The Enantioselective Synthesis of Marmelo Oxides A and B and the Assignment of the Absolute Configurations of Marmelo Oxides

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(+)-Marmelo oxide A and (–)-marmelo oxide B were stereoselectively synthesized from D-glutamic acid via (–)-marmelo lactones A and B. The absolute configurations of marmelo oxides were thus determined to be the (+)-oxide A having the (2*R*, 4*R*) and (+)-oxide B having (2*S*, 4*R*) configurations.

Marmelo oxides A and B have been isolated from the fruit of quince (*Cydonia oblonga* MILL, marmelo) by Tsuneya *et al.*, together with marmelo lactones A and B.^{1,2)} It was reported that the two oxides were responsible for the strong characteristic flavor of the fruit, which is sometimes used in the food industry.²⁾ They were assigned²⁾ as 2,4-*trans* and 2,4-*cis* stereoisomers of 4-methyl-2-(*E*-3-methyl-1,3-butadienyl) oxolane with a novel monoterpene skeleton related to *Rose oxides*³⁾ or *Lavender pyrans*.⁴⁾ However, the configurations of their chiral centers at C2 and C4 have not yet been reported. Previously, we reported the assignment of the absolute configurations of marmelo lactones A and B, based upon their stereoselective syntheses.⁵⁾ Here, similar attempts have been directed to the oxides.

In our preliminary communication,⁷⁾ the stereoselective syntheses of (+)-marmelo oxide A and (–)-oxide B and their absolute configurations were described. In this paper, we discuss the results in more detail.

The key compounds, (+)-marmelo lactones A and B, had already been synthesized from *erythro*- and *threo*- γ -methyl-L-glutamic acid.⁵⁾ Here, more facile syntheses of the (–)-lactones were carried out from D-glutamic acid (Fig. 1).

D-Glutamic acid was converted to the al-

dehyde (I) according to the established method.^{5,8)} The Wittig reaction of I with triphenylphosphonium methallylid¹²⁾ gave a mixture of II and its 5*Z* isomer (II') (II/II' = 5/4, GC analysis), from which II was isolated through silica gel column chromatography in a 30~40% yield from I (II, $[\alpha]_D^{23}$ –49.4° in methanol). The 5*Z* and 5*E* isomers were readily characterized by the $J_{H5,H6}$ values of their ¹H-NMR because the 5*Z* isomer had a smaller value (9.52 Hz) than the 5*E* isomer (15.6 Hz).⁶⁾

Methylation⁹⁾ of II with lithium diisopropylamide (LDA) and methyl iodide (MeI) proceeded stereoselectively to give IIIA and IIIB in a ratio of 6:1 (HPLC analysis⁵⁾). They were separated by silica gel column chromatography (IIIA: $[\alpha]_D^{23}$ –74.9° in methanol, lit.²⁾ +103° for (+)-IIIA). The kinetic protonation of the enolate of IIIA with the method of Takano *et al.*^{9,10)} gave a mixture of IIIA and IIIB (1:5), from which IIIB was isolated as a syrup by column chromatography on silica gel (IIIB: $[\alpha]_D^{23}$ –18.9° in methanol, lit.²⁾ –20°). The lower optical rotations of IIIA and IIIB suggested partial epimerization at the C4 position throughout these procedures. However, this was not a problem in this study because the stereochemistry of IIIA and IIIB had already been established.^{5,6)} The reduction of

FIG. 1. Syntheses of Marmelo Oxides A and B from D-Glutamic Acid via (–)-Marmelo Lactones A and B.

IIIA with lithium aluminium hydride (LiAlH_4) gave the diol (**IVA**) in a 90% yield, which was cyclized with an equimolar amount of *p*-toluenesulfonyl chloride (*p*-TsCl) in pyridine to give the (–)-2,4-*trans* oxide (**VA**) in a 60% yield (**VA**: $[\alpha]_{\text{D}}^{23} -33.4^\circ$ in ethyl ether).

In a similar way, the 2,4-*cis* oxide (**VB**) was synthesized from **IIIB**. However, the cyclization procedure needed a prolonged reaction time and high temperature and caused partial epimerization at C2 by approximately 15%, (HPLC and ^1H -NMR analysis) which might be attributed to the *cis* 1,3-substituents on the oxolane ring. The product containing approximately 15% of (+)-**VA** was used for spectroscopic studies without further purification. The NMR data of **VB** were obtained by

subtracting those of **VA** and the $[\alpha]_{\text{D}}$ value was calibrated by taking account of the 15% (+)-**VA**, **VB**: $[\alpha]_{\text{D}}^{23} = +23.5^\circ$ (ethyl ether).

The ^1H -NMR data of **VA** and **VB** agreed with those of the reported marmelo oxides **B** and **A**, respectively.²⁾ Here, the two oxides were differentiated from each other by the chemical shift of one of the methylene protons at C3; the 2,4-*trans* oxide (**VA**) gave 1.6~2.0 ppm (lit.²⁾ 1.55~1.85 ppm for oxide **B**), while the 2,4-*cis* oxide (**VB**) gave 1.1~1.5 ppm (lit.²⁾ 1.15~1.35 ppm for oxide **A**). For a determination of the configuration at C2, the sign of $[\alpha]_{\text{D}}$ and the CD results should be treated cautiously because **VB** showed a positive rotation in a longer wavelength region ($[\text{M}]_{589} = +36^\circ$, $[\text{M}]_{400} = +90^\circ$, $[\text{M}]_{300} =$

FIG. 2. Absolute Configurations of Marmelo Lactones and Oxides.

$+158^\circ$) in contrast with its negative Cotton effect at 231 nm (due to $\pi \rightarrow \pi^*$ of the conjugated double bond) to reflect its *2R* configuration (Fig. 2).

Since the reactions from **IIIA** and **IIIB** were expected to proceed with retention of the configurations, the absolute configurations of (+)- and (-)-marmelo oxides **A** and **B** were established as the (+)-oxide **A** having (*2R*, *4R*) and (+)-oxide **B** having (*2S*, *4R*) configurations. Although the optical rotations of the natural oxides have not yet been reported, their absolute configurations can be determined from the sign of their optical rotations.

The original nomenclature²⁾ of the oxide seems to be inconvenient or confusing since they referred to the 2,4-*trans* oxide as oxide **B** and the 2,4-*cis* oxide as oxide **A**, in spite of the fact that the 2,4-*trans* lactone is called marmelo lactone **A** and the 2,4-*cis* lactone is lactone **B**.^{1,2)} Therefore, we propose that 2,4-*trans* marmelo oxide and 2,4-*cis* oxide should be better called marmelo oxide and *epi*-marmelo oxide, respectively. In the same manner, 2,4-*trans* marmelo lactone would be marmelo lactone and 2,4-*cis* lactone would be *epi*-

marmelo lactone, as illustrated in Fig. 2.

In conclusion, (-)-marmelo oxide ((-)-oxide **B**) and (+)-*epi*-marmelo oxide ((+)-oxide **A**) were stereoselectively synthesized from D-glutamic acid via (-)-marmelo lactone ((-)-lactone **A**) and (-)-*epi*-marmelo lactone ((-)-marmelo lactone **B**), respectively. Thus, the absolute configurations of all the possible diastereomers of the oxides were established synthetically.

EXPERIMENTAL

Melting points and boiling points were uncorrected. IR spectra were recorded on a Jasco A-202 spectrometer and NMR spectra on a JEOL JNM-FX 100 Fourier transform spectrometer in CDCl_3 with TMS as an internal standard. Direct Mass spectra were recorded on a HITACHI M52 spectrometer and CD spectra on a Dichrograph Mark III-J. Optical rotations were measured on a Jasco ORD/UV-5. Kiesel gel 60 GF₂₅₄ (Merck) was used for both analytical and preparative TLC. HPLC was performed with a Jasco TRIROTAR equipped with a Jasco UV/DEC-100-II.

(*4R*, *5E*)-7-Methyl-5,7-octadien-4-olide (**II**). To the stirred suspension of $\text{Ph}_3\text{PCH}_2\text{C}(=\text{CH}_2)\text{CH}_3\text{Cl}^{-12)}$ (4 g, 10 mmol) in dry THF (20 ml) was added dropwise *n*-BuLi

(15% in *n*-hexane (w/w), 7 ml) under N_2 . The mixture turned red immediately and was left for 40 min at room temperature under N_2 . To the vigorously stirred solution was added the crude aldehyde (**I**) (800 mg, 7 mmol) during a period of 10 min at 20°C. After being maintained for 3 hr at room temperature, the reaction mixture was poured into a sat. NaCl solution and extracted with ethyl ether (15 ml $\times$ 3). The aqueous layer was acidified with dil. HCl, stirred for an hour and then extracted with ethyl ether (10 ml $\times$ 3). The ethereal extracts were combined and washed with sat. NaCl solution and dried over Na_2SO_4 . After evaporating the solvents, the residue was chromatographed on a silica gel column (2.5 cm ϕ $\times$ 60 cm) and eluted with a mixture of petroleum ether–ethyl ether (6:1, v/v). The fractions containing the faster moving compound (R_f =0.5, petroleum ether–ethyl ether=1:2) were collected and evaporated *in vacuo* to give a 5Z isomer of **II** (**II'**), 180 mg (17%), creamy flavor oil, $[\alpha]_D^{23} +52.6^\circ$ ($c=0.2$, CH_3OH), MS m/z : 152 (M^+), 136, 124, 110, 109, 95. ^{13}C -NMR: 22.9, 29.1, 29.8, 76.9, 117.2, 128.1, 136.1, 140.6, 177.5. ^1H -NMR: 1.90 (3H, s, $-CH_3$), 4.90 (1H, s, H8a), 5.10 (1H, s, H8b), 5.30 (1H, dd, $J_{H5,H6}=9.52$ Hz, H5), 6.14 (1H, d, $J=9.52$ Hz, H6).

The slower moving fractions (R_f =0.4) gave a waxy odor syrup of **II**, 220 mg (21%), $[\alpha]_D^{23} +54.3^\circ$ ($c=0.2$, CH_3OH), MS m/z : 152 (M^+), 136, 124, 110, 109, 97, 95, 85. ^1H -NMR: 1.85 (3H, s, $-CH_3$), 5.04 (2H, broad s, H8a and H8b), 5.63 (1H, dd, $J=6.1$ and 15.6 Hz, H5), 6.38 (1H, d, $J=15.6$ Hz, H6). ^{13}C -NMR: 18.4, 28.6, 29.0, 80.7, 118.7, 126.5, 135.8, 140.7, 176.8.

(2S, 4R, 5E)-2,7-Dimethyl-5,7-octadien-4-olide ((-)-marmelo lactone), (**IIIA**). To a cooled solution ($-76^\circ C$, dry-ice/acetone) of diisopropylamine (0.18 ml) in THF (3 ml, dried over Na) was added dropwise *n*-BuLi (15% in *n*-hexane, 0.85 ml, w/w) to give an LDA solution (1.2 mmol). After stirring for 30 min at $-76^\circ C$ under N_2 , **IIA** (150 mg, 1 mmol in 1 ml of THF) was added dropwise over 10 min with a glass syringe and the mixture was kept for 10 min at $-76^\circ C$ under N_2 . To the solution was added in one portion MeI (0.08 ml, 1.2 mmol in 1 ml of THF) with a glass syringe. The temperature of the solution was gradually raised to $-30^\circ C$ over 2 hr. To the solution was added 10% HCl (10 ml) and the solution was kept at room temperature for 2 hr before being poured into a sat. NaCl solution. The NaCl solution was extracted with ethyl ether (10 ml $\times$ 3) and the ethereal extracts were combined and dried over $MgSO_4$. After removing the solvent *in vacuo*, the residue was mounted on a silica gel column (2.5 cm ϕ $\times$ 60 cm) and eluted with *n*-hexane–ethyl acetate (6:1, v/v). The fractions containing a fast moving compound (R_f =0.33, *n*-hexane–ethyl acetate=4:1) were collected and concentrated to give a sweet flavor syrup of **IIIA**, 100 mg (61% yield from **IIA**), $[\alpha]_D^{23} -74.9^\circ$ ($c=0.2$, CH_3OH). The ^1H -NMR, ^{13}C -NMR and mass spectral data agreed with those of the authentic sample.^{5,7)} The slower moving fractions gave a syrup of **IIIB**, 14 mg (9%) with a sweet

flavor similar to **IIIA**, $[\alpha]_D^{23} -19.0^\circ$ ($c=0.2$, CH_3OH). The spectral data agreed with those of the authentic material.^{5,7)}

(2R, 4R, 5E)-2,7-Dimethyl-5,7-octadien-4-olide ((-)-epimarmelo lactone), (**IIIB**). To the LDA solution (1.2 mmol in THF at $-76^\circ C$) was added dropwise **IIIA** (150 mg in 1 ml of THF) and the solution was stirred for 20 min at $-76^\circ C$ under N_2 . A sat. Na_2SO_4 solution (10 ml) was added rapidly and the mixture was warmed to room temperature before being poured into a sat. NaCl solution. The solution was extracted with ethyl ether (10 ml $\times$ 3). The aqueous layer was acidified with dil. HCl, stirred for 30 min at room temperature and then extracted with ethyl ether (10 ml $\times$ 3). The ethereal extracts were combined, washed with a sat. NaCl solution and dried over Na_2SO_4 . After removing the solvent *in vacuo*, the residue gave a mixture of **IIIA** and **IIIB** (1:5) as a syrup (130 mg, 87%), which was mounted on a silica gel column and eluted with *n*-hexane–ethyl acetate (6:1, v/v). The slower moving eluents were collected to give a syrup of **IIIB**, 83 mg (53%), $[\alpha]_D^{23} -18.9^\circ$ ($c=0.2$, CH_3OH). The ^1H -NMR, ^{13}C -NMR and mass spectral data agreed with those of the authentic materials.^{5,7)}

(2S, 4R, 5E)-2,7-Dimethyl-5,7-octadiene-1,4-diol (**IVA**). To the suspension of $LiAlH_4$ (91 mg, 2.4 mmol) in ethyl ether (20 ml) was added dropwise **IIIA** (200 mg, 1.2 mmol in 10 ml of THF) over 10 min at room temperature. After the mixture had been stirred for an hour, water saturated with ethyl ether (15 ml of water and 1 ml of ethyl ether) was added dropwise over 30 min. The mixture was vigorously stirred for 3 hr and concentrated *in vacuo*. The residue was eluted with hot ethanol and the eluent concentrated to give a crude syrup of **IVA**, 200 mg (98% yield). The syrup was purified by a silica gel column eluted with benzene–ethyl acetate (4:1, v/v). **IVA**: syrup, $[\alpha]_D^{23} -12.7^\circ$ ($c=0.2$, CH_3OH), $[\alpha]_{400}^{23} -40.7^\circ$. ^{13}C -NMR $\delta_{CD_3OD}^{TMS}$: 17.6, 18.8, 33.5, 42.3, 68.2, 71.7, 116.7, 133.9, 134.0, 143.0. ^1H -NMR $\delta_{CD_3OD}^{TMS}$: 0.93 (3H, d), 1.31~1.83 (3H, m), 1.84 (3H, s), 3.31~3.49 (2H, m), 4.11~4.30 (1H, m), 4.96 (2H, s), 5.63 (1H, dd), 6.32 (1H, d).

(2R, 4R, 5E)-2,7-Dimethyl-5,7-octadiene-1,4-diol (**IVB**). In a similar manner to that described for the synthesis of **IVA**, **IIIB** (100 mg) yielded 90 mg of a viscous syrup of **IVB**, $[\alpha]_D^{23} -0.08^\circ$ ($c=0.15$, CH_3OH), $[\alpha]_{400} -7.7^\circ$. ^{13}C -NMR $\delta_{CD_3OD}^{TMS}$: 17.3, 18.8, 33.8, 42.7, 68.8, 71.4, 116.6, 134.4, 143.0. ^1H -NMR $\delta_{CD_3OD}^{TMS}$: 0.95 (3H, d), 1.11~1.40 (1H, m), 1.51~1.80 (2H, m), 1.84 (3H, s), 3.30~3.41 (2H, m), 4.08~4.31 (1H, m), 4.95 (2H, s), 5.67 (1H, dd), 6.32 (1H, d).

(2R, 4S)-4-Methyl-2-((E)-3-methyl-1,3-butadienyl) oxo-lane ((-)-marmelo oxide) (**VA**). *p*-Toluenesulfonyl chloride (120 mg, 6.3 mmol in 3 ml of $CHCl_3$) was added

dropwise to a stirred and ice-cooled solution of **IVA** (100 mg, 5.9 mmol) in dry pyridine (12 ml). The reaction mixture was stirred for 2 hr below 4°C and then for 12 hr at room temperature, while the reaction was checked with a TLC (petroleum ether–ethyl ether=2:1, **VA**: R_f =0.7 (I_2 or $KMnO_4$ positive)). The reaction mixture was poured into the ice-cooled water and extracted with ethyl ether (15 ml $\times$ 3). The ethereal extracts were combined and washed with dil. HCl and sat. NaCl solution to remove the pyridine. After drying over $MgSO_4$, the solvent was removed under a reduced pressure to give a colorless oil of **VA**, 60 mg (67% yield). This crude **VA** was purified by preparative TLC developed with petroleum ether–ethyl ether (4:1, v/v) to give 56 mg (56%) of a fruity flavored oil of **VA**: $[\alpha]_D^{23}$ –33.4° (c =0.18, ethyl ether). MS m/z : 152 (M^+), 137 ($M^+ - CH_3$), 96, 95, 93, 81, 69, 68, 67, 55, 41. ^{13}C -NMR: 17.8, 18.6, 33.4, 40.6, 75.2, 79.1, 116.5, 130.8, 133.3, 141.5. ^1H -NMR: 1.05 (3H, d), 1.84 (3H, s), 1.62~2.0 (2H, m), 2.10~2.61 (1H, m), 3.34 (1H, dd), 4.04 (1H, dd), 4.49 (1H, dd), 4.96 (2H, s), 5.63 (1H, dd), 6.30 (1H, d).

(2*R*, 4*R*)-4-Methyl-2-((*E*)-3-methyl-1,3-butadienyl) oxolane ((+)-*epi*-marmelo oxide) (**VB**). Similarly to the preparation of **VA**, 100 mg of **IVB** afforded a fruity oil of **VB** (+15% (+)-**VA**), 50 mg in a 56% yield. Here, the reaction mixture was first kept at 4°C for 2 hr and then at 45~50°C for 12 hr to complete the cyclization. The spectral data of **VB** were obtained by taking account of the 15% (+)-**VA**. **VB**: $[\alpha]_D^{23}$ +23.5° (c =0.15, ethyl ether). MS m/z : 152 (M^+), 137 ($M^+ - CH_3$), 96, 95, 93, 81, 79, 69, 67, 55, 41. ^{13}C -NMR: 17.6, 18.6, 34.8, 41.8, 74.9, 80.6, 116.5, 130.7,

133.6, 141.5. ^1H -NMR: 1.06 (3H, d), 1.10~1.50 (1H, m), 1.85 (3H, s), 2.0~2.59 (2H, m), 3.41 (1H, dd), 3.95 (1H, dd), 4.21~4.59 (1H, m), 4.96 (2H, s), 5.67 (1H, dd), 6.31 (1H, d).

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