Phenylglycine Methyl Ester, a Useful Tool for Absolute Configuration Determination of Various Chiral Carboxylic Acids

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A new chiral anisotropic reagent, phenylglycine methyl ester (PGME), developed for the elucidation of the absolute configuration of chiral α,α-disubstituted acetic acids, has turned out to be applicable to other substituted carboxylic acids, such as chiral α-hydroxy-, α-alkoxy-, and α-acyloxy-α,α-disubstituted acetic acids, as well as to chiral *β*,*β*-disubstituted propionic acids. Because a carboxylic moiety is convertible from other functional groups, e.g., ozonolysis of an olefin and oxidative cleavage of a glycol, the present findings can expand the utility of the PGME method to the absolute configuration determination of various types of organic compounds, even those which initially lack oxygen functions. Several examples of the combination of chemical reactions and the PGME method are described.

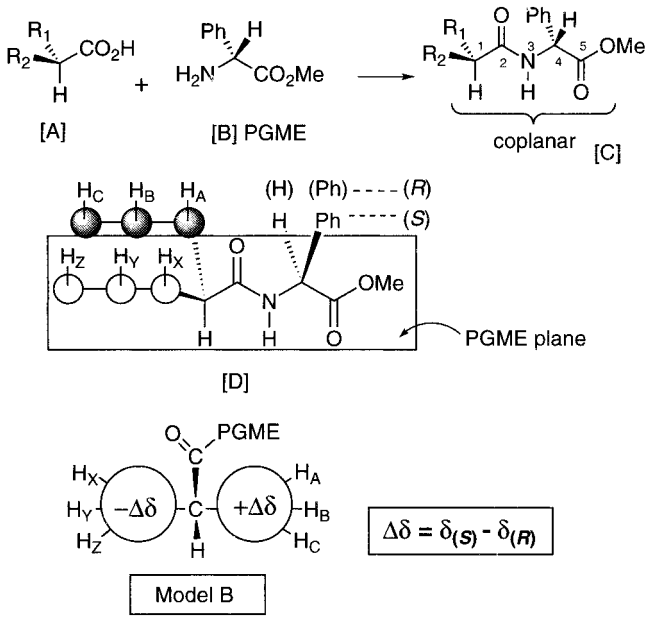
Introduction

Since the modified Mosher method for determining the absolute configuration of secondary alcohols,[1] which was principally based on Mosher's method using MTPA esters,[2] was reported, an increasing number of unique NMR methods have appeared in various journals.[3] While most of them are for application to secondary alcohols, like the modified Mosher method, we developed another new NMR methodology using (*R*)- and (*S*)-phenylglycine methyl ester (PGME method), which enabled the determination of the absolute configurations of carboxylic acids.[4]

The principle of the PGME method is summarized in Scheme 1: a chiral α,α-disubstituted acetic acid [A] is condensed with (*R*)- and (*S*)-PGME [B], now commercially available, giving the amide [C]. Coplanarity of the atoms from position 1 to position 4 is guaranteed owing to the *s-trans* amide linkage, which is well established in peptide chemistry. The planarity can be extended to the methoxycarbonyl group at the 5-position, because a polar ester group will prefer the conformation anti (with respect to the C_3-C_4 bond) to the polar carbonyl group at the 2-position. This assumption was verified by X-ray crystallography and NOE studies.[4]

In the diastereomeric pair of PGME amide [D], the protons, X−Z, of the (*S*)-isomer will have the more upfield chemical shifts than those of the (*R*)-isomer owing to the diamagnetic anisotropic effect of the benzene ring. The same will stand for H_A to H_C. Therefore, model B,[5] in which $\Delta\delta = \delta_{(S)} - \delta_{(R)}$, illustrates the correct absolute configuration of the carboxylic acid.

Scheme 1



Results and Discussion[6]

Application to Chiral *β*,*β*-Disubstituted Propionic Acids. As discussed above, in the most stable conformation of the PGME amide of an α,α-disubstituted acetic acid, the planarity of C_1 to C_5 is well interpreted by the presence of an amide linkage and dipole−dipole interaction between the methoxycarbonyl group and the amide carbonyl. Here, the rotation around the C_1-C_2 bond is

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(4) Nagai, Y.; Kusumi, T. *Tetrahedron Lett.* **1995**, *36*, 1853.

(5) Model A has been used in ref 1. In the present study, models C and D are built up so that the positive and negative Δδ values are always on the right and left sides of the models, respectively, as in the case of model A.

(6) A part of the results has appeared in Yabuuchi, T.; Ooi, T.; Kusumi, T. 2I08, The 41st Symposium on the Chemistry of Terpenes, Essential Oils, and Aromatics, Summary Papers, Iwate, Japan, 1997.

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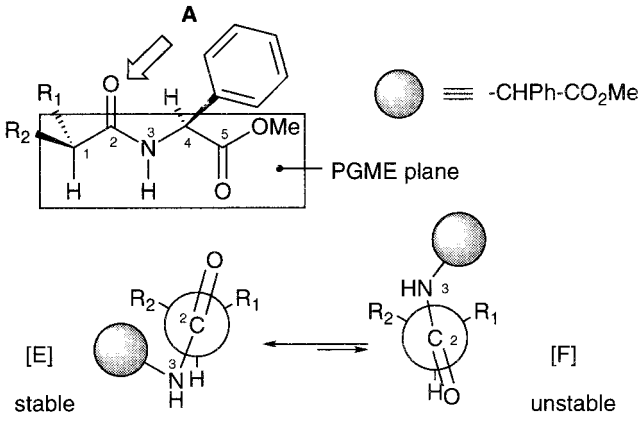


Figure 1. Stable conformation of the PGME amide of α,α-disubstituted acetic acid. The Newman model [E] is a view from the direction A. Rotation around C_1-C_2 by 180° gives another conformation, [F]. The gray circle represents the methoxycarbonylphenylmethyl group of the PGME moiety.

discussed. When the methoxycarbonyphenylmethyl group is represented by a gray circle, and the PGME amide is viewed from the direction A, two major rotamers, [E] and [F], can be drawn as in Figure 1. Rotamer [E] is more stable than rotamer [F], in which steric repulsion between the bulky methoxycarbonyphenylmethyl group and R_1/R_2 is anticipated.

This "molecular models consideration" can be extended to the PGME amide of chiral *β,β*-disubstituted propionic acid. In Figure 2, three staggered conformations of the (*R*)-PGME amide, [G], [H], and [I], resulting from rotation around C_1-C_2 and viewed from direction B, are illustrated. Of the three rotamers, [I] must be the least stable because the largest group on C-2 is placed between R_1 and R_2. Rotamers [G] and [H] are in almost the same energy level. Therefore, the PGME amide of *β,β*-disubstituted propionic acid can be considered to exist in conformer [J], which is an averaged conformation of [G] and [H].

When the PGME amide of chiral *β,β*-disubstituted propionic acid takes the conformation [J], the absolute configuration at the *β*-position of the propionic acid should be determined in a way analogous to that of the modified Mosher method using model C [note: $\Delta\delta = \delta_{(R)} - \delta_{(S)}$]. Before the validity of this assumption is demonstrated, the reason this methodology is important will be explained.

There are a number of natural products, especially terpenoids, having a structure unit [K] (Figure 3). Four terpenoids, having the unit [K] are shown. All of these compounds possess only olefinic linkages as chemically active functional groups, and there has been no convenient method to elucidate the absolute configuration, except for enantiospecific total syntheses or a series of degradation reactions leading to known compounds. It was noticed that the oxidative cleavage of the olefinic bond of [K] would give rise to a chiral *β,β*-disubstituted propionic acid. Therefore, if it can be established that the PGME method is actually applicable to a chiral *β,β*-disubstituted propionic acid, the PGME method can be extended to such olefinic compounds by combination with an oxidative cleavage of the olefinic bonds.

Carboxylic acids **1**−**4**, with known absolute configurations, were prepared from commercially available (1*R*)-(+)-pinene, D-Δ^3-carene, (3a*R*)-(+)-sclareolide, and (*R*)-(+)-citronellol by ozonolysis, hydrolysis, or oxidation,

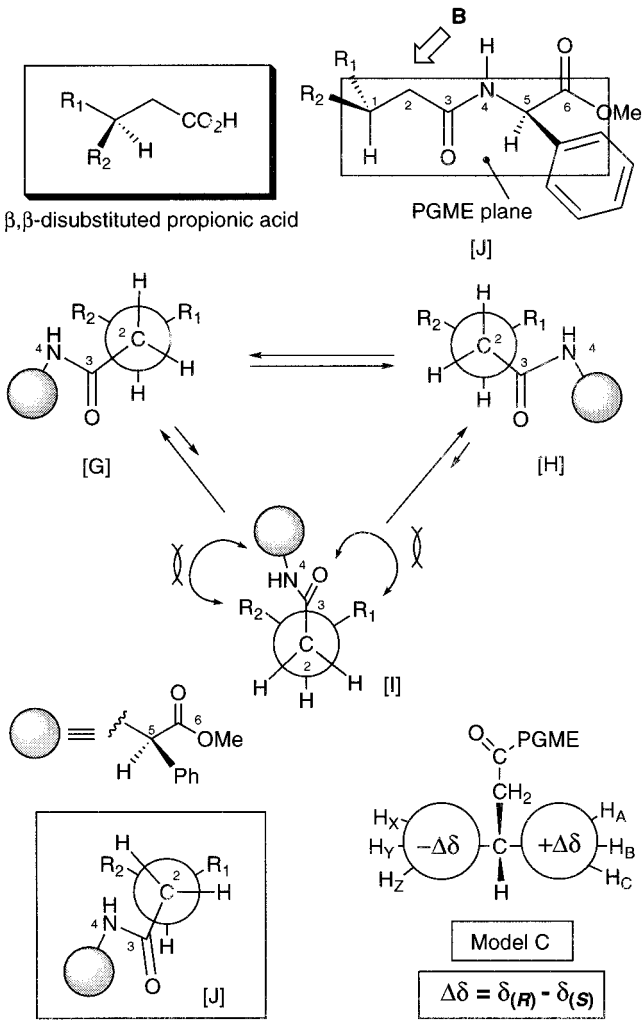


Figure 2. Ideal conformation of the (*R*)-PGME amide of *β,β*-disubstituted propionic acid (top). Three Newman projection models, [G], [H], and [I], resulting from rotation around C_1-C_2 (bottom). The gray circle represents the methoxycarbonylphenylmethyl moiety. The conformation [J] is the averaged conformation between two stable conformers, [G] and [H]. Model C, in which $\Delta\delta = \delta_{(R)} - \delta_{(S)}$, shows the absolute configuration of the *β,β*-disubstituted propionic acid.

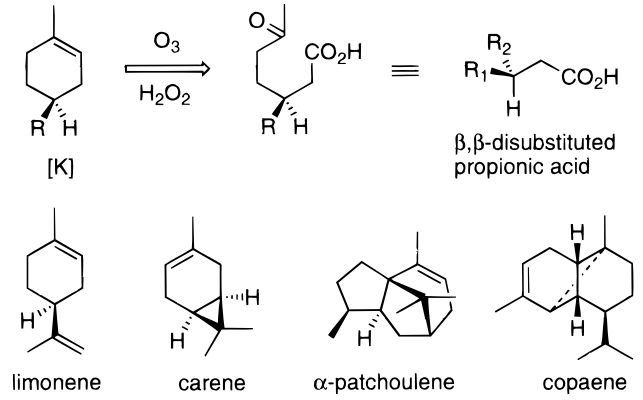
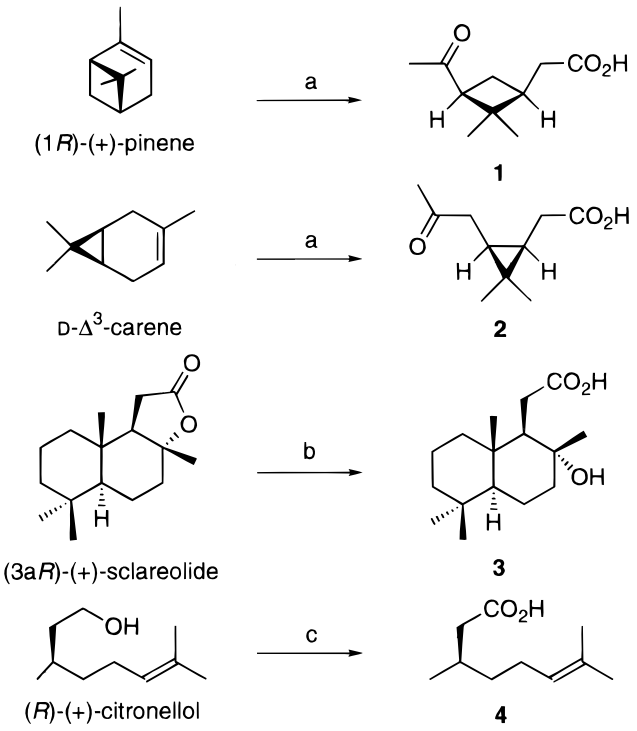


Figure 3. Four terpenes possessing unit [K]. Cleavage of the olefinic bond of [K] by, e.g., ozone gives a *β,β*-disubstituted propionic acid.

respectively, as shown in Figure 4. They were converted to (*R*)- and (*S*)-PGME amides, and the $\Delta\delta$ values [$\delta_{(R)} - \delta_{(S)}$] were calculated. The results are shown in the structures **1a**−**4a** (Figure 4). Without exception, the



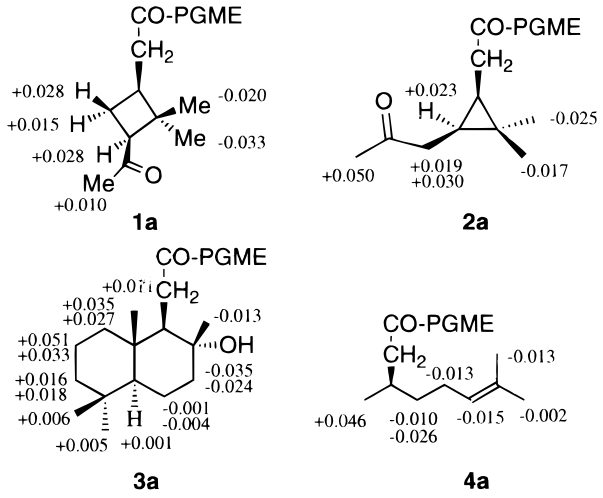


Figure 4. (Top) Transformation of (1*R*)-(+)-α-pinene, D-Δ^3-carene, (3a*R*)-(+)-sclareolide, and (*R*)-(+)-citronellol to the corresponding *β*,*β*-disubstituted propionic acids. (Bottom) $\Delta\delta$ [$\delta_{(R)} - \delta_{(S)}$] values obtained for the PGME amides **1a**−**4a**.

positive and negative $\Delta\delta$ values are oriented systematically on the right and left sides of the PGME plane, respectively, and the absolute configurations deduced from these results were identical with the known ones, thus suggesting the validity of this extended use of the PGME method.

It should be emphasized that the PGME method can be applied to the acyclic carboxylic acid **4**. The PGME amide of **4** [in Figure 5, the (*S*)-PGME amide is shown] can exist in, besides **4**[J] (Figure 2), the conformation **4**[Zig], in which the PGME moiety is a zigzag extension of the long aliphatic chain. Even in **4**[Zig], however, the methyl group is oriented in the same side of the phenyl group, and it experiences an upfield anisotropic shift. The 4-methyl-3-pentenyl chain is situated on the PGME plane in **4**[Zig], the $\Delta\delta$ values of its protons being null.

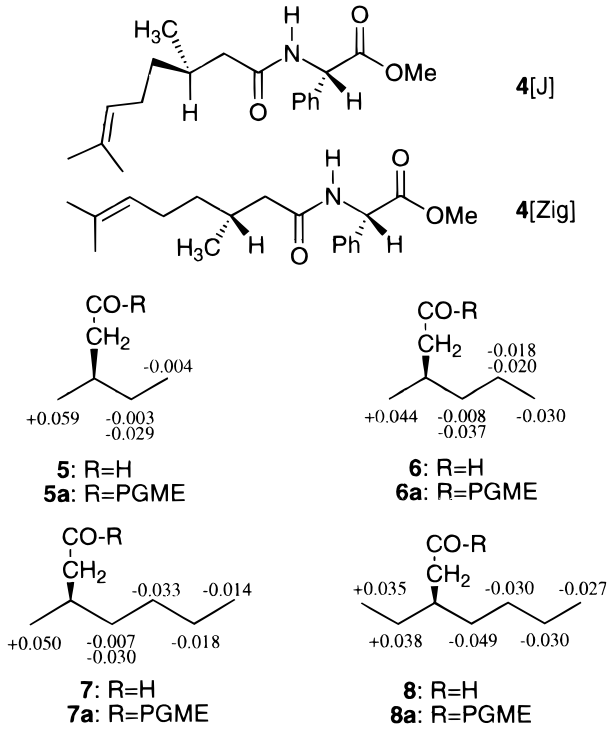


Figure 5. (Top) Two possible conformers of the (*S*)-PGME amide of (3*S*)-3,7-dimethyl-6-octenoic acid. (Bottom) $\Delta\delta$ values obtained for the (*S*)-enantiomers of 3-methylpentanoic (**5**), 3-methylhexanoic (**6**), 3-methylheptanoic (**7**), and 3-ethylheptanoic (**8**) acids.

The applicability of the extended PGME method to acyclic compounds was further confirmed by employing several synthetic carboxylic acids, **5**−**8**. The $\Delta\delta$ values obtained for these long-chain carboxylic acids (Figure 5) reinforce the validity of the PGME method for these *β*,*β*-disubstituted propionic acids.

This methodology has been quickly applied to absolute configuration determination of some complex marine natural products.[7]

Application to α-Oxy-α,α-Disubstituted Acetic Acids. When an oxy group is present at C-1 of the PGME amide, conformation [L] will become much more stable than [M], resulting from rotation around the C_1-C_2 bond, owing to the strong dipole−dipole repulsion between the electronegative oxygens, together with the steric interaction of the bulky PGME moiety with R_1 and R_2 in the latter conformation. This consideration suggests that the PGME method is also possible for the absolute configuration determination of various types of quaternary α-oxy carboxylic acids by means of model D [$\Delta\delta = \delta_{(S)} - \delta_{(R)}$].[5]

At first, the validity of the PGME method was examined by using acyclic α-oxy-α,α-disubstituted acetic acids. The linear carboxylic acids of type [N] were synthesized in racemic forms,[8] and the racemates were optically resolved (Figure 6). One example is as follows: 2-Pentanone was treated with tribromomethane and KOH in water to give *rac*-2-hydroxy-2-methylpentanoic acid (**9**). The racemic mixture was condensed with (*S*)-PGME (PyBOP, HOBT, and *N*-methylmorpholine), and the resulting diastereomeric mixture (**10a**) was separated by silica gel column chromatography. One diastereomer, the first-eluting one, was treated with 10 M KOH in metha-

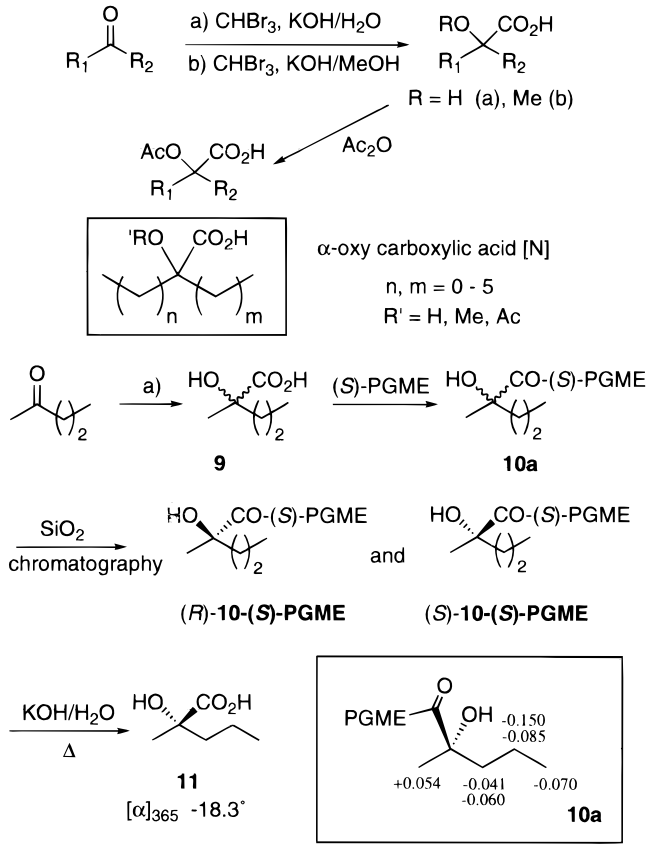
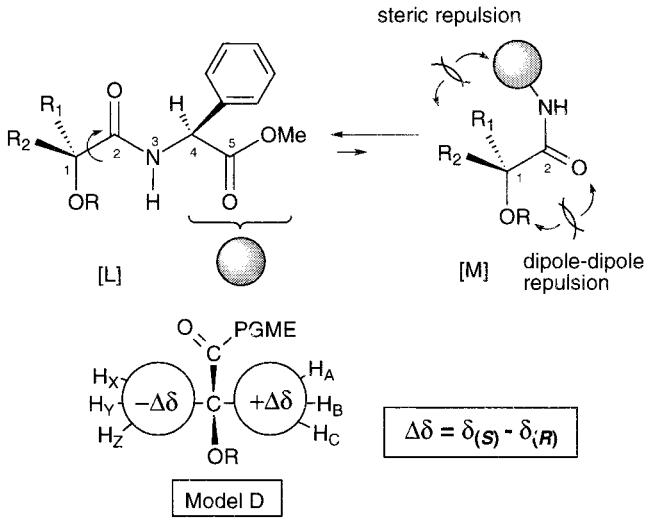


Figure 6. (Top) Reactions a and b to give α-oxy carboxylic acids of type [N] are shown. (Bottom) Scheme to afford 2-hydroxy-2-methylhexanoic acid (**9**) and optical resolution of it by (*S*)-PGME. Structure **10a** exhibits the Δδ values obtained for (*S*)-**9** (=**11**).



nol, and the specific rotation of the obtained carboxylic acid (**11**), $[\alpha]_{365}$ −18.3° (*c* 0.08, H_2O), was compared to that of (*S*)-2-hydroxy-2-methylbutanoic acid, $[\alpha]_{365}$ −24.3° (*c* 2.07, H_2O).[9] From this result, the first-eluting diastereomer was proved to be (*S*)-**10**−(*S*)-PGME and the second-eluting one to be (*R*)-**10**−(*S*)-PGME. The Δδ values [$\delta_{(S)} - \delta_{(R)}$] were calculated by subtracting the proton chemical shifts of (*R*)-**10**−(*S*)-PGME from those of (*S*)-**10**−(*S*)-PGME. [Note that the NMR spectrum of (*R*)-**10**−(*S*)-PGME is identical with that of its enantiomer, (*S*)-**10**−(*R*)-PGME.] The results are shown in **10a**, which is consistent with the (*S*)-configuration of **11**.

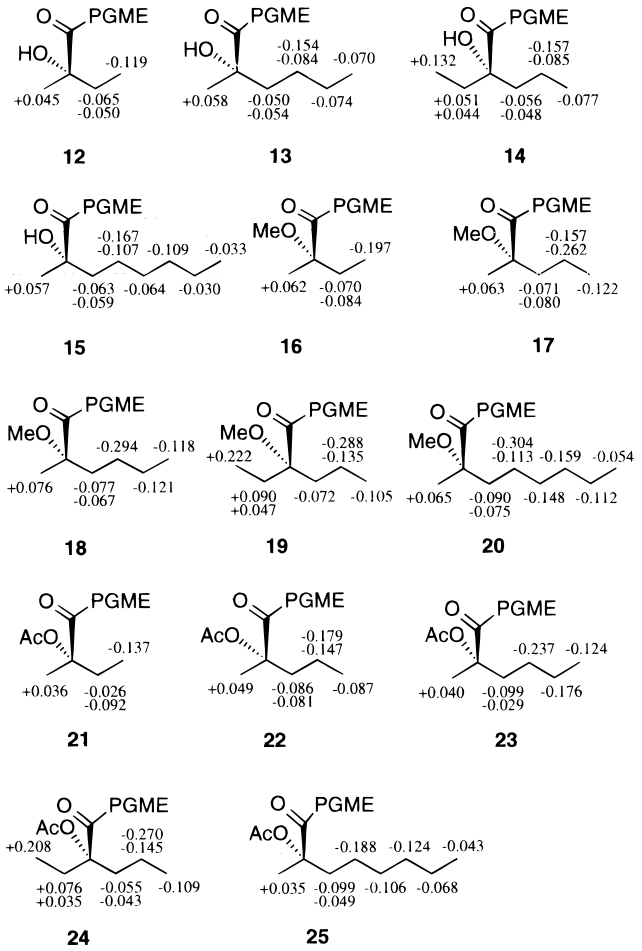


Figure 7. Δδ values obtained for the acyclic α-hydroxy (**12**−**15**), α-methoxy (**16**−**20**), and α-acetoxy (**21**−**25**) α,α-disubstituted acetic acids.

In a similar manner, α-hydroxy-, methoxy-, and acetoxy-α,α-disubstituted acetic acids of type [N] were examined, and the results are summarized in Figure 7. Without exception, the PGME method was found to be valid for determining the absolute configurations of these acyclic carboxylic acids. The Δδ values of these α-oxy quaternary acids are significantly larger than those of α,α-disubstituted acetic acids, which implied that conformation [L] was actually predominant.

Versatility of the PGME method was further confirmed when it was applied to natural α-oxy carboxylic acids **26**−**29** (Figure 8). As can been seen in structures **26a**−**29a**, the absolute configurations predicted by the Δδ values are all identical with the known absolute stereochemistry.

An interesting example of this PGME method is shown: A methyl vinyl carbinol moiety, included in a compound such as sclareol (**30**), is frequently encountered, particularly in terpenoids. Because it usually exists at the terminus of the terpenoid side chain, as understood by biosynthetic consideration, even the stereochemistry relative to the cyclic moiety is extremely difficult to be

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(8) Yabuuchi, T.; Kusumi, T. *Chem. Pharm. Bull.* **1999**, *47*, 684.
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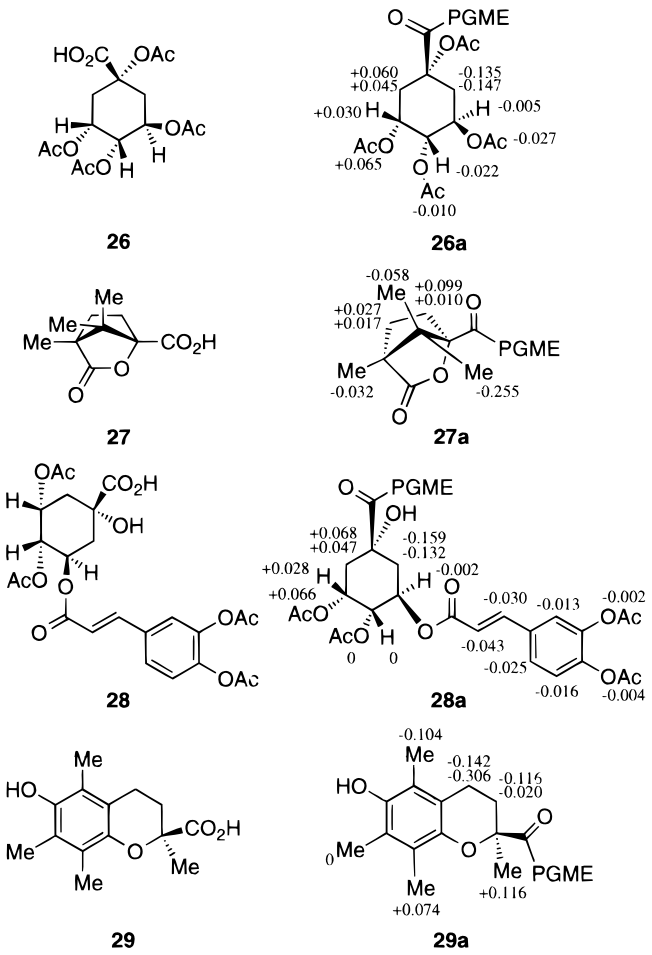


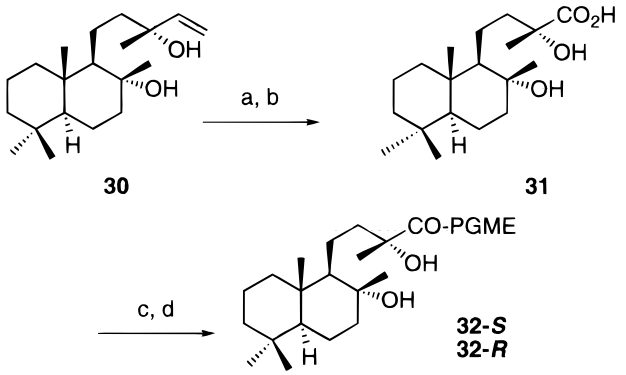
Figure 8. Application of the PGME method to natural products possessing an α-oxy-α,α-disubstituted acetic acid moiety.

solved. In many terpenoids, the stereochemistry of the methyl vinyl carbinol moiety has remained unsolved. An oxidative cleavage of the vinyl group, however, will give an α-hydroxy carboxylic acid, the absolute configuration of which will be conveniently determined by the PGME method.

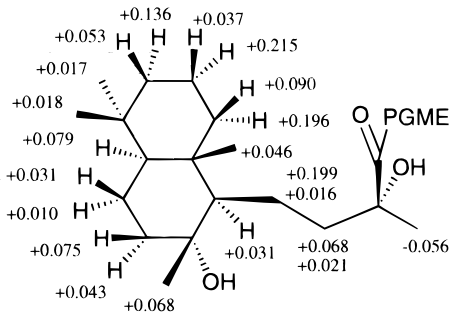
Sclareol (**30**) was treated with ozone in a mixed solvent (MeOH:AcOH = 2:1) at −78 °C, and the subsequent workup with hydrogen peroxide at −78 °C afforded the carboxylic acid **31** in good yield. The quaternary α-hydroxycarboxylic acid **31** was condensed with (*S*)- and (*R*)-PGME to give **32**-(*S*) and **32**-(*R*). The Δδ values calculated from the chemical shifts of each diastereomer are illustrated in **32a**. Only the methyl group at the α-position has negative Δδ values, and the other protons have positive Δδ values. These results led to the (*R*)-configuration at the carbinol carbon, which was coincident with the known absolute configuration. The configuration of many terpenoids having a methyl vinyl carbinol system can, therefore, be elucidated by means of the PGME method.

Application to α-Oxy-α-monosubstituted Acetic Acid. On the basis of considerations similar to those for α-oxy-α,α-disubstituted acetic acid, we deduced that the PGME method might be applied to an α-oxy-α-monosubstituted acetic acid by utilizing model D, in which one of the α-substituents is a hydrogen.

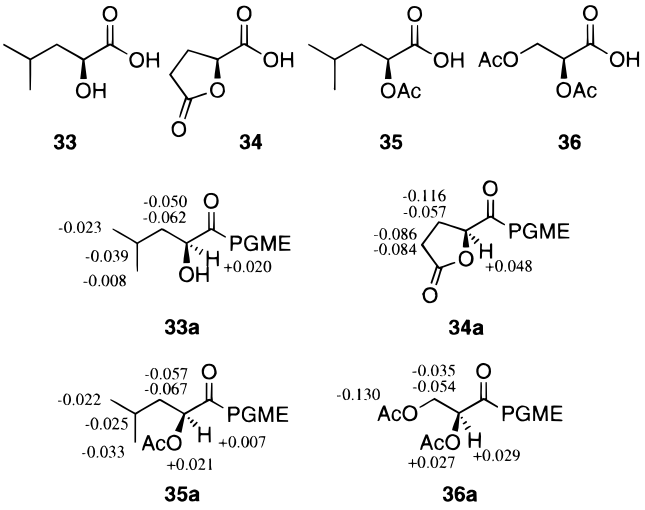
L-Leucic acid (**33**), (*S*)-(+)-5-oxo-2-tetrahydrofurancarboxylic acid (**34**), L-leucic acid acetate (**35**), and L-glyceric



a; O_3 in a mixed solvent (MeOH : AcOH = 2 : 1) at -78 °C, b; H_2O_2 at -78 °C, c; (*S*)-PGME, PyBOP®, HOBT, *N*-methylmorpholine in DMF, 5 h, d; (*R*)-PGME, PyBOP®, HOBT, *N*-methylmorpholine in DMF, 5 h.



acid (**36**) were subjected to the PGME method. The Δδ values denoted in **33a**−**36a** are in accordance with those expected from their absolute configurations.



Conclusions

The PGME method, using (*R*)- and (*S*)-phenylglycine methyl esters, originally developed for elucidating the absolute configuration of α,α-disubstituted acetic acids, is applicable to *β*,*β*-disubstituted acetic acids [model C: $\Delta\delta = \delta_{(R)} - \delta_{(S)}$], α-oxy-α,α-disubstituted acetic acids [model D: $\Delta\delta = \delta_{(S)} - \delta_{(R)}$], and α-oxy-α-monosubstituted acetic acids (model D).[10] Because a carboxylic acid is

(10) The ^{1}H NMR spectra were recorded for the 1−15 mM solutions of the PGME amides. The concentration of the solution did not affect the magnitude of the Δδ values.

derived from various kinds of synthons such as an ester, primary alcohol, and olefin, the PGME method can be extended to the absolute configuration determination of compounds without a carboxyl group by combination with the appropriate chemical reactions.

Experimental Section

Materials. (*S*)- and (*R*)-PGME, (1*R*)-(+)-α-pinene, D-Δ^3-carene, (3a*R*)-(+)-sclareolide, (*R*)-(+)-citronellol, (1*R*,3*R*,4*R*,5*R*)-(−)-quinic acid (deacetylated **26**), (*S*)-(−)-camphoric acid (**27**), chlorogenic acid (deacetylated **28**), (*R*)-(+)-Trolox (**29**), sclareol (**30**), L-leucic acid (**33**), (*S*)-(+)-5-oxo-2-tetrahydrofurancarboxylic acid (**34**), and L-glyceric acid (deacetylated **36**) were purchased from Aldrich, and were used without purification.

General Procedure To Prepare the (*S*)- and (*R*)-PGME Amides of a Carboxylic Acid. To a stirred solution of a carboxylic acid (0.39 mmol) and (*S*)-PGME (0.49 mmol) in dry DMF (2 mL) were successively added PyBOP (0.49 mmol), HOBT (0.49 mmol), and *N*-methylmorpholine (270 μL) at 0 °C. After the mixture was stirred at room temperature for 3 h, ethyl acetate was added, and the resulting solution was successively washed with 5% HCl, saturated $NaHCO_3$ solution, and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give a residue which was chromatographed on silica gel with 3:1 hexanes−ethyl acetate as developing solvent to afford the (*S*)-PGME amide in 70−80% yield.

(1*S*,3*S*)-(3-Acetyl-2,2-dimethylcyclobutyl)acetic Acid (1). Into a solution of (1*R*)-(+)-pinene (500 mg) in methanol (20 mL) cooled to −78 °C was bubbled ozone gas for 20 min. After addition of triphenylphosphine (2 g) and ether (5 mL) and stirring for 1 h, 0.1 M HCl was added and the mixed solution was extracted with ethyl acetate three times. The extract was treated with Jones reagent (8 N, 10 mL) at room temperature for 1 h. After addition of 2-propanol and removal of the solvent, 0.1 M HCl was added to the residue, and the solution was extracted with ethyl acetate. Drying over Na_2SO_4 and concentration afforded the carboxylic acid **1** (510 mg, 75%) as a colorless oil. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.13; H, 8.72.

Methyl (1′*S*,2*S*,3′*S*)-[(3-Acetyl-2,2-dimethylcyclobutyl)-acetamido]phenylethanoate (1a-*S*). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 38.86; H, 7.60; N, 4.23. Found: C, 38.61; H, 7.67; N, 4.41.

Methyl (1′*S*,2*R*,3′*S*)-[(3-Acetyl-2,2-dimethylcyclobutyl)-acetamido]phenylethanoate (1a-*R*). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 38.86; H, 7.60; N, 4.23. Found: C, 38.66; H, 7.62; N, 4.39.

(1*S*,3*S*)-[2,2-Dimethyl-3-(2-oxopropyl)cyclopropyl]acetic Acid (2). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.16; H, 8.61.

Methyl (1′*S*,2*S*,3′*S*)-[2′,2′-Dimethyl-3′-(2-oxopropyl)cyclopropyl]phenylethanoate (2a-*S*). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 38.86; H, 7.60; N, 4.23. Found: C, 38.71; H, 7.45; N, 4.36.

Methyl (1′*S*,2*R*,3′*S*)-[2′,2′-Dimethyl-3′-(2-oxopropyl)cyclopropyl]phenylethanoate (2a-*R*). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 38.86; H, 7.60; N, 4.23. Found: C, 38.82; H, 7.78; N, 4.31.

(1*R*,2*R*,4a*S*,8a*S*)-(2-Hydroxy-5,5,8a-Trimethylperhydronaphthyl)acetic Acid (3). (3a*R*)-(+)-Sclareolide (100 mg, 0.4 mmol) in methanol (3 mL) was added to 3 M KOH, and the mixture was refluxed for 20 h. The reaction mixture was washed with ether, and the aqueous layer was acidified with 12 M HCl. The product was extracted with ethyl acetate three times. The organic layer was dried over anhydrous Na_2SO_4 and concentrated, affording the carboxylic acid **3** (103 mg, 96%) as a colorless oil. Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.51. Found: C, 71.28; H, 10.60.

Methyl (1′*R*,2*S*,2′*R*,4a′*S*,8a′*S*)-[2′-Hydroxy-5′,5′,8a′-trimethylperhydronaphthyl)acetamido]phenylethanoate (3a-*S*). Anal. Calcd for $C_{25}H_{37}NO_4$: C, 72.26; H, 8.97; N, 3.37. Found: C, 72.34; H, 9.12; N, 3.39.

Methyl (1′*R*,2*R*,2′*R*,4a′*S*,8a′*S*)-[2′-Hydroxy-5′,5′,8a′-trimethylperhydronaphthyl)acetamido]phenylethanoate (3a-*R*). Anal. Calcd for $C_{25}H_{37}NO_4$: C, 72.26; H, 8.97; N, 3.37. Found: C, 72.38; H, 9.10; N, 3.36.

(3*R*)-3,7-Dimethyl-6-octenoic Acid (4). (*S*)-(+)-Citronellol (200 mg, 1.3 mmol) was treated with Jones reagent (8 N, 5 mL) at room temperature for 2 h. After addition of isopropyl alcohol, the solution was concentrated. Hydrochloric acid (5%; 20 mL) was added to the residue, and the mixture was extracted with ethyl acetate three times. The organic layer was dried over anhydrous Na_2SO_4 and concentrated, affording the carboxylic acid **4** (217 mg, 98%). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.51; H, 10.53.

Methyl (2*S*,3′*R*)-(3,7-Dimethyl-6-octenamido)phenylethanoate (4a-*S*). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.68; H, 8.55; N, 4.46.

Methyl (2*R*,3′*R*)-(3,7-Dimethyl-6-octenamido)phenylethanoate (4a-*R*). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.64; H, 8.46; N, 4.43.

3-Methylpentanoic Acid (5). A mixture of racemic 2-methylbutanoic acid (1 g, 8.6 mmol) and thionyl chloride (3 mL, 34 mmol) was refluxed at 90 °C for 3 h. After thionyl chloride was removed by evaporation with benzene, the residue was dissolved in dry ether (10 mL). The solution was added to an excess (>10 mol equiv) of the diazomethane in ether (50 mL), and the mixture was stirred for 15 h at room temperature. The solution was concentrated, and the residue was refluxed in a mixture of 10% silver nitrate solution (10 mL) and concentrated, NH_4OH (20 mL) for 6 h. The reaction mixture was washed with ether. After acidification with 1 M HCl, the product was extracted with ethyl acetate three times, affording crude 2-methylpentanamide (1.24 g) after evaporation of the solvent. The product was refluxed with 3 M KOH (20 mL) for 20 h. After washing of the mixture with ether, acidification with 12 M HCl, and extraction with ethyl acetate, racemic 3-methylpentanoic acid **9** (0.99 g, 89%) was obtained as a pale yellow oil. This material was purified by bulb-to-bulb distillation (150 °C, 5 Torr). Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 62.28; H, 10.34.

The carboxylic acids **6**, **7**, and **8** were obtained by the same procedure.

3-Methylhexanoic Acid (6). Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.41; H, 10.56.

3-Methylheptanoic Acid (7). Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.81; H, 11.21.

3-Ethylheptanoic Acid (8). Anal. Calcd for $C_9H_{18}O_2$: C, 68.42; H, 11.66. Found: C, 64.41; H, 10.56.

Separation of the Diastereomers of the (*S*)-PGME Amides 5a−8a. The (*S*)-PGME amides **5a**−**8a** were prepared according to the general procedure. Each diastereomer was separated by HPLC (LiChrosorb, 2:1 to 3:1 hexanes−ethyl acetate) except for **8a** which was subjected to recycling HPLC. In each case, the first-eluting compound was deduced to be the (*S*)-PGME amide of the (*R*)-carboxylic acid, because the (*S*)-PGME amide of (3*R*)-3,7-dimethyl-6-octenoic acid (**4**) eluted faster than the (*S*)-PGME amide of (3*S*)-**4**.

Methyl (2*S*,3′*S*)-(3′-Methylpentanamido)phenylethanoate (5a-*S*). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.53; H, 8.36; N, 5.41.

Methyl (2*S*,3′*R*)-(3′-Methylpentanamido)phenylethanoate (5a-*R*). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.51; H, 8.24; N, 5.45.

Methyl (2*S*,3′*S*)-(3′-Methylhexnamido)phenylethanoate (6a-*S*). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.41; H, 8.41; N, 5.33.

Methyl (2*S*,3′*R*)-(3′-Methylhexnamido)phenylethanoate (6a-*R*). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.45; H, 8.39; N, 5.02.

Methyl (2*S*,3′*S*)-(3′-Methylheptanamido)phenylethanoate (7a-*S*). Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.21; H, 8.57; N, 4.79.

Methyl (2*S*,3′*R*)-(3′-Methylheptanamido)phenylethanoate (7a-*R*). Anal. Calcd for $C_{17}H_{25}NO$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.18; H, 8.55; N, 4.68.

Methyl (2*S*,3′*S*)-(3′-Methyloctanamido)phenylethanoate (8a-*S*). Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.59; H, 8.91; N, 4.59. Found: C, 70.39; H, 8.66; N, 4.58.

Methyl (2*S*,3′*R*)-(3′-Methyloctanamido)phenylethanoate (8a-*R*). Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.59; H, 8.91; N, 4.59. Found: C, 70.51; H, 8.88; N, 4.57.

2-Hydroxy-2-methylpentanoic Acid (9). 2-Pentanone (2 mL, 22.0 mmol) and tribromomethane (20 mL) were placed in a three-necked flask equipped with a magnetic stirrer and a dropping funnel. To this solution was slowly added KOH (30 g) in methanol (30 mL). The resulting mixture was stirred vigorously for 1 h. Water was added to the suspension, and the solution was washed with two portions of ether. The aqueous layer was collected and acidified with 12 M HCl. The resulting suspension was extracted with three portions of ethyl acetate. The organic solution was dried over anhydrous Na_2SO_4 and concentrated to give 2.07 g (80%) of racemic **9**: HRMS (EI) calcd for $C_6H_{12}O_3$ 132.0786, found 132.0779. Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.63; H, 9.35.

Methyl (2*S*,2′*S*)-(2′-Hydroxy-2′-methylpentanamido)phenylethanoate [(*S*)-10−(*S*)-PGME]: HRMS (EI) calcd for $C_{15}H_{21}NO_4$ 279.1469, found 279.1463.

Methyl (2*S*,2′*R*)-(2′-Hydroxy-2′-methylpentanamido)phenylethanoate [(*R*)-10−(*S*)-PGME]: HRMS (EI) calcd for $C_{15}H_{21}NO_4$ 279.1469, found 279.1471.

Condensation of α-Hydroxy-α,α-disubstituted Acetic Acids with PGME. The general procedure is as follows: To a solution of a mixture of racemic 2-hydroxy-2-methylbutanoic acid (100 mg, 0.98 mmol) and (*S*)-PGME (245 mg, 1.23 mmol) were successively added PyBOP (640 mg, 1.23 mmol), HOBT (166 mg, 1.23 mmol), and *N*-methylmorpholine (0.2 mL) at 0 °C for 3 h. After addition of ethyl acetate, the reaction mixture was washed with diluted HCl solution, saturated sodium bicarbonate solution, and brine, and the organic layer was dried over anhydrous Na_2SO_4. Concentration of the dried solution and subsequent purification by preparative TLC method afforded the respective diastereomers (**12-*S***; 108 mg, **12-*R***; 113 mg, 85%).

Methyl (2*S*,2′*S*)-(2′-Hydroxy-2′-methylbutanamido)phenylethanoate (12-*S*): MS (EI) *m*/*z* 265 (M^+); HRMS (EI) calcd for $C_{14}H_{19}NO_4$ 265.1313, found 265.1311.

Methyl (2*S*,2′*R*)-(2′-Hydroxy-2′-methylbutanamido)phenylethanoate (12-*R*): MS (EI) *m*/*z* 265 (M^+); HRMS (EI) calcd for $C_{14}H_{19}NO_4$ 265.1313, found 265.1315.

Methyl (2*S*,2′*S*)-(2′-Hydroxy-2′-methylhexanamido)phenylethanoate (13-*S*): MS (EI) *m*/*z* 293 (M^+); HRMS (EI) calcd for $C_{16}H_{23}NO_4$, 293.1626, found 293.1622.

Methyl (2*S*,2′*R*)-(2′-Hydroxy-2′-methylhexanamido)phenylethanoate (13-*R*): MS (EI) *m*/*z* 293 (M^+); HRMS (EI) calcd for $C_{16}H_{23}NO_4$ 293.1626, found 293.1629.

Methyl (2*S*,2′*S*)-(2′-Ethyl-2′-hydroxypentanamido)phenylethanoate (14-*S*): MS (EI) *m*/*z* 293 (M^+); HRMS (EI) calcd for $C_{16}H_{23}NO_4$ 293.1626, found 293.1627.

Methyl (2*S*,2′*R*)-(2′-Ethyl-2′-hydroxypentanamido)phenylethanoate (14-*R*): MS (EI) *m*/*z* 293 (M^+); HRMS (EI) calcd for $C_{16}H_{23}NO_4$ 293.1626, found 293.1621.

Methyl (2*S*,2′*S*)-(2′-Hydroxy-2′-methyloctanamido)phenylethanoate (15-*S*): MS (EI) *m*/*z* 321 (M^+); HRMS (EI) calcd for $C_{18}H_{27}NO_4$ 321.1938, found 321.1933.

Methyl (2*S*,2′*R*)-(2′-Hydroxy-2′-methyloctanamido)phenylethanoate (15-*R*): MS (EI) *m*/*z* 321 (M^+); HRMS (EI) calcd for $C_{18}H_{27}NO_4$ 321.1938, found 321.1934.

Condensation of α-Methoxy-α,α-disubstituted Acetic Acids. The procedures are similar to those of quaternary α-hydroxycarboxylic acids described above.

Methyl (2*S*,2′*S*)-(2′-Methoxy-2′-methylbutanamido)phenylethanoate (16-*S*): MS (EI) *m*/*z* 279 (M^+); HRMS (EI) calcd for $C_{15}H_{21}NO_4$ 279.1469, found 279.1489.

Methyl (2*S*,2′*R*)-(2′-Methoxy-2′-methylbutanamido)phenylethanoate (16-*R*): MS (EI) *m*/*z* 279 (M^+); HRMS (EI) calcd for $C_{15}H_{21}NO_4$ 279.1469, found 279.1473.

Methyl (2*S*,2′*S*)-(2′-Methoxy-2′-methylpentanamido)phenylethanoate (17-*S*): MS (EI) *m*/*z* 293 (M^+); HRMS (EI) calcd for $C_{16}H_{23}NO_4$ 293.1626, found 293.1645.

Methyl (2*S*,2′*R*)-(2′-Methoxy-2′-methylpentanamido)phenylethanoate (17-*R*): MS (EI) *m*/*z* 293 (M^+); HRMS (EI) calcd for $C_{16}H_{23}NO_4$ 293.1626, found 293.1627.

Methyl (2*S*,2′*S*)-(2′-Methoxy-2′-methylhexanamido)phenylethanoate (18-*S*): MS (EI) *m*/*z* 307 (M^+); HRMS (EI) calcd for $C_{17}H_{25}NO_4$ 307.1782, found 307.1780.

Methyl (2*S*,2′*R*)-(2′-Methoxy-2′-methylhexanamido)phenylethanoate (18-*R*): MS (EI) *m*/*z* 307 (M^+); HRMS (EI) calcd for $C_{17}H_{25}NO_4$ 307.1782, found 307.1807.

Methyl (2*S*,2′*S*)-(2′-Ethyl-2′-methoxypentanamido)phenylethanoate (19-*S*): MS (EI) *m*/*z* 307 (M^+); HRMS (EI) calcd for $C_{17}H_{25}NO_4$ 307.1782, found 307.1788.

Methyl (2*S*,2′*R*)-(2′-Ethyl-2′-methoxypentanamido)phenylethanoate (19-*R*): MS (EI) *m*/*z* 307 (M^+); HRMS (EI) calcd for $C_{17}H_{25}NO_4$ 307.1782, found 307.1785.

Methyl (2*S*,2′*S*)-(2′-Methoxy-2′-methyloctanamido)phenylethanoate (20-*S*): MS (EI) *m*/*z* 335 (M^+); HRMS (EI) calcd for $C_{19}H_{29}NO_4$ 335.2095, found 335.2091.

Methyl (2*S*,2′*R*)-(2′-Methoxy-2′-methyloctanamido)phenylethanoate (20-*R*): MS (EI) *m*/*z* 335 (M^+); HRMS (EI) calcd for $C_{19}H_{29}NO_4$ 335.2093, found 335.2091.

Condensation of α-Acetoxy-α,α-disubstituted Acetic Acids. The procedures are similar to those of quaternary α-hydroxycarboxylic acids described above.

Methyl (2*S*,2′*S*)-(2′-Acetoxy-2′-methylbutanamido)phenylethanoate (21-*S*): MS (EI) *m*/*z* 307 (M^+); HRMS (EI) calcd for $C_{16}H_{21}NO_5$ 307.1418, found 307.1418.

Methyl (2*S*,2′*R*)-(2′-Acetoxy-2′-methylbutanamido)phenylethanoate (21-*R*): MS (EI) *m*/*z* 307 (M^+); HRMS (EI) calcd for $C_{16}H_{21}NO_5$ 307.1418, found 307.1411.

Methyl (2*S*,2′*S*)-(2′-Acetoxy-2′-methylpentanamido)phenylethanoate (22-*S*): MS (EI) *m*/*z* 321 (M^+); HRMS (EI) calcd for $C_{17}H_{23}NO_5$ 321.1575, found 321.1577.

Methyl (2*S*,2′*R*)-(2′-Acetoxy-2′-methylpentanamido)phenylethanoate (22-*R*): MS (EI) *m*/*z* 321 (M^+); HRMS (EI) calcd for $C_{17}H_{23}NO_5$ 321.1575, found 321.1570.

Methyl (2*S*,2′*S*)-(2′-Acetoxy-2′-methylhexanamido)phenylethanoate (23-*S*): MS (EI) *m*/*z* 335 (M^+); HRMS (EI) calcd for $C_{18}H_{25}NO_5$ 335.1731, found 335.1733.

Methyl (2*S*,2′*R*)-(2′-Acetoxy-2′-methylhexanamido)phenylethanoate (23-*R*): MS (EI) *m*/*z* 335 (M^+); HRMS (EI) calcd for $C_{18}H_{25}NO_5$ 335.1731, found 335.1735.

Methyl (2*S*,2′*S*)-(2′-Acetoxy-2′-ethylpentanamido)phenylethanoate (24-*S*): MS (EI) *m*/*z* 335 (M^+); HRMS (EI) calcd for $C_{18}H_{25}NO_5$ 335.1731, found 335.1729.

Methyl (2*S*,2′*R*)-(2′-Acetoxy-2′-ethylpentanamido)phenylethanoate (24-*R*): MS (EI) *m*/*z* 335 (M^+); HRMS (EI) calcd for $C_{18}H_{25}NO_5$ 335.1731, found 335.1728.

Methyl (2*S*,2′*S*)-(2′-Acetoxy-2′-methyloctanamido)phenylethanoate (25-*S*): MS (EI) *m*/*z* 363 (M^+); HRMS (EI) calcd for $C_{20}H_{29}NO_5$ 363.2044, found 363.2041.

Methyl (2*S*,2′*R*)-(2′-Acetoxy-2′-methyloctanamido)phenylethanoate (25-*R*): MS (EI) *m*/*z* 363 (M^+); HRMS (EI) calcd for $C_{20}H_{29}NO_5$ 363.2044, found 363.2040.

Condensation of Natural Products Having an α-Oxy Moiety with (*S*)- and (*R*)-PGME. (1*R*,3*R*,4*R*,5*R*)-(−)-Quinic acid (100 mg, 0.52 mmol) and chlorogenic acid (100 mg, 0.282 mmol) were converted to the corresponding tetraacetyl quinic acids (166 mg) and tetraacetyl chlorogenic acid (159 mg) by treatment with acetic anhydride and pyridine. These two acetylated acids, (*S*)-(−)-camphanic acid, and (*R*)-(+)-Trolox were condensed with (*S*)- and (*R*)-PGME according to the general procedure.

Methyl (1′*R*′,2*S*,3′*R*,4′*R*,5′*R*)-Phenyl-(1′,3′,4′,5′-tetraacetoxycyclohexanecarboxamido)ethanoate (26a-*S*): HRMS (EI) calcd for $C_{24}H_{29}NO_{11}$ 507.1739, found 507.1733.

Methyl (1′*R*′,2*R*,3′*R*,4′*R*,5′*R*)-Phenyl-(1′,3′,4′,5′-tetraacetoxycyclohexanecarboxamido)ethanoate (26a-*R*): HRMS (EI) calcd for $C_{24}H_{29}NO_{11}$ 507.1739, found 507.1738.

Methyl (1′*R*,2*S*,4′*R*)-(2′-Oxa-3′-oxo-4′,7′,7′-trimethylbicyclo[2.2.1]heptanecarboxamido)phenylethanoate (27a-*S*): HRMS (EI) calcd for $C_{19}H_{23}NO_5$ 345.1612, found 345.1611.

Methyl (1′*R*,2*R*,4′*R*)-(2′-Oxa-3′-oxo-4′,7′,7′-trimethylbicyclo[2.2.1]heptanecarboxamido)phenylethanoate (27a-*R*): HRMS (EI) calcd for $C_{19}H_{23}NO_5$ 345.1614, found 345.1611.

(*S*)-PGME Amide of Chlorogenic Acid (28a-*S*): HRMS (EI) calcd for $C_{23}H_{27}NO_5$ 669.2057, found 669.2050.

(*R*)-PGME Amide of Chlorogenic Acid (28a-*R*): HRMS (EI) calcd for $C_{23}H_{27}NO_5$ 669.2057, found 669.2058.

(2*S*,2′*R*)-(6′-Hydroxy-2′,5′,7′,8′-tetramethylchroman-2′-carboxamido)phenylethanoate (29a-*S*): HRMS (EI) calcd for $C_{23}H_{27}NO_5$ 397.1887, found 397.1871.

(2*R*,2′*R*)-(6′-Hydroxy-2′,5′,7′,8′-tetramethylchroman-2′-carboxamido)phenylethanoate (29a-*R*): HRMS (EI) calcd for $C_{23}H_{27}NO_5$ 397.1887, found 397.1886.

Ozonolysis of Sclareol. A solution of sclareol (**30**; 50 mg, 0.16 mmol) in a mixed solvent (2:1 methanol−acetic acid) was cooled to −78 °C in dry ice−methanol. Ozone was introduced into the solution, and the reaction was monitored by TLC. After 10 min, the bubbling of ozone was stopped, and hydrogen peroxide (30%; 10 mL) was added to the solution. The mixture was stirred for 1 h at −78 °C. Dilute HCl (5%; 30 mL) and sodium sulfate (excess) were added to the solution, and the mixture was extracted with ethyl acetate three times. After the organic layer was dried over anhydrous Na_2SO_4, the solution was concentrated, affording the carboxylic acid **31** (61 mg) as a colorless oil: HRMS (EI) calcd for $C_{19}H_{34}O_4$ 326.2457, found 326.2455.

Methyl (2*S*,2′*R*,2″*R*,4a″*S*,8a″*S*)-[4′-(2″-Hydroxy-2″,5″,5″,-8a″-tetramethylperhydronaphthyl)-2′-hydroxy-2′-methylbutanamido]phenylethanoate (32a-*S*): HRMS (EI) calcd for $C_{28}H_{43}NO_5$ 473.3138, found 473.3133.

Methyl (2*R*,2′*R*,2″*R*,4a″*S*,8a″*S*)-[4′-(2″-Hydroxy-2″,5″,5″,-8a″-tetramethylperhydronaphthyl)-2′-hydroxy-2′-methylbutanamido]phenylethanoate (32a-*R*): HRMS (EI) calcd for $C_{28}H_{43}NO_5$ 473.3138, found 473.3130.

Methyl (2*S*,2′*S*)-(2′-Hydroxy-4′-methylpentanamido)-phenylethanoate (33a-*S*): HRMS (EI) calcd for $C_{15}H_{21}NO_4$ 279.1469, found 279.1460.

Methyl (2*R*,2′*S*)-(2′-Hydroxy-4′-methylpentanamido)-phenylethanoate (33a-*R*): HRMS (EI) calcd for $C_{15}H_{21}NO_4$ 279.1469, found 279.1455.

Methyl (2*S*,2′*S*)-(5-Oxo-2-furancarboxamido)phenylethanoate (34a-*S*): HRMS (EI) calcd for $C_{14}H_{15}NO_5$ 281.1262, found 281.1256.

Methyl (2*S*,2′*R*)-(5-Oxo-2-furancarboxamido)phenylethanoate (34a-*R*): HRMS (EI) calcd for $C_{14}H_{15}NO_5$ 281.1262, found 281.1266.

Methyl (2*S*,2′*S*)-(2′-Acetoxy-4′-methylpentanamido)-phenylethanoate (35a-*S*): HRMS (EI) calcd for $C_{17}H_{23}NO_5$ 321.1575, found 321.1570.

Methyl (2*R*,2′*S*)-(2′-Acetoxy-4′-methylpentanamido)-phenylethanoate (35a-*R*): HRMS (EI) calcd for $C_{17}H_{23}NO_5$ 321.1575, found 321.1577.

Methyl (2*S*,2′*S*)-(2′,3′-Diacetoxypropanamido)phenylethanoate (36a-*S*): HRMS (EI) calcd for $C_{16}H_{19}NO_3$ 273.1364, found 273.1366.

Methyl (2*R*,2′*S*)-(2′,3′-Diacetoxypropanamido)phenylethanoate (36a-*R*): HRMS (EI) calcd for $C_{16}H_{19}NO_3$ 273.1364, found 273.1365.

Supporting Information Available: ^1H and ^{13}C NMR data of the compounds described in the Experimental Section and numberings of the positions used for assignment of the ^1H and ^{13}C NMR signals. This material is available free of charge via the Internet at http://pubs.acs.org.

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