Pyrrolizidine Alkaloids. The Synthesis and Absolute Configuration of All Stereoisomers of Monocrotalic Acid

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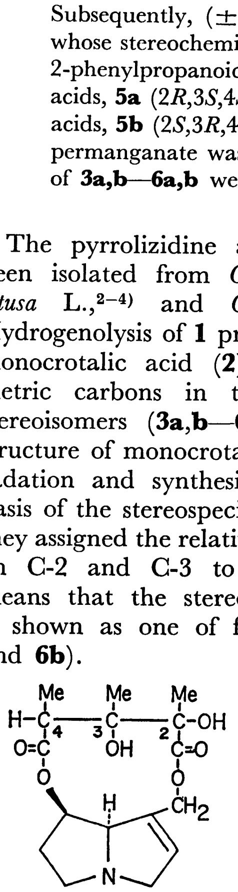
All stereoisomers (**3a, b—6a, b**) of monocrotalic acid have been synthesized. Methylation of (±)-*cis*-2,3,4-trimethyl-2-pentenedioic acid with diazomethane followed by *cis*-hydroxylation with potassium permanganate afforded two epimeric γ-lactone esters in a ratio of *ca.* 1:5. These esters were then hydrolyzed with dilute hydrochloric acid to the corresponding acids, (±)-**3** and racemic monocrotalic acid (**4**). Optical resolution of (±)-**3** with brucine afforded **3a** (2*R*,3*R*,4*S*) and **3b** (2*S*,3*S*,4*R*). The racemic monocrotalic acid was also resolved by means of brucine to give natural monocrotalic acid (**4a**: 2*R*,3*R*,4*R*) and its enantiomer (**4b**: 2*S*,3*S*,4*S*). Subsequently, (±)-*trans*-2,3,4-trimethyl-2-pentenedioic acid was resolved with cinchonidine to give **8a** and **8b**, whose stereochemistry was assigned respectively as *S*- and *R*-configuration by correlation to the known (*R*)-(−)-2-phenylpropanoic acid. Methylation of **8a** followed by *cis*-hydroxylation and hydrolyses afforded γ-lactone acids, **5a** (2*R*,3*S*,4*S*) and **6b** (2*S*,3*R*,4*S*). Similarly, the enantiomer **8b** was also converted into the corresponding acids, **5b** (2*S*,3*R*,4*R*) and **6a** (2*R*,3*S*,4*R*). The stereochemical course of the above hydroxylations with potassium permanganate was well explained by a modification of Cram's rule of asymmetric induction. The CD spectra of **3a,b—6a,b** were also discussed.

The pyrrolizidine alkaloid monocrotaline (**1**) has been isolated from *Crotalaria spectabilis* Roth.,[1,2] *C. retusa* L.,[2-4] and *C. grahamiana* Wight *et* Arn.[5] Hydrogenolysis of **1** produced a necic acid component, monocrotalic acid (**2**), which possesses three asymmetric carbons in the molecule. Therefore, eight stereoisomers (**3a,b—6a,b**) are possible for **2**. The structure of monocrotalic acid was established by degradation and synthesis by Adams *et al.*[6,7] On the basis of the stereospecificity of the synthetic reaction,[7] they assigned the relative configuration of methyl groups on C-2 and C-3 to be *cis* (2*R*,3*S* or 2*S*,3*R*). This means that the stereostructure of monocrotalic acid is shown as one of four diastereomers (**5a**, **5b**, **6a**, and **6b**).



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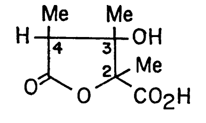
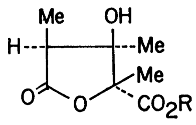
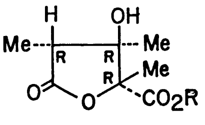


2

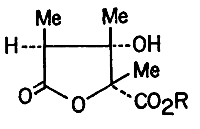
Cervinka *et al.*[8,9] also studied the stereochemistry of monocrotalic acid and assigned the absolute configuration of C-2 to be *R* by the method of asymmetric transformation and by means of the optical rotatory dispersion. On the other hand, Crout *et al.*[10,11] disagreed with the result of Adams *et al.*[7] and found the chirality of three asymmetric centers in monocrotalic acid to be 2*R*,3*R*,4*R* (**4a**) by comparing the rate constant of dehydration of methyl monocrotalate with those of methyl trichodesmate,[12] 3-hydroxy-4-butyrolactone, and mevalonolactone, and by correlation of C-2 and C-4 to the known compounds, (2*R*,3*S*)-2,3-dihydroxy-2-methylbutanoic acid and (*S*)-3-hydroxy-2-methylpropanohydrazide. Although this discrepancy concerning the configuration of C-3 had been explained by Crout *et al.*,[10] it was desirable to obtain the direct confirmation of the stereochemistry of C-3 by an unambigous synthesis. The key step in the reported synthesis[7] was the stereospecific hydroxylation of (±)-*cis*-2,3,4-trimethyl-2-pentenedioic acid (**7**) with pertungstic acid, which is known to give predominantly *trans*-hydroxylation of olefinic double bonds. However, Crout *et al.*[10] have reported that the above hydroxylation actually proceeded in



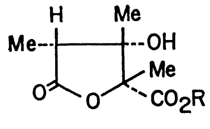
3a R=H
11a R=Me



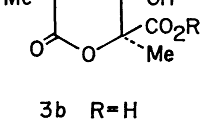
4a R=H
12a R=Me



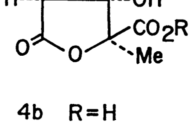
5a R=H
13a R=Me



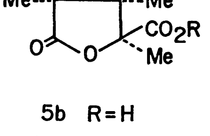
6a R=H
14a R=Me



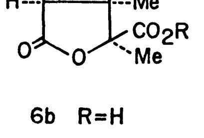
3b R=H
11b R=Me



4b R=H
12b R=Me



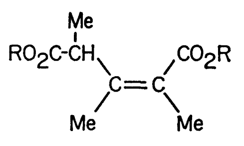
5b R=H
13b R=Me



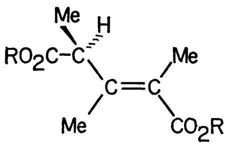
6b R=H
14b R=Me

a stereospecifically *cis* manner. This confusion about the stereochemical course of the synthetic reaction seemed to have occurred because of using the acidic compound (**7**) which did not react with potassium permanganate or osmium tetraoxide.[7] In previous papers,[13] we have reported that similar compounds, methyl *trans*-3-methoxycarbonyl-2-methyl-3-pentenoate and its *cis*-isomer, were easily hydroxylated with potassium permanganate in a *cis* manner. Therefore, it was of interest to study the hydroxylation of dimethyl *cis*-2,3,4-trimethyl-2-pentenedioate (**9**) and its *trans*-isomer (**10**) with potassium permanganate. We were further interested in studying the steric course of the hydroxylation to the olefinic double bonds directly bonded to asymmetric carbon atoms. This paper describes the syntheses and absolute configurations of all stereoisomers of monocrotalic acid, and the stereochemistry of the potassium permanganate hydroxylations. In addition, the relationship between the absolute configurations and the circular dichroism (CD) spectra of the synthetic γ-lactone acids was also discussed.

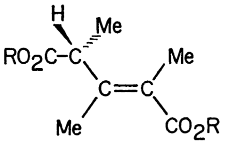
A mixture of racemic *cis*- (**7**) and *trans*-2,3,4-trimethyl-2-pentenedioic acid (**8**) was prepared by the procedure of Adams *et al.* and then successfully separated by column chromatography on silica gel. The NMR spectrum of (±)-**7** showed a methine proton quartet at δ 4.43 ppm and two methyl singlets at δ 1.75 and 1.90 ppm, while that of (±)-**8** showed the corresponding signals at δ 3.74 (q) ppm and at δ 1.94 (6H, s) ppm. The appearance of the methine proton signal of (±)-**7** in the field lower than that of (±)-**8** suggested that these dioic acids, (±)-**7** and (±)-**8**, have respectively *cis*- and *trans*-configuration. Methylation of the *cis*-isomer, (±)-**7**, with diazomethane afforded the dimethyl ester (**9**), which was submitted to oxidation with aqueous potassium permanganate in the presence of magnesium sulfate at −20 °C. Purification of the crude product by column chromatography on silica gel produced, as expected, two epimeric γ-lactone esters, (±)-**11** and (±)-**12**, in a ratio of *ca.* 1:5. The IR and NMR spectra of the major product, (±)-**12**, were identical with those of natural methyl monocrotalate. Since it is well known that potassium permanganate reacts with olefins to add two hydroxyl functions to the double bond in a *cis* manner, the relative configuration of the methyl groups on C-2 and C-3 in both (±)-**11** and (±)-**12** is *trans*, supporting the assignment of Crout *et al.*[10] The γ-lactone esters, (±)-**11** and (±)-**12**, were hydrolyzed with dilute hydrochloric acid to the corresponding acids, (±)-**3** and (±)-**4**, which were subsequently methylated back into (±)-**11** and (±)-**12** with diazomethane. This proved that there was no configurational change during the hydrolyses. The (±)-**4** acid was then resolved by means of brucine to give monocrotalic acid (**4a**), $[\alpha]_D$ −5.6° (EtOH), and its enantiomer (**4b**), $[\alpha]_D$ +5.3° (EtOH). Methylation of **4a** and **4b** with diazomethane, followed by dehydration of the resulting esters, **12a** and **12b**, with phosphoryl chloride in pyridine afforded respectively methyl (*R*)-(+)-anhydromonocrotalate (**15a**),[10,11] $[\alpha]_D$ +205° ($CHCl_3$), and its (*S*)-(−)-enantiomer (**15b**), $[\alpha]_D$ −195° ($CHCl_3$). From the above synthesis the absolute configuration of monocrotalic acid was conclusively assigned as being 2*R*,3*R*,4*R* (**4a**). The (±)-**3** acid was also resolved by means of brucine to give **3a**, $[\alpha]_D$ −32° (EtOH), and **3b**, $[\alpha]_D$ +22° (EtOH),[14] which, after methylation with diazomethane, were dehydrated with phosphoryl chloride in pyridine to afford **15a** and **15b** respectively. Thus, the absolute configurations of **3a** and **3b** were also assigned as being 2*R*,3*R*,4*S* and 2*S*,3*S*,4*R* respectively.



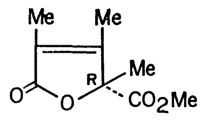
7 R=H
9 R=Me



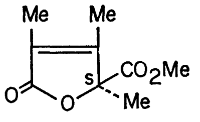
8a R=H
10a R=Me



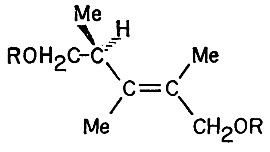
8b R=H
10b R=Me



15a

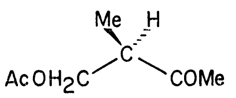


15b

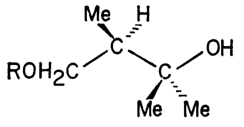


16 R=H
17 R=Ac

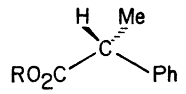
Subsequently, our attention was directed toward the syntheses of the other four diastereomers. For this purpose, (±)-**8** was resolved by means of cinchonidine to give **8a**, $[\alpha]_D$ +121° (ether), and **8b**, $[\alpha]_D$ −120° (ether), which were methylated with diazomethane to yield dimethyl esters, **10a** and **10b**. The absolute configurations of **8a** and **8b** were determined by the following correlation. Reduction of **10a**[15] with lithium aluminium hydride, followed by acetylation of the resulting diol (**16**) with acetic anhydride in pyridine, afforded a diacetate (**17**), $[\alpha]_D$ +9.1° (CHCl$_3$). This was then submitted to ozonization to yield 4-acetoxy-3-methyl-2-butanone (**18**). The Grignard reaction of the crude **18** with methylmagnesium iodide gave a diol (**19a**) which was characterized as its monoacetate, 3-hydroxy-2,3-dimethylbutyl acetate (**20a**), $[\alpha]_D$ +16.9° (CHCl$_3$). Transformation of the known (*R*)-(−)-2-phenylpropanoic acid (**21**)[16] into **20a** or its enantiomer (**20b**) was also carried out as follows. Methylation of **21** with diazomethane afforded the corresponding methyl ester (**22**), which was converted into (*R*)-(−)-2-phenylpropyl acetate (**24**) by reduction with lithium aluminium hydride and subsequent acetylation of the resulting alcohol (**23**) with acetic anhydride in pyridine. Ozonization of **24** followed by methylation of the resulting acid (**25**) with diazomethane afforded methyl (*S*)-(+)-3-acetoxy-2-methylpropanoate (**26**), $[\alpha]_D$ +18.2° (CHCl$_3$), which was then converted into (*S*)-(−)-3-hydroxy-2,3-dimethylbutyl acetate (**20b**), $[\alpha]_D$ −27.1° (CHCl$_3$), by the Grignard reaction with methylmagnesium iodide and subsequent acetylation. The IR and NMR spectra of **20b** was identical in every respect with those of **20a**. Thus, the stereochemistry of **20a** was assigned to be *R*-configuration and **8a** and **8b** consequently have *S*- and *R*-configuration respectively.



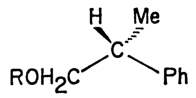
18



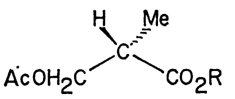
19a R=H
20a R=Ac



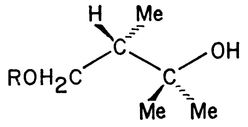
21 R=H
22 R=Me



23 R=H
24 R=Ac



25 R=H
26 R=Me



19b R=H
20b R=Ac

Oxidation of **10b** with potassium permanganate afforded two γ-lactone esters, **13b** and **14a**, in a ratio of *ca.* 5:2. The NMR spectrum of **13b** showed a quartet at δ 3.04 ppm due to a methine proton at C-4, while that of **14a** showed the corresponding signal at δ 2.61 ppm. These chemical shifts suggested that the relative configuration of the methine proton and a hydroxyl group at C-3 is *cis* in **13b** and *trans* in **14a**. From the above spectral data and the consideration of the stereochemical course of the oxidation, the absolute configurations of **13b** and **14a** were assigned as 2*S*,3*R*,4*R* and 2*R*,3*S*,4*R* respectively. These assignments were further supported by the dehydration of **13b** and **14a** with phosphoryl chloride in pyridine, yielding **15b** and **15a** respectively. Hydrolyses of **13b** and **14a** with dilute hydrochloric acid yielded the corresponding acids, **5b** (2*S*,3*R*,4*R*), $[\alpha]_D$ +60° (EtOH), and **6a** (2*R*,3*S*,4*R*), $[\alpha]_D$ −5.1° (EtOH). The enantiomers, **5a** (2*R*,3*S*,4*S*) and **6b** (2*S*,3*R*,4*S*), were also synthesized from **10a** by oxidation and subsequent

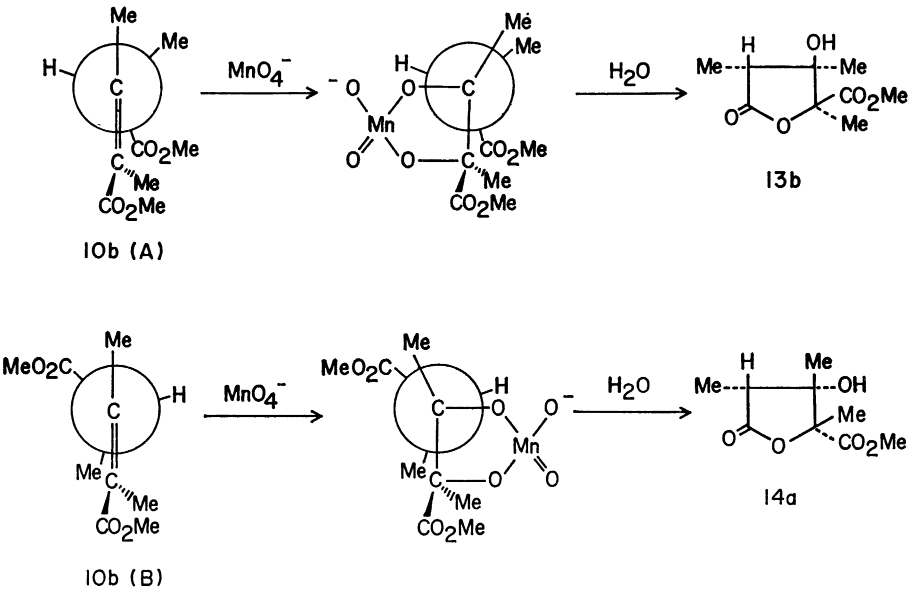


Fig. 1.

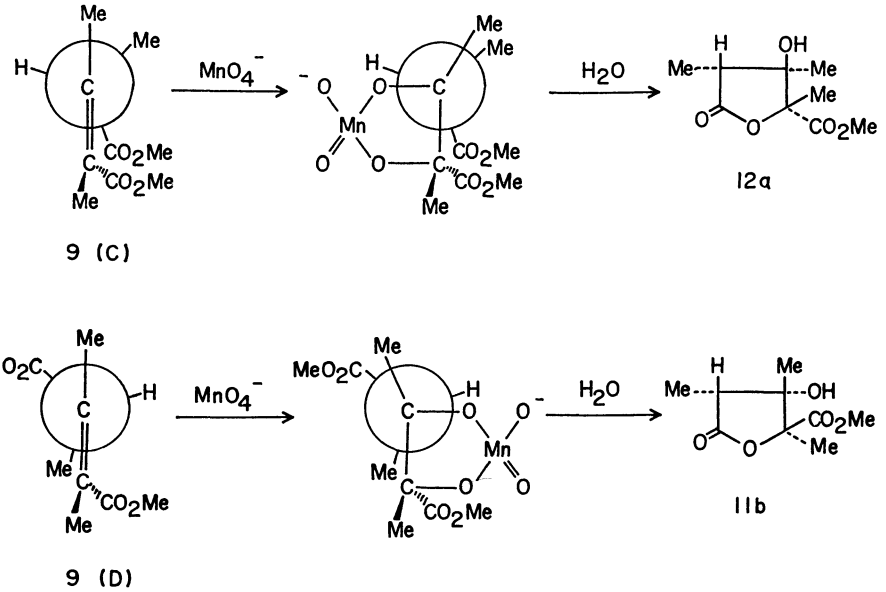


Fig. 2.

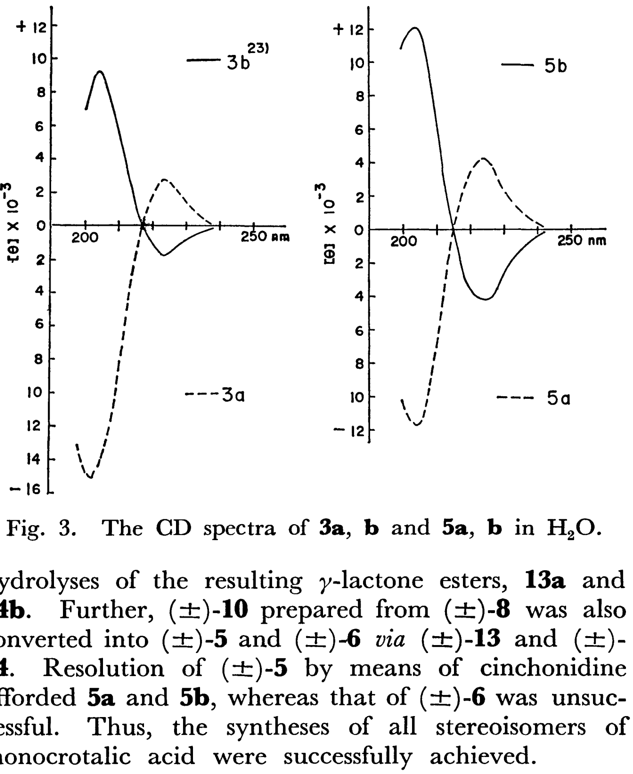


Fig. 3. The CD spectra of **3a**, **b** and **5a**, **b** in H_2O.

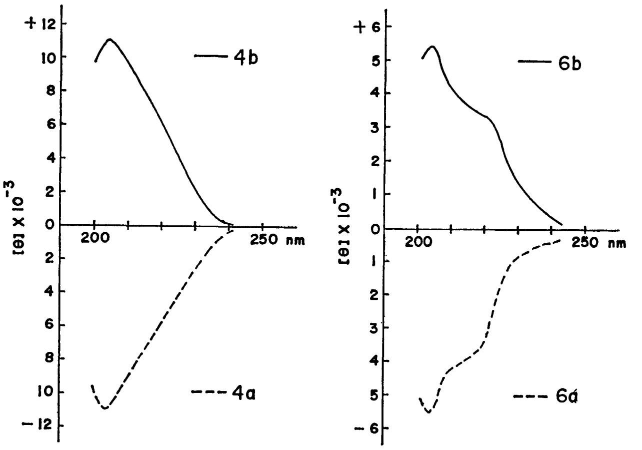


Fig. 4. The CD spectra of **4a**, **b** and **6a**, **b** in H_2O.

hydrolyses of the resulting γ-lactone esters, **13a** and **14b**. Further, (±)-**10** prepared from (±)-**8** was also converted into (±)-**5** and (±)-**6** *via* (±)-**13** and (±)-**14**. Resolution of (±)-**5** by means of cinchonidine afforded **5a** and **5b**, whereas that of (±)-**6** was unsuccessful. Thus, the syntheses of all stereoisomers of monocrotalic acid were successfully achieved.

The stereochemical course of the potassium permanganate hydroxylation of olefinic esters having an asymmetric carbon atom adjacent to the double bond can be well explained by a modification of Cram's rule of asymmetric induction (open-chain model)[17,18] as shown in Figs. 1 and 2. For example, in the *trans* ester **10b** and its *cis*-isomer **9** which is shown only one enantiomer of the racemate, the A and C conformations should be more stable than the corresponding B and D conformations, as has been reported by Karabatsos,[18] because the effective steric size of three substituents on the asymmetric carbon atom is $Me > CO_2Me > H$.[19] Therefore, the double bonds in the A and B conformations are attacked by the permanganate anion from the side of the smallest hydrogen atom, as pictured, leading to the major product **13b** and the minor one **14a**. Similarly, the C and D conformations also lead to the major product **12a** and the minor one **11b** respectively.

It has been reported that the sign of the Cotton effect in the CD spectra of γ-lactones depends on the configuration of C-4,[20–22] while in the cases of γ-lactones possessing a carboxyl group at C-2 it depends on the configuration of C-2.[8,9] On the other hand, we have also reported that when γ-lactones possess a carboxyl group at C-3, the sign is influenced by the configuration of C-4.[13] In connection with these previous works, the CD spectra of our synthetic acids (**3a,b**—**6a,b**) were also measured to obtain further information on the relationship between the absolute configuration and the sign of the CD spectrum. The CD spectra of the present samples may be divided into two classes. The compounds of the first class, **3a,b** and **5a,b**, which have the opposite absolute configurations at C-2 and C-4 (2*R*,4*S* or 2*S*,4*R*), show two distinct Cotton effects at 204 and 224 nm; these respectively represent the configurations of C-2 and C-4. Those of the second class, **4a,b** and **6a,b**, which have the same absolute configurations at C-2 and C-4 (2*R*,4*R* or 2*S*,4*S*), exhibit only one effect at 204 nm. It is clear that when the absolute configuration of C-2 or C-4 is *R*, the sign is negative, and when *S*, it is positive. It is also evident that the Cotton effect due to the configuration of C-2 is superior to that of C-4, as has been reported by Cervinka *et al.*[8,9] In the cases of **4a,b** and **6a,b**, the two Cotton effects are apparently overlapped and, consequently, only the strong effect due to the configuration of C-2 is observed at 204 nm. These results in the CD study seemed to be very useful for the prediction of the absolute configurations of both C-2 and C-4 in γ-lactones carrying a carboxyl group at C-2.

Experimental

All melting points are uncorrected. The IR spectra and optical rotations were measured in chloroform, and the NMR spectra in carbon tetrachloride at 60 MHz, with tetramethylsilane as the internal standard, unless otherwise stated. The chemical shifts are presented in terms of δ values; s: singlet, bs: broad singlet, d: doublet, dd: double doublet, q: quartet, m: multiplet. The CD spectra were recorded on a JASCO J-40CS spectropolarimeter. Column chromatography was performed using Merck silica gel (0.063 mm).

*(±)-*cis*-2,3,4-Trimethyl-2-pentenedioic Acid (7) and Its (±)-*trans*-Isomer (8).* A mixture of (±)-**7** and (±)-**8** prepared by the procedure of Adams *et al.*[7] was chromatographed on silica gel[24] using acetone-benzene (3:97) as the eluent to give an anhydride of (±)-**7**; IR: 1790, 1736, 1657 cm^{-1}; NMR: 1.51 (3H, d, *J*=7 Hz, $\mathrm{C\underline{H}_3\overset{|}{C}H-}$), 1.95 and 2.01 (each 3H and s, $\mathrm{2{=}\overset{|}{C}CH_3}$), 3.25 (1H, q, *J*=7 Hz, $\mathrm{CH_3\overset{|}{C}\underline{H}-}$). Further elution gave (±)-**7**, which was recrystallized from ether-petroleum benzine: mp 118—120 °C; NMR (CD_3COCD_3): 1.20 (3H, d, *J*=7 Hz, $\mathrm{C\underline{H}_3\overset{|}{C}H-}$), 1.75 and 1.90 (each 3H and bs, $\mathrm{2{=}\overset{|}{C}CH_3}$), 4.43 (1H, q, *J*=7 Hz, $\mathrm{CH_3\overset{|}{C}\underline{H}-}$). Found: C, 55.71; H, 7.18%. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.03%.

Further elution with acetone–benzene (1:9) afforded (±)-**8**, which was recrystallized from ether–petroleum benzine: mp 132—133 °C; NMR (CD_3COCD_3): 1.23 (3H, d, *J*=7 Hz, $\mathrm{C\underline{H}_3\overset{|}{C}H-}$), 1.94 (6H, s, $\mathrm{2{=}\overset{|}{C}CH_3}$), 3.74 (1H, q, *J*=7 Hz, $\mathrm{CH_3\overset{|}{C}\underline{H}-}$). Found: C, 55.97; H, 6.96%. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.03%.

The above anhydride was hydrolyzed with aqueous sodium hydroxide at 40 °C for 2 h to give (±)-**7**.

*Dimethyl (±)-*cis*-2,3,4-Trimethyl-2-pentenedioate (9) and Its (±)-*trans*-Isomer (10).* *a)*: A sample of (±)-**7** in ether was methylated with diazomethane to give the corresponding dimethyl ester (**9**); NMR: 1.20 (3H, d, *J*=7 Hz, $\mathrm{C\underline{H}_3\overset{|}{C}H-}$), 1.68 and 1.85 (each 3H and s, $\mathrm{2{=}\overset{|}{C}CH_3}$), 3.60 and 3.68 (each 3H and bs, 2-CO_2CH_3), 4.34 (1H, q, *J*=7 Hz, $\mathrm{CH_3\overset{|}{C}\underline{H}-}$).

b): Similarly, (±)-**8** was methylated with diazomethane to afford the corresponding ester (**10**); NMR: 1.16 (3H, d, *J*=7 Hz, $\mathrm{C\underline{H}_3\overset{|}{C}H-}$), 1.79 and 1.81 (6H, m, $\mathrm{2{=}\overset{|}{C}CH_3}$), 3.58 and 3.62 (each 3H and s, 2-CO_2CH_3), *ca.* 3.6 (1H, overlap, $\mathrm{CH_3\overset{|}{C}\underline{H}-}$).

Oxidation of (±)-9 with Potassium Permanganate. A solution of potassium permanganate (182 mg) and magnesium sulfate heptahydrate (254 mg) in water (9.0 ml) was added at −20±2 °C into a solution of (±)-**9** (170 mg) in methanol (5.0 ml) with stirring. The mixture was further stirred for 3 h at this temperature, and sodium hydrogensulfite was then added. After the methanol had been evaporated under a vacuum, the mixture was extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and then evaporated under a vacuum. The residue was purified by column chromatography on silica gel using ether-benzene (15:85) as the eluent to give a γ-lactone ester (**11**) (19 mg: 11.1%) as an oil; IR: 3590, 3450, 1777, 1737 cm^{-1}; NMR ($CDCl_3$): 1.16 (3H, d, *J*=7 Hz, C_4–CH_3), 1.23 (3H, s, C_3–CH_3), 1.59 (3H, s, C_2–CH_3), *ca.* 2.4 (1H, bs, -OH), 2.76 (1H, q, *J*=7 Hz, C_4–H), 3.77 (3H, s, -CO_2CH_3). Found: C, 53.20; H, 7.06%. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98%.

Further elution gave another γ-lactone ester (**12**) (91 mg: 53.0%) which was recrystallized from ether-petroleum benzine: mp 76—77 °C; IR: 3580, 3450, 1780, 1732 cm^{-1}; NMR ($CDCl_3$): 1.18 (3H, d, *J*=7 Hz, C_4–CH_3), 1.19 (3H, s, C_3–CH_3), 1.62 (3H, s, C_2–CH_3), *ca.* 2.5 (1H, bs, -OH), 2.87 (1H, q, *J*=7 Hz, C_4–H), 3.78 (3H, s, -CO_2CH_3). Found: C, 53.47; H, 6.97%. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98%. The IR and NMR spectra of (±)-**12** were identical with those of natural methyl monocrotalate.

Hydrolyses of (±)-11 and (±)-12. *a)*: A mixture of (±)-**11** (826 mg) and dilute hydrochloric acid (4 mol dm^{-3}: 33 ml) was refluxed for 2 h and then evaporated with benzene under a vacuum to dryness. The residue was chromatographed on silica gel[24] using acetone-benzene (1:4) as the eluent to give an acid (**3**) (587 mg: 76.4%) which was recrystallized from acetone-petroleum benzine; mp 156—158 °C; NMR (CD_3COCD_3): 1.13 (3H, d, *J*=7 Hz, C_4–CH_3), 1.38 (3H, s, C_3–CH_3), 1.57 (3H, s, C_2–CH_3), 2.80 (1H, q, *J*=7 Hz, C_4–H). Found: C, 51.16; H, 6.51%. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43%. Methylation of (±)-**3** with diazomethane yielded (±)-**11**.

b): A mixture of (±)-**12** (1.738 g) and dilute hydrochloric acid (4 mol dm^{-3}: 65 ml) was refluxed for 2 h and then treated as described for the preparation of (±)-**3**. The crude product was recrystallized from acetone-petroleum benzine to give the racemic monocrotalic acid (**4**) (659 mg: 40.8%); mp 187—189 °C; NMR (CD_3COCD_3): 1.14 (3H, d, *J*=7 Hz, C_4–CH_3), 1.27 (3H, s, C_3–CH_3), 1.62 (3H, s, C_2–CH_3), 2.84 (1H, q, *J*=7 Hz, C_4–H). Found: C, 51.30; H, 6.53%. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43%. The mother liquor of the above crystallization was evaporated under a vacuum and the residue was chromatographed on silica gel[24] using acetone–benzene (1:4) as the eluent to give some additional (±)-**4** (451 mg: 27.9%). Methylation of (±)-**4** with diazomethane afforded (±)-**12**.

Resolution of (±)-3. A mixture of (±)-**3** (551 mg) and brucine dihydrate (1.262 g) was dissolved in ethanol (100 ml) by heating. The solution was concentrated, allowed to stand at room temperature, and then filtered to give colorless crystals (870 mg), which were recrystallized three times from ethanol to give a brucine salt (464 mg); mp 218—225 °C dec; $[\alpha]_D$ −39.4°.

The salt was suspended in dilute hydrochloric acid and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and then evaporated to dryness. The residue was purified by column chromatography on silica gel[24] to give **3a** (2*R*,3*R*,4*S*) (120 mg); $[\alpha]_D$ −32° (EtOH); CD (H_2O): $[\theta]_{204}$ −15000, $[\theta]_{224}$ +2700.

The filtrate from the above salt was evaporated under a vacuum and the residue was recrystallized from ethanol to yield another brucine salt (550 mg); mp 165—168 °C;

$[\alpha]_D$ −11.1°.

This salt was also treated with dilute hydrochloric acid as described above and the crude product was purified by column chromatography on silica gel[24] to give **3b** (2*S*,3*S*,4*R*) (103 mg); $[\alpha]_D$ +22° (EtOH); CD (H_2O):[23] $[\theta]_{204}$ +9200, $[\theta]_{224}$ −1800.

Resolution of (±)-4. A mixture of (±)-**4** (1.112 g) and brucine dihydrate (2.545 g) in ethanol (150 ml) was refluxed, concentrated, and then allowed to stand at room temperature. The crystals (1.790 g, mp 207—208 °C dec) were collected by filtration and recrystallized twice from ethanol to give a brucine salt (1.165 g); mp 208—209 °C dec; $[\alpha]_D$ −11.4°.

The salt was suspended in dilute hydrochloric acid, extracted with ether, and the ether extract was washed with brine. After drying over sodium sulfate, the solution was evaporated to afford a colorless solid (210 mg), which was recrystallized from acetone–petroleum benzine, giving monocrotalic acid (**4a**) (2*R*,3*R*,4*R*); mp 185—187 °C; $[\alpha]_D$ −5.6° (EtOH) (lit, mp 181—182 °C,[2] $[\alpha]_D$ −4.65±0.5° (EtOH)[7]); CD (H_2O): $[\theta]_{204}$ −11000.

The filtrate from the above salt was evaporated and the residue was recrystallized from ethanol to give another salt (1.145 g); mp 214—216 °C dec; $[\alpha]_D$ −32°.

This salt was also treated with dilute hydrochloric acid and the product (228 mg) was recrystallized from acetone–petroleum benzine to give **4b** (2*S*,3*S*,4*S*); mp 185—187 °C; $[\alpha]_D$ +5.3° (EtOH); CD (H_2O): $[\theta]_{204}$ +11000.

*Dehydration of **11a** and **11b**.* *a)*: A sample of **3a** (59 mg) was methylated with diazomethane to yield the corresponding methyl ester (**11a**), which was dissolved in a mixture of phosphoryl chloride (246 mg) and pyridine (0.6 ml). The solution was refluxed for 30 min, cooled, diluted with a mixture of ice and dilute hydrochloric acid, and then extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using ether-benzene (2:98) as the eluent to give methyl (*R*)-(+)-anhydromonocrotalate (**15a**) as an oil (35 mg: 60%); $[\alpha]_D$ 203°; IR: 1757, 1732, 1675 cm^{-1}; NMR ($CDCl_3$): 1.64 (3H, s, C_2–CH_3), 1.83 and 1.99 (each 3H and s, $2{=}\overset{|}{C}CH_3$), 3.76 (3H, s, $-CO_2CH_3$). Found: C, 58.58; H, 6.67%. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57%.

b): A sample of **3b** (60 mg: $[\alpha]_D$ +18° (EtOH)) was methylated with diazomethane to afford a methyl ester (**11b**), which was refluxed with a mixture of phosphoryl chloride (248 mg) and pyridine (0.5 ml) for 30 min. After the same work-up as described in a) above the crude product was purified by column chromatography on silica gel to give methyl (*S*)-(−)-anhydromonocrotalate (**15b**) (47 mg: 76%) as an oil, $[\alpha]_D$ −101°, whose IR and NMR spectra were identical with those of **15a**.

*Dehydration of **12a** and **12b**.* *a)*: A sample of monocrotalic acid (**4a**) (143 mg) was methylated with diazomethane to give methyl monocrotalate (**12a**), which was refluxed with phosphoryl chloride (560 mg) in pyridine (1.2 ml) for 30 min. After the same work-up as described above, the crude product was purified by column chromatography on silica gel to afford an oil (100 mg: 72%), $[\alpha]_D$ +205°, whose IR and NMR spectra were identical with those of methyl (*R*)-(+)-anhydromonocrotalate (**15a**).

b): Methylation of **4b** (43 mg) with diazomethane gave the corresponding methyl ester (**12b**), which was dehydrated with phosphoryl chloride (170 mg) in pyridine (0.5 ml) as described above. Purification of the crude product by column chromatography on silica gel afforded methyl (*S*)-(−)-anhydromonocrotalate (**15b**) (35 mg: 83%) as an oil, $[\alpha]_D$ −195°.

*(S)-(+)-3-Acetoxy-2-methylpropanoic Acid (**25**).* (*R*)-(−)-2-Phenylpropanoic acid (**21**)[16] (6.136 g, $[\alpha]_D$ −63.8°) was methylated with diazomethane to give a methyl ester (**22**) (6.701 g), $[\alpha]_D$ −85°.

A sample of **22** (6.137 g) was reduced with lithium aluminium hydride (852 mg) in ether (60 ml) at room temperature for 2 h. After the usual work-up, the crude alcohol (**23**) (5.038 g: $[\alpha]_D$ +4.5°) was immediately acetylated at 80 °C for 1.5 h with acetic anhydride (19 ml) in pyridine (25 ml) to give (*R*)-(−)-2-phenylpropyl acetate (**24**) (6.254 g); $[\alpha]_D$ −4.5°; NMR: 1.30 (3H, d, *J*=7 Hz, $C\underline{H}_3\overset{|}{C}H-$), 1.96 (3H, s, $-OCOCH_3$), 3.05 (1H, m, $CH_3\overset{|}{C}\underline{H}-$), 4.10 (2H, bd, *J*=7 Hz, $-CH_2O-$), 7.21 (5H, s, $-C_6H_5$).

A solution of **24** (5.810 g) in chloroform (30 ml) was ozonized at 0—15 °C for *ca.* 70 h. The solution was evaporated under a vacuum and the residue was chromatographed on silica gel[24] using ether-benzene (1:9) as the eluent to afford an acid (**25**) as an oil (1.813 g); $[\alpha]_D$ +16.2°; NMR: 1.25 (3H, d, *J*=7 Hz, $C\underline{H}_3\overset{|}{C}H-$), 2.23 (3H, s, $-OCOCH_3$), 2.78 (1H, m, $CH_3\overset{|}{C}\underline{H}-$), 4.16 (2H, d, *J*=7 Hz, $-CH_2O-$).

*Methyl (S)-(+)-3-Acetoxy-2-methylpropanoate (**26**).* A solution of **25** (1.508 g) in ether (10 ml) was methylated with diazomethane to give the corresponding methyl ester (**26**) (1.567 g); $[\alpha]_D$ +18.2°; NMR: 1.19 (3H, d, *J*=7 Hz, $C\underline{H}_3\overset{|}{C}H-$), 2.00 (3H, s, $-OCOCH_3$), 2.70 (1H, m, $CH_3\overset{|}{C}\underline{H}-$), 3.69 (3H, s, $-CO_2CH_3$), 4.13 (2H, d, *J*=7 Hz, $-CH_2O-$).

*(S)-(−)-3-Hydroxy-2,3-dimethylbutyl Acetate (**20b**).* The Grignard reagent, prepared from methyl iodide (5.0 ml) and magnesium (1.306 g) in dry ether (10 ml), was diluted with dry benzene (15 ml), and then the ether was distilled off. After the addition of a solution of **26** (1.323 g) in dry benzene (3.0 ml), the mixture was stirred at room temperature for 30 min and then refluxed for 1.5 h. The reaction mixture was poured into a mixture of ice and dilute hydrochloric acid, and extracted with ether. The aqueous layer was further extracted continuously with ether for *ca.* 2.5 h. The ether extracts were combined, washed successively with aqueous sodium thiosulfate and brine, dried over sodium sulfate, and then evaporated. The residual oil (925 mg) was purified by column chromatography on silica gel using ether–chloroform (1:1) as the eluent to give (*S*)-2,3-dimethyl-1,3-butanediol (**19b**) (615 mg); NMR: 0.82 (3H, d, *J*=7 Hz, $C\underline{H}_3\overset{|}{C}H-$), 1.12 and 1.19 (each 3H and s, $(CH_3)_2\overset{|}{C}-$), 3.58 (2H, d, *J*=7 Hz, $-C\underline{H}_2OH$).

The above diol **19b** (64.8 mg) was acetylated with acetic anhydride (0.3 ml) in pyridine (0.5 ml) at room temperature for 36 h. After the usual work-up, the crude product was purified by column chromatography on silica gel using ether–chloroform (1:9) as the eluent to give (*S*)-(−)-3-hydroxy-2,3-dimethylbutyl acetate (**20b**) (54.3 mg) as an oil: $[\alpha]_D$ −27.1°; IR: 3605, 3460, 1725 cm^{-1}; NMR: 0.94 (3H, d, *J*=7 Hz, $C\underline{H}_3\overset{|}{C}H-$), 1.12 and 1.17 (each 3H and s, $(CH_3)_2\overset{|}{C}-$), 2.00 (3H, s, $-OCOCH_3$), 3.6—4.4 (2H, m, $-CH_2O-$). Found: C, 59.69; H, 9.78%. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07%.

*Resolution of (±)-trans-2,3,4-Trimethyl-2-pentenedioic Acid (**8**).* A mixture of (±)-**8** (3.455 g) and cinchonidine (11.812 g) was dissolved in ethyl acetate (2.3 l) by refluxing, concentrated to about half volume, and then allowed to stand at room temperature. The colorless crystals (8.14 g) were collected by filtration and recrystallized twice from ethyl acetate to afford a cinchonidine salt (5.537 g); mp 185—187 °C; $[\alpha]_D$ −64°.

An aliquot of the above salt (500 mg) was suspended in dilute hydrochloric acid, extracted with ether, and the ether extract was washed with brine. After drying over sodium sulfate, the solution was evaporated to give (*S*)-(+)-*trans*-2,3,4-trimethyl-2-pentenedioic acid (**8a**) (121 mg), which was recrystallized from ether-petroleum benzine; mp 108—110 °C; $[\alpha]_D$ +121° (ether).

The filtrate from the above salt was evaporated under a vacuum and the residue was recrystallized several times from ethyl acetate to give another cinchonidine salt (1.787 g); mp 166—168 °C; $[\alpha]_D$ −97°.

This salt was also treated with dilute hydrochloric acid to afford (*R*)-(−)-*trans*-2,3,4-trimethyl-2-pentenedioic acid (**8b**) (375 mg); mp 108—110 °C; $[\alpha]_D$ −120° (ether).

*Methylation of **8a** and **8b**.* *a)*: Methylation of **8a** with diazomethane afforded dimethyl (*S*)-(+)-*trans*-2,3,4-trimethyl-2-pentenedioate (**10a**) as an oil, $[\alpha]_D$ +114° (ether), whose IR and NMR spectra were identical with those of (±)-**10**.

b): Methylation of **8b** with diazomethane afforded dimethyl (*R*)-(−)-*trans*-2,3,4-trimethyl-2-pentenedioate (**10b**) as an oil, $[\alpha]_D$ −111° (ether), whose IR and NMR spectra were identical with those of (±)-**10**.

*(*S*)-(+)-1,5-Diacetoxy-2,3,4-trimethyl-2-pentene (**17**).* A solution of **10a** (1.670 g, $[\alpha]_D$ +102° (ether)) in dry ether (15 ml) was added dropwise to a suspension of lithium aluminium hydride (950 mg) in dry ether (20 ml) with stirring. The mixture was refluxed for 2 h, poured into a mixture of ice and dilute hydrochloric acid, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and then evaporated to give a diol (**16**) (1.101 g) as an oil, $[\alpha]_D$ +7.4° (ether).

The above crude diol (**16**) (1.101 g) was immediately acetylated with acetic anhydride (4.4 ml) in pyridine (6.0 ml) at 80 °C for 2 h. After the usual work-up, the crude product was purified by column chromatography on silica gel using ether–benzene (2:98) as the eluent to give a diacetate (**17**) (665 mg) as an oil: $[\alpha]_D$ +9.1°; IR: 1725 cm^{-1}; NMR: 0.98 (3H, d, *J*=7 Hz, $C\underline{H}_3\overset{|}{C}H-$), 1.70 (6H, br, $2{=}\overset{|}{C}CH_3$), 1.95 and 1.99 (each 3H and s, $2-OCOCH_3$), 3.92 (2H, d, *J*=7 Hz, $-CH_2O-$), 4.51 (2H, s, $=\overset{|}{C}CH_2O-$). Found: C, 63.02; H, 9.13%. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83%.

*(*R*)-(+)-3-Hydroxy-2,3-dimethylbutyl Acetate (**20a**).* A solution of **17** (323 mg) in chloroform (10 ml) was ozonized at −10 °C for 3 h and then evaporated to give a crude ketone (**18**) (331 mg).

A solution of the above ketone (**18**) (321 mg) in dry benzene (3.0 ml) was refluxed for 1.5 h with the Grignard reagent, prepared from methyl iodide (1.1 ml) and magnesium (345 mg) in dry ether (5.0 ml) and benzene (5.0 ml). After the same work-up as described for the preparation of **19b**, the crude product was purified by column chromatography on silica gel using ether-chloroform (1:1) as the eluent to give a diol (**19a**) (83 mg) whose IR and NMR spectra were identical with those of **19b**.

The above diol **19a** (68 mg) was acetylated with acetic anhydride (0.3 ml) in pyridine (0.5 ml) at room temperature for 36 h. After the same work-up as described for the preparation of **20b**, the crude product was purified by column chromatography on silica gel to afford (*R*)-(+)-3-hydroxy-2,3-dimethylbutyl acetate (**20a**) (52 mg) as an oil, $[\alpha]_D$ +16.9°, whose IR and NMR spectra were identical with those of **20b**. Found: C, 59.73; H, 10.17%. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07%.

*Oxidation of **10b** with Potassium Permanganate.* A solution of **10b** (355 mg) in methanol (10 ml) was oxidized at −20±2 °C with a solution of potassium permanganate (380 mg) and magnesium sulfate heptahydrate (531 mg) in water (18 ml) as described above. The crude product was purified by column chromatography on silica gel using ether-benzene (15:85) as the eluent to give a γ-lactone ester (**13b**) (2*S*,3*R*,4*R*) (104 mg), which was recrystallized from ether-petroleum benzine; mp 93—95 °C; $[\alpha]_D$ +28.5°; IR: 3450, 1780, 1740 cm^{-1}; NMR ($CDCl_3$): 1.19 (3H, d, *J*=7 Hz, C_4-CH_3), 1.28 (3H, s, C_3-CH_3), 1.58 (3H, s, C_2-CH_3), 3.04 (1H, q, *J*=7 Hz, C_4-H), 3.82 (3H, s, $-CO_2CH_3$). Found: C, 53.62; H, 6.84%. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98%.

Further elution gave another γ-lactone ester (**14a**) (2*R*, 3*S*,4*R*) (44 mg) which was recrystallized from ether; mp 133—135 °C; $[\alpha]_D$ +5.1°; IR: 3450, 1780, 1730 cm^{-1}; NMR ($CDCl_3$): 1.22 (3H, d, *J*=7 Hz, C_4-CH_3), 1.53 (3H, s, C_3-CH_3), 1.58 (3H, s, C_2-CH_3), 2.61 (1H, q, *J*=7 Hz, C_4-H), 3.83 (3H, s, $-CO_2CH_3$). Found: C, 53.58; H, 7.18%. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98%.

*Dehydration of **13b** and **14a**.* *a)*: A sample of **13b** (86 mg) was dehydrated with phosphoryl chloride (324 mg) in pyridine (0.8 ml) as described above. The crude product was purified by column chromatography on silica gel to afford methyl (*S*)-(−)-anhydromonocrotalate (**15b**) (40 mg: 51%) as an oil, $[\alpha]_D$ −199°.

b): A sample of **14a** (39 mg) was also dehydrated with phosphoryl chloride (148 mg) in pyridine (0.5 ml) to yield methyl (*R*)-(+)-anhydromonocrotalate (**15a**) (13 mg: 35%) as an oil, $[\alpha]_D$ +170°.

*Hydrolyses of **13b** and **14a**.* *a)*: A sample of **13b** (88 mg) was refluxed with dilute hydrochloric acid (4 mol dm^{-3}:4.0 ml) for 2 h. The product (71 mg) was recrystallized from acetone-petroleum benzine to give the corresponding γ-lactone acid (**5b**) (2*S*,3*R*,4*R*); mp 185—188 °C; $[\alpha]_D$ +60° (EtOH); NMR (CD_3COCD_3): 1.11 (3H, d, *J*=7 Hz, C_4-CH_3), 1.28 (3H, s, C_3-CH_3), 1.53 (3H, s, C_2-CH_3), 3.09 (1H, q, *J*=7 Hz, C_4-H). Found: C, 51.08; H, 6.46%. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43%.

Methylation of **5b** with diazomethane gave **13b**.

b): A sample of **14a** (39 mg) was hydrolyzed with dilute hydrochloric acid. The product (27 mg) was recrystallized from acetone-petroleum benzine to give the corresponding γ-lactone acid (**6a**) (2*R*,3*S*,4*R*); mp 185—187.5 °C; $[\alpha]_D$ −5.1° (EtOH); CD (H_2O): $[\theta]_{204}$ −5500; NMR (CD_3COCD_3): 1.13 (3H, d, *J*=7 Hz, C_4-CH_3), 1.53 (3H, s, C_3-CH_3), 1.56 (3H, s, C_2-CH_3), 2.82 (1H, q, *J*=7 Hz, C_4-H). Found: C, 51.10; H, 6.45%. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43%.

Methylation of **6a** with diazomethane gave **14a**.

*Oxidation of **10a** with Potassium Permanganate.* A solution of **10a** (1.075 g) in methanol (32 ml) was oxidized at −20±2 °C with a solution of potassium permanganate (1.150 g) and magnesium sulfate heptahydrate (1.607 g) in water (60 ml), as described for (±)-**9**. The crude product was chromatographed on silica gel using ether-benzene (15:85) as the eluent to give a γ-lactone ester (**13a**) (2*R*, 3*S*,4*S*) (432 mg), which was recrystallized from ether-petroleum benzine; mp 94—96 °C; $[\alpha]_D$ −29.6°. The IR and NMR spectra of **13a** were identical with those of **13b**.

Further elution gave another γ-lactone ester (**14b**) (2*S*, 3*R*,4*S*) (188 mg), which was recrystallized from ether: mp 133—135 °C; $[\alpha]_D$ −5.4°. The IR and NMR spectra of **14b** were identical with those of **14a**.

*Hydrolyses of **13a** and **14b**.* *a)*: A sample of **13a** was refluxed with dilute hydrochloric acid for 2 h. Purification of the product gave **5a** (2*R*,3*S*,4*S*); mp 186—189 °C; $[\alpha]_D$ −69° (EtOH). The NMR spectrum of **5a** was identical with that of **5b**.

Methylation of **5a** with diazomethane gave **13a**.

b): A sample of **14b** was hydrolyzed with dilute hydrochloric acid to afford **6b** (2*S*,3*R*,4*S*); mp 185.5—188 °C; $[\alpha]_D$ +6.3° (EtOH); CD (H_2O): $[\theta]_{204}$ +5400. The NMR spectrum of **6b** was identical with that of **6a**.

Methylation of **6b** with diazomethane gave **14b**.

*Oxidation of (±)-**10** with Potassium Permanganate.* A sample of (±)-**10** was oxidized with potassium permanganate as described for (±)-**9**. Chromatographic purification of the crude product yielded a γ-lactone ester, (±)-**13**, which was recrystallized from ether-petroleum benzine: mp 93—94.5 °C. Found: C, 53.73; H, 6.96%. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98%.

Further elution gave another γ-lactone ester, (±)-**14**, which was recrystallized from ether, mp 110—111.5 °C. Found: C, 53.55; H, 7.06%. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98%.

*Hydrolyses of (±)-**13** and (±)-**14**.* *a)*: A sample of (±)-**13** was hydrolyzed with dilute hydrochloric acid to give (±)-**5**, mp 161—165 °C. Found: C, 50.78; H, 6.50%. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43%.

b): A similar hydrolysis of (±)-**14** afforded (±)-**6**, mp 199—203 °C. Found: C, 51.10; H, 6.45%. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43%.

*Resolution of (±)-**5**.* A mixture of (±)-**5** (1.048 g) and cinchonidine (1.639 g) was dissolved in hot ethyl acetate (600 ml) and then concentrated. The crystals were collected by filtration and recrystallized from ethyl acetate to afford a cinchonidine salt (930 mg); mp 199.5—201 °C dec; $[\alpha]_D$ −77.2°.

The salt was suspended in dilute hydrochloric acid and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and then evaporated to give **5b** (2*S*,3*R*,4*R*) (311 mg), which was recrystallized from acetone-petroleum benzine; mp 186—189 °C; $[\alpha]_D$ +70.0° (EtOH); CD (H_2O): $[\theta]_{204}$ +12000, $[\theta]_{224}$ −4200.

The filtrate from the above salt was evaporated and the residue was recrystallized from ethyl acetate to give another cinchonidine salt (788 mg); mp 187—189 °C; $[\alpha]_D$ −62.9°.

This salt was also treated with dilute hydrochloric acid to give **5a** (2*R*,3*S*,4*S*) (279 mg), which was recrystallized from acetone-petroleum benzine; mp 186—189 °C; $[\alpha]_D$ −69.4° (EtOH); CD (H_2O): $[\theta]_{204}$ −12000, $[\theta]_{224}$ +4200.

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