}C-NMR (125 MHz, methanol-d_4): δ 180.3, 168.9, 142.7, 132.2, 132.2, 130.1, 130.1, 122.3, 93.0, 75.1, 74.0, 67.7, 56.0, 55.4, 31.5, 30.0, 17.1, 17.0, 9.9; HRESIMS refer to compounds **3a**.

((2*R*,3*R*)-3-(4-Nitrophenyl)oxiran-2-yl)methanol and ((2*S*,3*S*)-3-(4-nitrophenyl)oxiran-2-yl) methanol. The asymmetric epoxidation was also carried out according to the Sharpless asymmetric Epoxidation. Colorless oil; the specific rotations were $[\alpha]_D^{20}$ +44 (c 0.1 methanol) and $[\alpha]_D^{20}$ −46 (c 0.1 methanol), respectively. ^{1}H-NMR (500 MHz, methanol-d_4): δ 8.21 (2H, d, J = 9.0 Hz), 7.53 (2H, d, J = 9.0 Hz), 4.00 (1H, d, J = 2.0 Hz), 3.89 (1H, dd, J = 13.0, 3.0 Hz), 3.71 (1H, dd, J = 13.0, 4.5 Hz), 3.17 (1H, m); ^{13}C-NMR (125 MHz, methanol-d_4): δ 149.1, 146.6, 127.7, 127.7, 124.6, 124.6, 64.5, 62.3, 55.7; HRESIMS m/z 196.0604 $[M + H]^+$ (calcd for $C_9H_{10}O_4N$ 196.0608).

(1*R*,2*S*)-1-(4-Nitrophenyl)propane-1,2,3-triol and (1*S*,2*R*)-1-(4-nitrophenyl)propane-1,2,3-triol (7 and 8). A solution of ((2*R*,3*R*)-3-(4-nitrophenyl)oxiran-2-yl)methanol (80 mg, 0.25 mmol) (which was dissolved by THF) and acetic acid (0.5 ml) in water was stirred at 80 °C until the solution was dry. Through the analysis of HPLC, the ((2*R*,3*R*)-3-(4-nitrophenyl)oxiran-2-yl) methanol was completely hydrolyzed. The residue was separated by chiral column on preparative HPLC (*n*-hexane/isopropanol, 80 : 20, v\v) to afford **7** (50 mg) and **8** (30 mg). The hydrolysis of ((2*S*,3*S*)-3-(4-nitrophenyl)oxiran-2-yl)methanol was also produce compounds **7** and **8**. Compounds **7** and **8** are known compounds and they were identified by comparing their spectral data with those of the known compounds.[29] Colorless oil; the specific rotations were $[\alpha]_D^{20}$ −14 (c 0.3 acetone) and $[\alpha]_D^{20}$ +15 (c 0.3 acetone), respectively. ^{1}H-NMR (500 MHz, methanol-d_4): δ 8.23 (2H, d, J = 8.5 Hz), 7.66 (2H, d, J = 8.5 Hz), 4.74 (1H, d, J = 7.0 Hz), 3.74 (1H, m), 3.68 (1H, dd, J = 11.5, 4.5 Hz), 3.65 (1H, dd, J = 11.5, 6.0 Hz). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 8.17 (2H, d, J = 8.5 Hz), 7.60 (2H, d, J = 8.5 Hz), 4.72 (1H, d, J = 5.5 Hz), 3.52 (1H, m), 3.42 (2H, overlap). ^{1}H-NMR (500 MHz, acetone-d_6): δ 8.19 (2H, d, J = 8.5 Hz), 7.70 (2H, d, J = 8.5 Hz), 4.82 (1H, t, J = 6.0 Hz), 3.75 (1H, m), 3.67 (1H, dd, J = 11.0, 5.0 Hz), 3.63 (1H, dd, J = 11.0, 5.0 Hz). ^{13}C-NMR (125 MHz, DMSO-d_6): δ 151.8, 146.4, 128.5, 128.5, 122.6, 122.6, 75.2, 72.9, 62.9; found 258.0619. HRESIMS m/z 258.0619 $[M + HCOO]^+$ (calcd for $C_{10}H_{12}O_7N$ 258.0620).

(2*S*,3*R*)-2,3-Dihydroxy-3-(4-nitrophenyl)propyl(1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (7a). The synthesis procedure of **7a** was same with the **M1a.** Colorless oil; ^{1}H-NMR (500 MHz, methanol-d_4): δ 8.23 (2H, d, J = 8.5 Hz), 7.66 (2H, d, J = 8.5 Hz), 4.72 (1H, d, J = 7.0 Hz), 4.46 (1H, dd, J = 11.5, 3.5 Hz), 4.35 (1H, dd, J = 11.5, 6.5 Hz), 3.91 (1H, m), 2.50 (1H, m), 2.03 (1H, m), 1.98 (1H, m), 1.63 (1H, m), 1.11 (3H, s), 1.09 (3H, s), 0.94 (3H, s). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 8.20 (2H, d, J = 9.0 Hz), 7.62 (2H, d, J = 9.0 Hz), 4.58 (1H, dd, J = 6.5, 3.5 Hz), 4.39 (1H, dd, J = 11.5, 3.0 Hz), 4.22 (1H, dd, J = 11.5, 6.5 Hz), 3.73 (1H, m), 2.39 (1H, m), 1.98 (1H, m), 1.91 (1H, m), 1.55 (1H, m), 1.03 (3H, s), 1.00 (3H, s), 0.83 (3H, s). ^{13}C-NMR (125 MHz, methanol-d_4): δ 180.3, 168.9, 151.4, 148.8, 129.3, 129.3, 124.1, 124.1, 92.9, 74.8, 74.0, 67.6, 56.0, 55.4, 31.5, 29.9, 17.0, 17.0, 9.9; HRESIMS m/z 394.1496 $[M + H]^+$ (calcd for $C_{19}H_{24}O_8N$ 394.1494).

(2*R*,3*S*)-2,3-Dihydroxy-3-(4-nitrophenyl)propyl(1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (8a). The synthesis procedure of **8a** was same with the **M1a**. Colorless oil; ^{1}H-NMR (500 MHz, methanol-d_4): δ 8.23 (2H, d, J = 8.5 Hz), 7.66 (2H, d, J = 8.5 Hz), 4.71 (1H, d, J = 7.5 Hz), 4.42 (1H, dd, J = 11.5, 4.0 Hz), 4.39 (1H, dd, J = 11.5, 5.5 Hz), 3.92 (1H, m), 2.50 (1H, m), 2.03 (1H, m), 1.97 (1H, m), 1.62 (1H, m), 1.10 (3H, s), 1.09 (3H, s), 0.95 (3H, s). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 8.20 (2H, d, J = 9.0 Hz), 7.63 (2H, d, J = 9.0 Hz), 4.59 (1H, d, J = 7.0 Hz), 4.31 (1H, dd, J = 11.5, 3.5 Hz), 4.26 (1H, dd, J = 11.5, 6.5 Hz), 3.74 (1H, m), 2.38 (1H, m), 1.97 (1H, m), 1.91 (1H, m), 1.54 (1H, m), 1.01 (3H, s), 1.00 (3H, s), 0.84 (3H, s). ^{13}C-NMR (125 MHz, methanol-d_4): δ 180.3, 168.9, 151.4, 148.8, 129.2, 129.2, 124.2, 124.2, 92.9, 74.9, 74.1, 67.6, 56.0, 55.4, 31.5, 30.0, 17.0, 17.0, 9.9; HRESIMS refer to compound **7a**.

(1*R*,2*R*)-1-(4-Hydroxy-3-methoxyphenyl)propane-1,2,3-triol and (1*S*,2*S*)-1-(4-hydroxy-3-methoxyphenyl)propane-1,2,3-triol (9 and 10). Colorless oil; the specific rotations were $[\alpha]_D^{20}$ −19 (c 0.1 methanol) and $[\alpha]_D^{20}$ +23 (c 0.1 methanol), respectively. ^{1}H-NMR (500 MHz, methanol-d_4): δ 6.99 (1H, d, J = 1.5 Hz), 6.80 (1H, dd, J = 8.5, 1.5 Hz), 6.76 (1H, d, J = 8.5 Hz), 4.52 (1H, d, J = 6.5 Hz), 3.86 (3H, s), 3.66 (1H, m), 3.47 (1H, dd, J = 11.0, 4.0 Hz), 3.34 (1H, dd, J = 11.0, 6.5 Hz). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 6.89 (1H, brs), 6.69 (2H, overlap), 4.38 (1H, d, J = 5.0 Hz), 3.74 (3H, s), 3.44 (1H, m), 3.31 (1H, dd, J = 11.0, 4.0 Hz), 3.14 (1H, dd, J = 11.0, 6.0 Hz). ^{13}C-NMR (125 MHz, DMSO-d_6): δ 147.0, 145.3, 134.3, 119.1, 114.7, 111.0, 75.9, 72.9, 62.6, 55.6; HRESIMS m/z 237.0733 $[M + Na]^+$ (calcd for $C_{10}H_{14}O_5Na$ 237.0719). Compounds **9** and **10** are known compounds and they were identified by comparing their spectral data with those of the known compounds.[7]

4-((1*S*,2*S*)-1,2-Dihydroxy-3-(((1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carbonyl)oxy)propyl)-2-methoxyphenyl(1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1] heptane-1-carboxylate (10a). Compound **10** (3 mg, 0.014 mmol) solution in dry CH_2Cl_2 or THF was added to a solution of camphanic acid chloride (6 mg, 0.028 mmol), EDCI (5.3 mg, 0.028 mmol) and DMAP (1.7 mg, 0.014 mmol) at 0 °C with the protection of argon gas. The reaction was stirred at 0 °C for 1 h and was detected by TLC. Then, the reaction was quenched by dropwise addition of H_2O. The suspension was extracted with CH_2Cl_2. Removal of the solvent under reduced pressure and purification of the residue by preparative HPLC, eluting with 55% methanol/H_2O, gave the **10a** 1.0 mg. Colorless oil; ^{1}H-NMR (500 MHz, methanol-d_4): δ 7.23 (1H, d, J = 1.5 Hz), 7.08 (1H, d, J = 8.0 Hz), 7.02 (1H, dd, J = 8.0, 1.5 Hz), 4.71 (1H, d, J = 5.0 Hz), 4.34 (1H, dd, J = 11.5, 4.0 Hz), 4.11 (1H, dd, J = 11.5, 6.5 Hz), 3.96 (1H, m), 3.86 (3H, s), 2.65 (1H, m), 2.49 (1H, m), 2.16 (2H, overlap), 2.02 (2H, overlap), 1.70 (1H, m), 1.63 (1H, m), 1.21 (3H, s), 1.14 (3H, s), 1.11 (3H, s), 1.09 (3H, s), 1.09 (3H, s), 0.94 (3H, s); HRESIMS m/z 575.2487 $[M + H]^+$ (calcd for $C_{30}H_{39}O_{11}$ 575.2490).

Compound 11. White powder; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 6.88 (2H, overlap), 6.64 (2H, brs), 5.41 (2H, overlap), 4.56 (1H, d, J = 6.0 Hz), 4.40 (1H, d, J = 7.5 Hz), 3.77 (3H, s), 3.73 (6H, s), 3.68 (2H, m), 3.64 (1H, m), 3.59 (1H, m), 3.46 (1H, m), 3.38

(2H, overlap), 3.17 (2H, overlap), 3.06 (3H, overlap). ^{13}C-NMR (125 MHz, methanol-d_4): δ 147.9, 147.9, 146.6, 142.9, 135.3, 133.5, 131.3, 128.7, 115.7, 112.2, 104.2, 103.7, 103.7, 87.3, 82.0, 76.9, 76.5, 75.2, 74.2, 70.0, 62.7, 61.9, 61.0, 56.0, 56.0, 55.7, 53.1; HRESIMS m/z 607.2026 $[M + Na]^+$ (calcd for $C_{27}H_{36}O_{14}Na$ 607.2000).

Conclusions

For natural AGs, there was previously no efficient method to determine their absolute configurations. Our present study presents a convenient and quick method for determining the relative and absolute configurations that only depends on the chemical shift difference ($\Delta\delta_{H3a-H3b}$) of the diastereotopic methylene protons (H-3) in ^{1}H NMR spectroscopy. In particular, the method is a good way to determine the limited amounts of natural AGs; such limited amounts prevent the use of other strategies. Remarkably, the empirical rule is invalid in $CDCl_3$. In addition, the introduction of an economic camphanoyl group with larger steric hindrance in this method may provide a reference for solving the stereochemistry problems of other flexible conformer compounds.

Conflicts of interest

There are no conflicts to declare.

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