Pyrrolizidine Alkaloids. The Synthesis and Absolute Configuration of All Stereoisomers of 4-Carboxy-4-ethyl-3-hydroxy-2-isopropyl-4-butanolide, the Necic Acid Component of Axillaridine

Takashi MATSUMOTO,* Hiromitsu TERAO, Natsuki ISHIZUKA,†,††† Shuji USUI,† and Hiroshi NOZAKI††

Department of Applied Material Science, Faculty of Integrated Arts and Sciences, University of Tokushima, Minamijosanjima, Tokushima 770

† Department of Chemistry, Faculty of Science, Hiroshima University, Kagamiyama, Higashi-Hiroshima 724

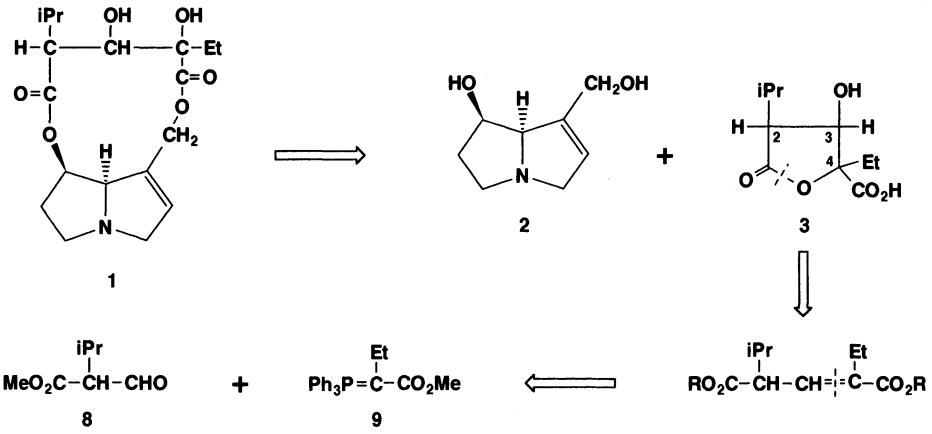
†† Department of Chemistry, Faculty of Science, Okayama University of Science, Ridai-cho, Okayama 700

(Received January 16, 1992)

All stereoisomers (**4a,b**—**7a,b**) of 4-carboxy-4-ethyl-3-hydroxy-2-isopropyl-4-butanolide, the necic acid component of axillaridine, have been synthesized. Methyl(*E*)-(*S*)-(+)-2-ethyl-4-methoxycarbonyl-5-methyl-2-hexenoate (**12a**) was converted into γ-lactone acids, **4a** (2*S*,3*S*,4*S*), **5a** (2*S*,3*R*,4*R*), and **5b** (2*R*,3*S*,4*S*), by a series of reactions: Epoxidation with *m*-chloroperbenzoic acid, treatment with acetone in the presence of tin(IV) chloride, acidic hydrolysis with formic acid, and alkaline hydrolysis with barium hydroxide. Similarly, (*R*)-(−)-enantiomer (**12b**) was also transformed into γ-lactone acids **4b** (2*R*,3*R*,4*R*), **5b** and **5a**. Subsequently, (*E*)-(*S*)-(+)-4-carboxy-2-ethyl-5-methyl-2-hexenoic acid (**13a**) and its (*R*)-(−)-enantiomer (**13b**) were esterified with chloromethyl methyl ether in the presence of triethylamine to give the corresponding bis(methoxymethyl) esters (**26a** and **26b**). Oxidation of **26a** with potassium permanganate and subsequent acidic hydrolysis afforded γ-lactone acids, **6a** (2*S*,3*R*,4*S*) and **7a** (2*S*,3*S*,4*R*). Similarly, ester **26b** was also converted into **6b** (2*R*,3*S*,4*R*) and **7b** (2*R*,3*R*,4*S*). The stereochemical courses of the above-mentioned *trans*- and *cis*-hydroxylations of olefinic esters (**12a,b** and **26a,b**) were well explained by applying the Felkin–Anh model. The CD spectra of the synthetic **4a,b**—**7a,b** are also discussed.

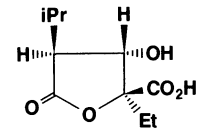
Axillaridine (**1**), a novel pyrrolizidine alkaloid, was isolated from the seeds of *Crotalaria axillaris* Ait[1] and *Crotalaria scassellatii* Chiov[2] (Leguminosae). The structure of axillaridine was assigned to an eleven-membered diester of retronecine by Crout.[1] The hydrolysis of axillaridine (**1**) might be expected to produce retronecine (**2**) as a necine and 4-carboxy-4-ethyl-3-hydroxy-2-isopropyl-4-butanolide (**3**) as a necic acid. However, the isolation and stereochemistry of the necic acid component in the natural compound have not been reported. Since butanolide **3** possesses three asymmetric carbons in the molecule, eight stereoisomers (**4a,b**—**7a,b**) are possible for **3**.

This paper describes the syntheses and absolute configurations of all the stereoisomers of **3**. In addition, the relationship between the absolute configurations and circular dichroism (CD) spectra of the synthetic butanolides is also discussed. Our synthetic strategy was developed from a retrosynthetic analysis of the necic acid **3**, which involved the disconnection illustrated in Scheme 1. That is, racemic methyl-2-formyl-3-methylbutanoate (**8**) was first condensed with [1-(methoxycarbonyl)propylidene]triphenylphosphorane[3] (**9**) to give an α,β-unsaturated ester which, after optical resolution, was submitted to stereoselective hydroxylation to give the butanolides (**4a,b**—**7a,b**).

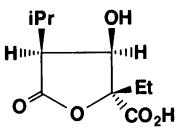


Scheme 1.

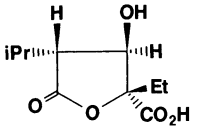
††† Present address: Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553.



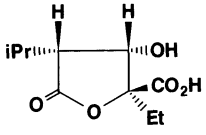
4a



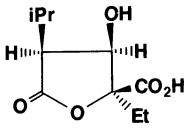
5a



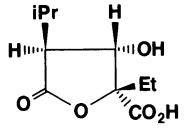
4b



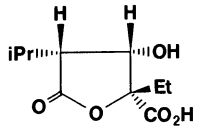
5b



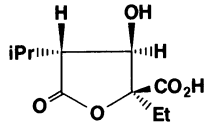
6a



7a

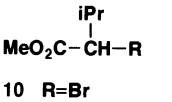


6b

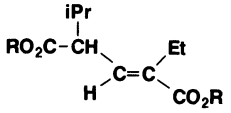


7b

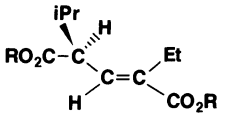
The preparation of the racemic formyl compound **8** was carried out starting from methyl 2-bromo-3-methylbutanoate (**10**) via methyl 2-(dimethoxymethyl)-3-methylbutanoate (**11**) by a modification of the method of Miyazaki et al.[4] The Wittig reaction of **8** with **9** in refluxing benzene afforded racemic methyl (*E*)-2-ethyl-4-methoxycarbonyl-5-methyl-2-hexenoate (**12**) in 84% yield. The *E*-configuration of **12** was supported by its ^{1}H NMR spectrum, which showed an olefinic proton signal in the low field (δ=6.50), suggesting the presence of a *cis*-methoxycarbonyl group relative to the olefinic proton.[5] Hydrolysis of **12** with concentrated hydrochloric acid afforded the corresponding dioic acid (**13**: 93% yield) which was resolved by means of cinchonidine to give the optically active dioic acids, **13a** $[\alpha]_D$ +114° ($CHCl_3$) and **13b** $[\alpha]_D$ −115° ($CHCl_3$). Each of the dioic acids, **13a** and **13b**, was esterified with diazomethane to give the corresponding dimethyl esters, **12a** and **12b**, respectively. In order to assign the absolute configurations of **13a** and **13b**, the following correlation was carried out. Ozonolysis of **12a** in chloroform, followed by sodium borohydride reduction and subsequent acetylation, produced methyl 2-(acetoxymethyl)-3-methylbutanoate (**14a**) $[\alpha]_D$ +16.5° ($CHCl_3$). On the other hand, transformation of the known (*R*)-(−)-α-isopropylphenylacetic acid[6,7] (**15**) into **14a** was also carried out as follows. Esterification of **15** with diazomethane afforded an ester (**16**). This was reduced with lithium aluminium hydride; the resulting alcohol was further acetylated to give an acetate (**17**). Ozonolysis of **17** in chloroform, followed by esterification of the resulting acid with diazomethane, produced methyl (*S*)-(+)-2-(acetoxymethyl)-3-methylbutanoate, $[\alpha]_D$ +17.5° ($CHCl_3$), the physical and spectral data of which were identical with those of **14a**. Thus, the stereochemistry of **14a** was assigned to be the *S*-configuration; **13a** and **13b** consequently have the *S*- and *R*-configuration, respectively.



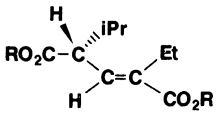
10 R=Br
11 R=CH(OMe)$_2$



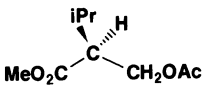
12 R=Me
13 R=H



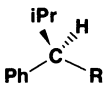
12a R=Me
13a R=H
26a R=CH$_2$OMe



12b R=Me
13b R=H
26b R=CH$_2$OMe



14a



15 R=CO$_2$H
16 R=CO$_2$Me
17 R=CH$_2$OAc

Syntheses of four stereoisomers, **4a**, **4b**, **5a**, and **5b**, were carried out as follows. Oxidation of the (*S*)-(+)-ester **12a** with *m*-chloroperbenzoic acid in refluxing 1,2-dichloroethane produced two epoxides, **18a** and **19a**, in 66 and 20% yields. The major epoxide **18a** was treated with acetone and anhydrous tin(IV) chloride in carbon tetrachloride[8] at room temperature to give an acetonide (**20a**: 70% yield) which was hydrolyzed with formic acid to give a γ-lactone ester (**22a**) in 78% yield. Similar treatment of the minor epoxide **19a** with acetone and anhydrous tin(IV) chloride in carbon tetrachloride afforded an acetonide (**21a**) and a γ-lactone ester (**23a**) in 15 and 55% yields, respectively. Hydrolysis of **21a** with formic acid afforded **23a** in 86% yield. The γ-lactone ester **22a** was then refluxed with barium hydroxide in aqueous methanol to give a mixture of the C-2 epimeric γ-lactone acids, **4a** (7% yield) and **5b** (71% yield). Esterifications of **4a** and **5b** with diazomethane afforded the corresponding methyl esters, **22a** and **23b**, respectively. The γ-lactone ester **23a** was also hydrolyzed with barium hydroxide to give a single γ-lactone acid (**5a**: 86% yield) which was subsequently methylated back into

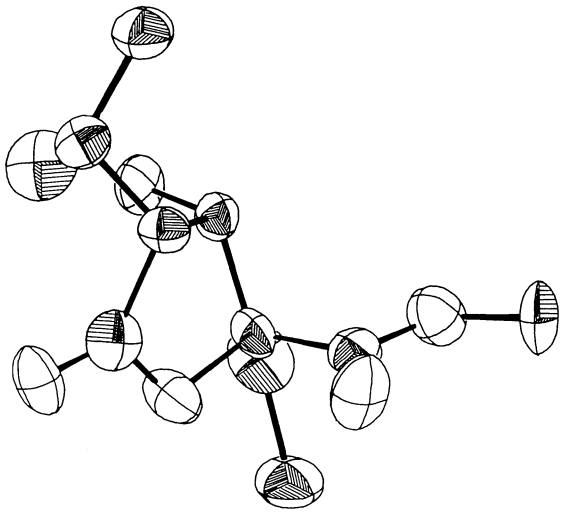
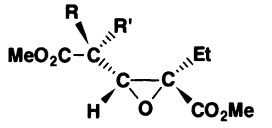


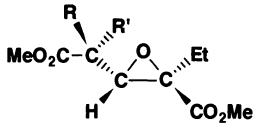
Fig. 1. The X-ray structure of 4-ethyl-3-hydroxy-2-isopropyl-4-methoxycarbonyl-4-butanolide (**23b**).

23a with diazomethane. In order to determine the absolute configurations of these synthetic γ-lactones, ester **23b** was submitted to an X-ray crystal analysis; its configuration was indicated as being 2*R*,3*S*,4*S*, as shown in Fig. 1.

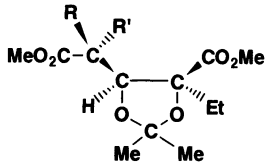
Since the absolute stereochemistry of C-2 in **22a** and **23a** was determined in **14a**, the absolute configurations of **4a** and **22a**, **5a** and **23a**, and **5b** were assigned to be (2*S*,3*S*,4*S*), (2*S*,3*R*,4*R*), and (2*R*,3*S*,4*S*), respectively. Dehydration of the γ-lactone esters, **22a** and **23b**, with phosphoryl chloride in pyridine afforded the same α,β-unsaturated (*S*)-γ-lactone ester (**24**) $[\alpha]_D$ −155° ($CHCl_3$), while ester **23a** afforded the (*R*)-isomer (**25**) $[\alpha]_D$ +156°($CHCl_3$).



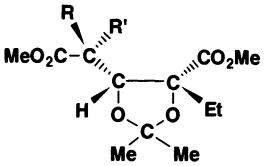
18a R=iPr, R'=H
19b R=H, R'=iPr



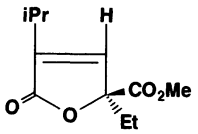
19a R=iPr, R'=H
18b R=H, R'=iPr



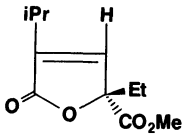
20a R=iPr, R'=H
21b R=H, R'=iPr



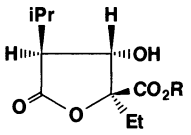
21a R=iPr, R'=H
20b R=H, R'=iPr



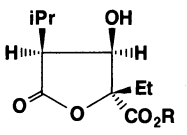
24



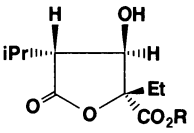
25



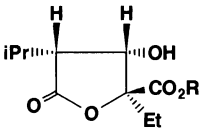
4a R=H
22a R=Me



5a R=H
23a R=Me



4b R=H
22b R=Me



5b R=H
23b R=Me

Similarly, the (*R*)-(−)-ester **12b** was also oxidized with *m*-chloroperbenzoic acid to give two epoxides, **18b** (44% yield) and **19b** (13% yield), which were treated, respectively, with acetone and anhydrous tin(IV) chloride in carbon tetrachloride to yield acetonides, **20b** (53% yield) and **21b** (79% yield). Each of these acetonides, **20b** and **21b**, was further treated with formic acid to afford γ-lactone esters, **22b** (78% yield) and **23b** (2*R*,3*S*,4*S*: 86% yield), respectively. The hydrolysis of **23b** with barium hydroxide in refluxing aqueous methanol afforded the (2*R*,3*S*,4*S*)-γ-lactone acid (**5b**) in 73% yield. Similar hydrolysis of **22b** with barium hydroxide afforded a mixture of the C-2 epimeric γ-lactone acids, **5a** (2*S*,3*R*,4*R*: 63% yield) and **4b** (24% yield). Thus, the absolute configurations of **4b** and **22b** were assigned to be the same 2*R*,3*R*,4*R*.

The stereochemical course of the above-mentioned *trans*-hydroxylation of olefinic esters (**12a** and **12b**) having an asymmetric carbon atom adjacent to the double bond can be well explained by applying the Felkin-Anh model,[9] as shown in Figs. 2 and 3. For example, in olefinic esters **12a** and **12b**, the A and C conformations should be more stable than the corresponding B and D conformations, since B and D have a large steric interaction between the ethyl and methoxycarbonyl groups. Therefore, the double bonds in the A and B conformations are attacked by *m*-chloroperbenzoic acid from the opposite side of the largest isopropyl group, leading to the major epoxide **18a** and the minor one **19a**. Similarly, the C and D conformations also lead to the major epoxide **18b** and the minor one **19b**, respectively. The S_N2 type substitutions of these epoxides (**18a**, **19a**, **18b**, and **19b**) starting at C-3 with acetone in the presence of anhydrous tin(IV) chloride afforded acetonides (**20a**, **21a**, **20b**, and **21b**), which were respectively hydrolyzed with formic acid to give γ-lactone esters (**22a**, **23a**, **22b**, and **23b**).

Subsequently, the remaining stereoisomers, **6a**, **6b**, **7a**, and **7b**, were also synthesized as follows. The dioic acids, **13a** and **13b**, were each esterified with chloromethyl methyl ether and triethylamine in *N*,*N*-dimethylformamide[10] to give the corresponding diesters,

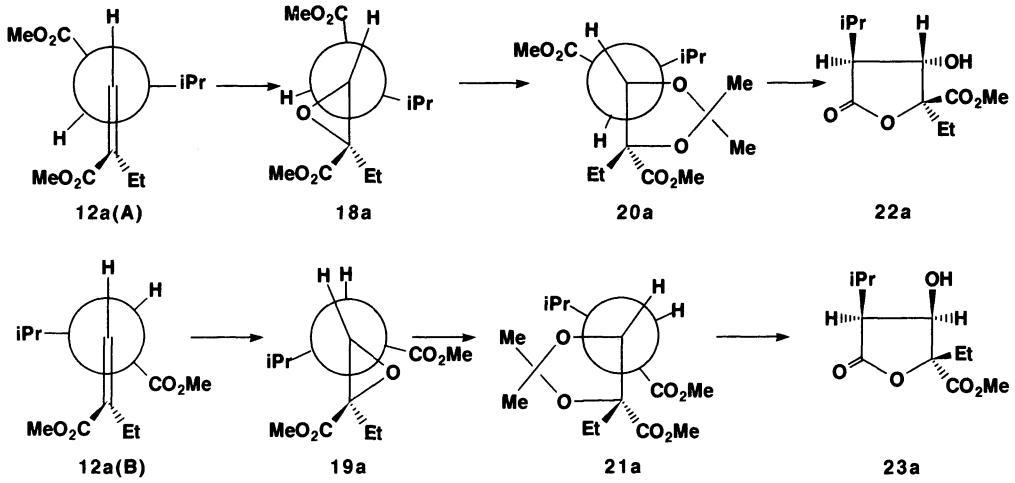


Fig. 2. The *trans*-hydroxylation of **12a**.

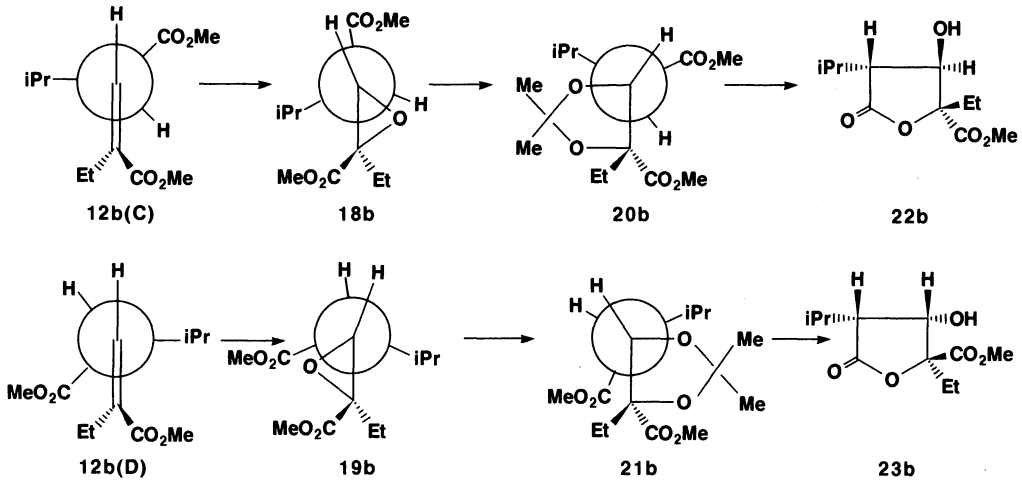
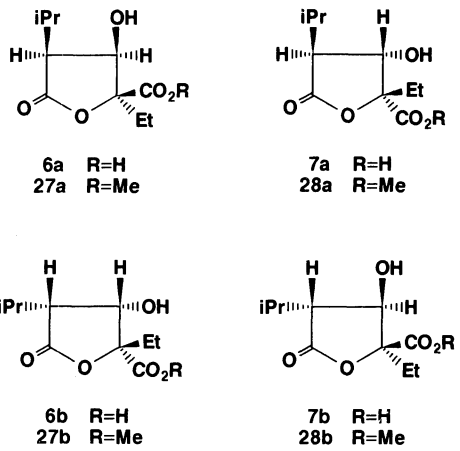


Fig. 3. The *trans*-hydroxylation of **12b**.

26a and **26b**. Oxidation of **26a** with potassium permanganate in aqueous methanol followed by hydrolysis with dilute hydrochloric acid afforded two γ-lactone acids, **6a** and **7a**, in 44 and 4% yields from **13a**. These acids, **6a** and **7a**, were further esterified with diazomethane to give the corresponding methyl esters, **27a** and **28a**. Similar oxidation of **26b** with potassium permanganate, and subsequent acidic hydrolysis, produced two γ-lactone acids, **6b** and **7b**, in 51 and 3% yields from **13b**. These acids, **6b** and **7b**, were also converted into the corresponding methyl esters, **27b** and **28b**, by esterification with diazomethane. The hydrolyses of **27a** and **28a** with barium hydroxide in refluxing aqueous methanol afforded γ-lactone acids, **6a** and **6b**, respectively. Dehydration of **27a** with phosphoryl chloride in pyridine afforded the α,β-unsaturated (*S*)-γ-lactone (**24**). Thus, the absolute configurations of **6a** and **27a**, **7a** and **28a**, **6b** and **27b**, and **7b** and **28b** were assigned to be (2*S*,3*R*,4*S*), (2*S*,3*S*,4*R*), (2*R*,3*S*,4*R*), and (2*R*,3*R*,4*S*), respectively.



The stereochemical course of the above-mentioned potassium permanganate *cis*-hydroxylation of olefinic esters (**26a** and **26b**) can also be explained as shown in Figs. 4 and 5. Since the E and G conformations

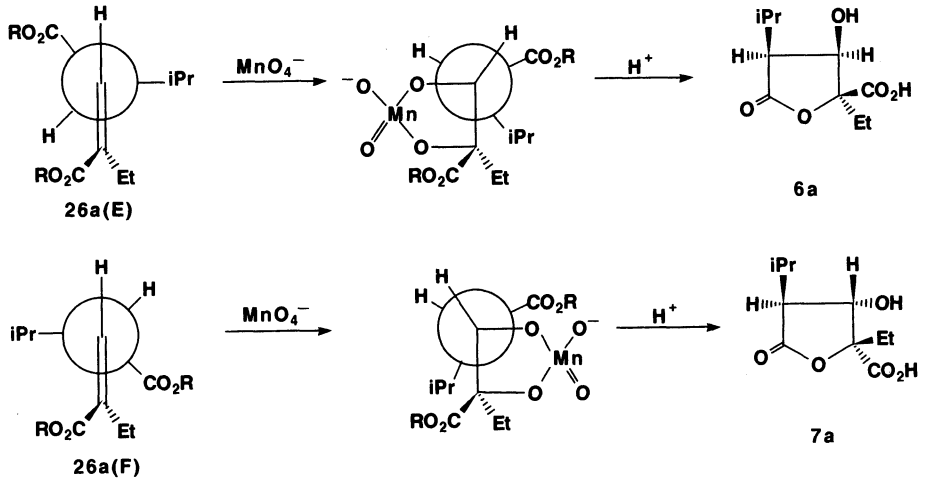


Fig. 4. The *cis*-hydroxylation of **26a**.

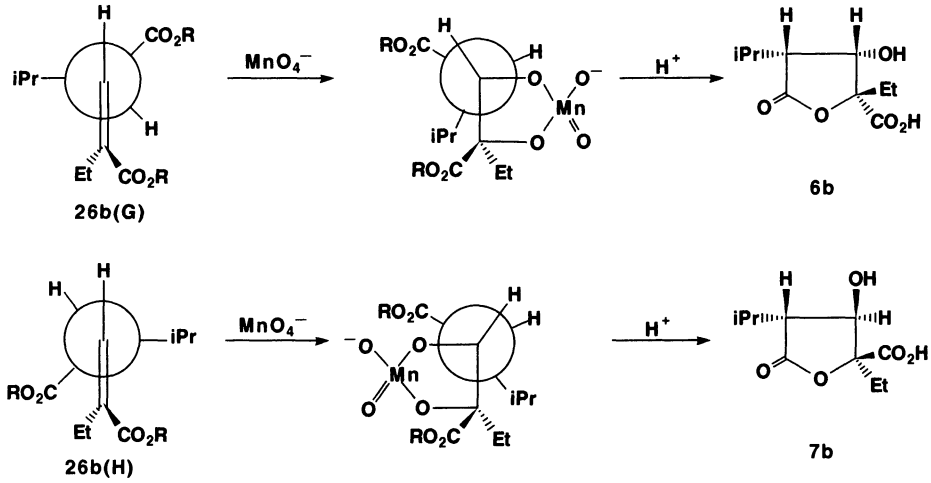


Fig. 5. The *cis*-hydroxylation of **26b**.

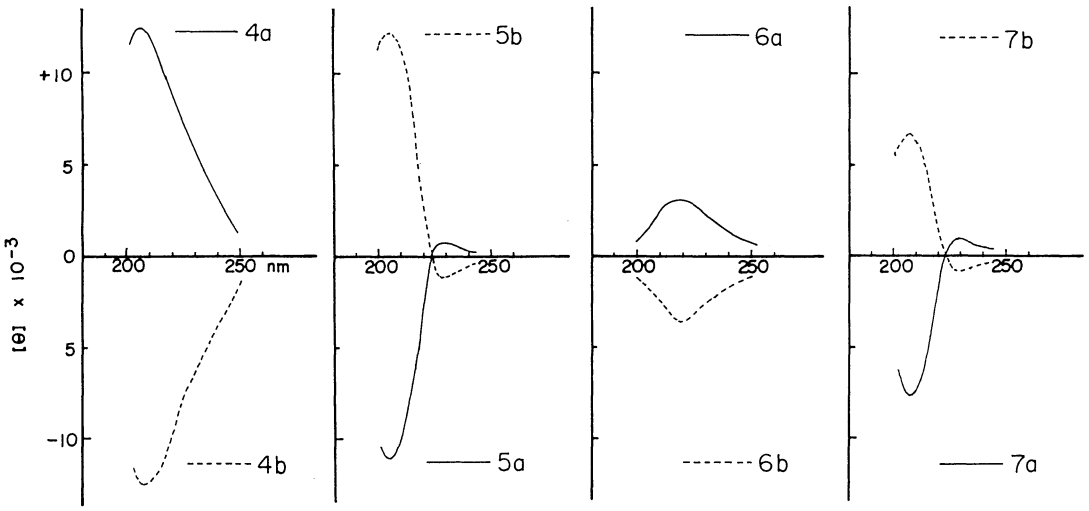


Fig. 6. The CD spectra of γ-lactone acids (**4a**,**b**—**7a**,**b**) in H_2O.

(R=CH_2OMe) are more stable than the corresponding F and H conformations (R=CH_2OMe), the double bonds in the E and F conformations are attacked by the permanganate anion from the opposite side of the largest isopropyl group, leading to the major product, **6a**, and the minor one, **7a**. Similarly, the G and H conformations also lead to the major product, **6b**, and the minor one, **7b**, respectively.

The CD spectra of the synthetic γ-lactone acids (**4a,b**—**7a,b**) were measured to obtain information concerning 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, **5a,b** and **7a,b** which have opposite absolute configurations at C-2 and C-4 (2*S*,4*R* or 2*R*,4*S*), show two distinct Cotton effects at 205 (or 207) and 228 nm; these, respectively, represent the configurations of C-4 and C-2. Those of the second class, **4a,b** and **6a,b**, which have the same absolute configurations at C-2 and C-4 (2*S*,4*S* or 2*R*,4*R*), exhibit only one effect at 206 (or 218) nm. It is clear that when the absolute configuration of C-2 or C-4 is *R*, the sign is negative; when *S*, it is positive. It is also evident that the Cotton effect due to the configuration of C-4 is superior to that of C-2. In the cases of **4a,b** and **6a,b**, the two Cotton effects apparently overlap and, consequently, only a strong effect due to the configuration of C-4 is observed at 206 (or 218) nm. These results from the CD study are in good agreement with those reported regarding the stereoisomers of monocrotalic acid;[5] they also seemed to be very useful for predicting the absolute configurations of both C-2 and C-4 in γ-lactones carrying a carboxyl group at C-4.

Experimental

All melting points are uncorrected. The IR spectra and optical rotations were measured in chloroform, and the ^1H NMR spectra in carbon tetrachloride at 60 MHz with tetramethylsilane used as an internal standard, unless otherwise stated; s: singlet, bs: broad singlet, d: doublet, dd: double doublet, t: triplet, q: quartet, m: multiplet. Column chromatography was performed using Merck silica gel (0.063 mm).

Methyl 2-(Dimethoxymethyl)-3-methylbutanoate (11). A solution of methyl 2-bromo-3-methylbutanoate (**10**) (52 g) and trimethyl orthoformate (36 g) in dry benzene (50 ml) was added dropwise to a stirred suspension of zinc powder (60 g) and a small amount of iodine in dry benzene (30 ml) under reflux for 90 min. The stirred mixture was further refluxed for 3 h, allowed to stand overnight at room temperature, and then filtered. The filtrate was poured into a mixture of ice (150 g) and ether (200 ml). The mixture was acidified with acetic acid (18 ml) and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated. The residual oil was distilled at 87—91 °C/15 mmHg (1 mmHg=133.322 Pa) to give **11** (29.3 g: 58% yield). IR 1725 cm^{-1}. ^1H NMR δ=0.91 and 0.94 (each 3H, d, *J*=7 Hz, $-CH(C\underline{H}_3)_2$), 2.00 (1H, m, $-C\underline{H}(CH_3)_2$), 2.52 (1H, dd, *J*=6 and 9 Hz, $-C\underline{H}(CO_2CH_3)-$), 3.21 and 3.26 (each 3H, s, $-CH(OC\underline{H}_3)_2$), 3.60 (3H, s, $-CO_2C\underline{H}_3$), and 4.51 (1H, d, *J*=9 Hz, $-C\underline{H}(OCH_3)_2$).

Methyl 2-Formyl-3-methylbutanoate (8). A stirred mixture of **11** (14.0 g) and 85% formic acid (120 ml) was heated at 60 °C for 1 h. The mixture was cooled, poured into ice-water, and extracted with ether. The ether extract was washed successively with aqueous sodium hydrogencarbonate and brine, dried, and evaporated in vacuo to give an oily **8** (8.9 g: 87% yield). ^1H NMR δ=1.02 (6H, d, *J*=7 Hz, $-CH(C\underline{H}_3)_2$), 2.40 (1H, m, $-C\underline{H}(CH_3)_2$), 2.91 (1H, dd, *J*=8 and 3 Hz, $-C\underline{H}(CO_2CH_3)-$), 3.73 (3H, s, $-CO_2CH_3$), and 9.65 (1H, d, *J*=3 Hz, -CHO).

Methyl (*E*)-2-Ethyl-4-methoxycarbonyl-5-methyl-2-hexenoate (12). A solution of **8** (17.77 g) and [1-(methoxycarbonyl)propylidene]triphenylphosphorane[3] (**9**) (57.50 g) in dry benzene (250 ml) was refluxed for 5 h. After removing the benzene in vacuo, the residue was stirred with ether, and the insoluble triphenylphosphine oxide removed by filtration. The filtrate was evaporated in vacuo. The residue was chromatographed on silica gel (400 g) using benzene and ether–benzene (1 : 99) as eluents, to give an oily **12** (23.51 g: 84% yield). IR 1725 and 1708 cm^{-1}. ^1H NMR δ=0.90 and 0.95 (each 3H, d, *J*=6.5 Hz, $-CH(C\underline{H}_3)_2$), 1.00 (3H, t, *J*=6.5 Hz, $-CH_2C\underline{H}_3$), 2.31 (2H, q, *J*=6.5 Hz, $-C\underline{H}_2CH_3$), 3.00 (1H, dd, *J*=9 and 10.5 Hz, $-C\underline{H}(CO_2CH_3)-$), 3.62 and 3.70 (each 3H, s, 2 $-CO_2CH_3$), and 6.50 (1H, d, *J*=10.5 Hz, $-C\underline{H}$=C(Et)–). Found: C, 62.99; H, 8.93%. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83%.

(*E*)-4-Carboxy-2-ethyl-5-methyl-2-hexenoic Acid (13). A stirred mixture of **12** (4.50 g) and concentrated hydrochloric acid (130 ml) was refluxed for 7 h. The mixture was cooled and extracted with ether. The ether extract was washed with brine, dried, and evaporated in vacuo. The residue was recrystallized from acetone–hexane to give **13** (3.30 g: 83.5% yield), mp 114—116 °C. ^1H NMR ($CDCl_3$) δ=0.90—1.15 (9H, m, $-CH(C\underline{H}_3)_2$ and $-CH_2C\underline{H}_3$), 1.9—2.6 (3H, m, $-C\underline{H}(CH_3)_2$ and $-C\underline{H}_2CH_3$), 3.0—3.6 (1H, m, $-C\underline{H}(CO_2H)-$), 6.87 (1H, d, *J*=10.5 Hz, $-C\underline{H}$=C(Et)–), and 11.80 (2H, s, 2 $-CO_2H$). Found: C, 59.81; H, 8.34%. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05%. The mother liquor of the above-mentioned recrystallization was evaporated in vacuo. The residue was chromatographed on silica gel (Mallinckrodt CC-4, 20 g), using acetone–benzene (1 : 9) as an eluent, to give an additional **13** (0.36 g: 9.1% yield).

Resolution of 13. A mixture of **13** (6.087 g) and cinchonidine (7.480 g) was dissolved in ethyl acetate (2000 ml) by heating. The solution was concentrated to ca. 1400 ml, allowed to stand at room temperature, and then filtered to give crystals (9.05 g), which were recrystallized three times from ethyl acetate to give a cinchonidine salt (5.509 g), mp 187—189 °C, $[\alpha]_D$ −63.6° (*c* 1.09).

The salt was suspended in dilute hydrochloric acid and extracted with ether. The ether extract was washed with brine, dried, and evaporated in vacuo. The residue was recrystallized from hexane to give a (+)-dioic acid (**13a**), mp 109—110 °C, $[\alpha]_D$ +114° (*c* 2.40). Found: C, 60.28; H, 8.14%. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05%.

The filtrate from the above-mentioned cichonidine salt was evaporated in vacuo. The residue was suspended in dilute hydrochloric acid and extracted with ether. The ether extract was washed with brine, dried, and evaporated in vacuo. The residue was recrystallized from ether–hexane to give a racemate (**13**) (1.02 g). The mother liquor of recrystallization was

evaporated in vacuo and the residue was purified by column chromatography on silica gel (Mallinckrodt CC-4, 100 g), using acetone–benzene (1 : 9) as an eluent, to give a dioic acid (1.83 g). This was recrystallized from hexane to give a (−)-dioic acid (**13b**), mp 109—110 °C, $[\alpha]_D$ −115° (*c* 2.65). Found: C, 60.23; H, 8.20%. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05%.

Dioic acids **13a** and **13b** were each esterified with diazomethane at room temperature for 30 min to give the corresponding dimethyl esters, **12a** $[\alpha]_D$ +83.3° (*c* 5.50) and **12b** $[\alpha]_D$ −80.5° (*c* 11.3).

Conversion of (*R*)-(−)-α-Isopropylphenylacetic Acid (15) into Methyl (*S*)-(+)-2-(Acetoxymethyl)-3-methylbutanoate (14a). An ether solution of **15** (1.716 g, $[\alpha]_D$ −61.4° (*c* 4.25)) was esterified with diazomethane at room temperature for 30 min. The solution was washed successively with dilute hydrochloric acid and brine, dried, and evaporated in vacuo to give a crude methyl ester (**16**) (1.747 g: 94% yield), $[\alpha]_D$ −62.4° (*c* 5.61).

A solution of the above-mentioned ester **16** (1.747 g) in dry ether (25 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (520 mg) in dry ether (20 ml) with cooling in an ice-water bath for 15 min. The mixture was refluxed for 3 h, poured into ice-dilute hydrochloric acid, and extracted with ether. The ether extract was washed with brine, dried, and evaporated in vacuo to give an alcohol (1.465 g: 99% yield), $[\alpha]_D$ −12.4° (*c* 6.86).

A solution of the above alcohol (1.465 g) and acetic anhydride (5.0 ml) in pyridine (5.0 ml) was allowed to stand at room temperature for 15.5 h. After the usual work-up, the crude product was chromatographed on silica gel (40 g), using benzene as an eluent, to give an oily acetate (**17**) (1.660 g: 90% yield), $[\alpha]_D$ −15.4° (*c* 10.5), IR 1729 cm^{-1}, ^1H NMR δ=0.77 and 1.00 (each 3H, d, *J*=7 Hz, $-CH(C\underline{H}_3)_2$), 1.87 (3H, s, $-OCOCH_3$), 2.63 (1H, q, *J*=6.5 Hz, $-C\underline{H}(C_6H_5)CH_2-$), 4.29 (2H, d, *J*=6.5 Hz, $-C\underline{H}_2OCOCH_3$), and 7.0—7.3 (5H, m, $-C_6H_5$). Found: C, 75.69; H, 8.80%. Calcd for $C_{13}H_{18}O_2$: C, 75.43; H, 8.86%.

A solution of **17** (1.630 g) in chloroform (20 ml) was ozonized at 0—5 °C for 20 h. The solution was evaporated in vacuo and the residue was esterified with diazomethane in ether at room temperature for 30 min. The ether solution was washed successively with dilute hydrochloric acid and brine, dried, and evaporated in vacuo. The residue was chromatographed on silica gel (50 g), using hexane–chloroform (1 : 1) as an eluent, to give **14a** as an oil (522 mg: 35% yield), $[\alpha]_D$ +17.5° (*c* 6.11), IR 1734 cm^{-1}, ^1H NMR δ=0.95 and 1.00 (each 3H, d, *J*=7 Hz, $-CH(C\underline{H}_3)_2$), 1.99 (3H s, $-OCOCH_3$), 2.45 (1H, m, $-C\underline{H}(CO_2CH_3)CH_2-$), 3.68 (3H, s, $-CO_2CH_3$), and 4.09 (1H, t, *J*=10 Hz) and 4.30 (1H, dd, *J*=10 and 6 Hz) ($-C\underline{H}_2OCOCH_3$). Found: C, 57.66; H, 8.45%. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57%.

Conversion of 12a into 14a. A solution of **12a** (850 mg) in chloroform (20 ml) was ozonized −10—0 °C for 2 h. A cold solution of sodium borohydride (1120 mg) and water (3.0 ml) in ethanol (7.0 ml) was then added dropwise to the above chloroform solution with stirring at −5—0 °C for 5 min. The mixture was further stirred at room temperature for 2 h, poured into dilute hydrochloric acid, and extracted with ether. The ether extract was washed with brine, dried, and evaporated in vacuo. The residue was acetylated with acetic anhydride (7.5 ml) in pyridine (7.5 ml) at room temperature for 12 h. After the usual work-up, the crude product was chromatographed on silica gel (25 g), using hexane–chloroform (1 : 1) as an eluent, to give an acetate (154 mg: 22% yield), $[\alpha]_D$ +16.5° (*c* 5.95), the IR and ^1H NMR spectra of which were identical with those of the authentic **14a**.

Epoxidations of 12a and 12b. a): A mixture of **12a** (2.108 g) and *m*-chloroperbenzoic acid (85%, 3.566 g) in 1,2-dichloroethane (60 ml) was refluxed for 3.5 h. The mixture was cooled and diluted with ether. The ether solution was washed successively with aqueous sodium hydrogensulfite, aqueous sodium hydrogencarbonate, and brine. The dried solution was evaporated in vacuo. The residue was chromatographed on silica gel (200 g), using ether–benzene (1 : 99) as an eluent, to give a minor epoxide (**19a**) (461 mg: 20% yield) as an oil, $[\alpha]_D$ +7.1° (*c* 4.36), IR 1735 cm^{-1}, ^1H NMR δ=1.02 and 1.10 (each 3H, d, *J*=6 Hz, $-CH(C\underline{H}_3)_2$), 1.00 (3H, t, *J*=7 Hz, $-CH_2C\underline{H}_3$), 3.21 (1H, d, *J*=9 Hz, –CH(–O–)–), and 3.67 and 3.72 (each 3H, s, $2-CO_2CH_3$). Found: C, 59.16; H, 8.35%. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25%.

Further elution gave a major epoxide (**18a**) (1.487 g: 66% yield) as an oil, $[\alpha]_D$ +12.9° (*c* 5.35), IR 1735 cm^{-1}, ^1H NMR δ=0.96 and 1.07 (each 3H, d, *J*=7 Hz, $-CH(C\underline{H}_3)_2$), 1.02 (3H, t, *J*=7 Hz, $-CH_2C\underline{H}_3$), 3.15 (1H, d, *J*=9 Hz, –CH(–O–)–), and 3.73 (6H, s, $2-CO_2CH_3$). Found: C, 58.95; H, 8.30%. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25%.

b): A mixture of **12b** (4.140 g) and *m*-chloroperbenzoic acid (85%, 7.400 g) in 1,2-dichloroethane (120 ml) was refluxed for 3.5 h. After the work-up described in **a)**, the crude product was chromatographed on silica gel (400 g), using ether–benzene (1 : 99) as an eluent, to give a minor epoxide (**19b**) (0.569 g: 13% yield) as an oil, $[\alpha]_D$ −6.2° (*c* 3.89). The IR and ^1H NMR spectra of **19b** were identical with those of **19a**. Found: C, 58.72; H, 8.38%. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25%.

Further elution gave a major epoxide (**18b**) (1.972 g: 44% yield) as an oil, $[\alpha]_D$ −13.8° (*c* 3.84). The IR and ^1H NMR spectra of **18b** were identical with those of **18a**. Found: C, 58.96; H, 8.39%. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25%.

Conversions of Epoxides (18a, 19a, 18b, and 19b) into Acetonides (20a, 21a, 20b, and 21b). a): Anhydrous tin(IV) chloride (0.35 ml) was added dropwise to a stirred solution of **18a** (342 mg) and acetone (1.03 ml) in carbon tetrachloride (3.42 ml) with cooling in an ice-water bath. The mixture was stirred at this temperature for 30 min and at room temperature for 32 h, and then poured into ice-aqueous potassium hydroxide (2.5%). The alkaline mixture was extracted with ether. The ether extract was washed with brine, dried, and evaporated in vacuo. The residue was chromatographed on silica gel (30 g), using ether–benzene (1 : 99) as an eluent, to give an oily acetonide (**20a**) (297 mg: 70% yield), $[\alpha]_D$ +17.2° (*c* 5.64), IR 1725 cm^{-1}, ^1H NMR δ=0.89 and 0.97 (each 3H, d, *J*=7 Hz, $-CH(C\underline{H}_3)_2$), 0.90 (3H, t, *J*=7 Hz, $-CH_2C\underline{H}_3$), 1.35 and 1.48 (each 3H, s, $-C(CH_3)_2-$), 3.66 (6H, s, $2-CO_2CH_3$), and 4.16 (1H, d, *J*=10 Hz, –CH(–O–)–). Found: C, 59.88; H, 8.84%. Calcd for $C_{15}H_{26}O_6$: C, 59.58; H, 8.67%.

b): Anhydrous tin(IV) chloride (0.12 ml) was added dropwise to a stirred solution of **19a** (119 mg) and acetone (0.36 ml) in carbon tetrachloride (1.19 ml) with cooling in an ice-water bath. The mixture was stirred at this temperature for 30 min and then at room temperature for 24 h. After the work-up described in **a)**, the crude product was chromatographed on silica gel (10 g), using ether–benzene (1 : 99) as an eluent, to give an oily acetonide (**21a**) (23 mg: 15% yield), $[\alpha]_D$ +7.9° (*c* 6.55), IR 1730 cm^{-1}, ^1H NMR δ=0.92 (6H,

d, J=6 Hz, $-CH(C\underline{H}_3)_2$), 0.97 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 1.35 and 1.48 (each 3H, s, $-C(CH_3)_2-$), 3.62 and 3.72 (each 3H, s, 2 $-CO_2CH_3$), and 4.10 (1H, d, J=10 Hz, -CH(-O-)-). Found: C, 59.39; H, 8.76%. Calcd for $C_{15}H_{26}O_6$: C, 59.58; H, 8.67%.

Further elution with ether–benzene (1 : 9) afforded a γ-lactone ester (**23a**) (61 mg: 55% yield). This was recrystallized from acetone–hexane, mp 82—83 °C, $[\alpha]_D$ +31.4° (c 5.10), IR 3410, 1780, and 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.99 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 1.05 and 1.24 (each 3H, d, J=6 Hz, $-CH(C\underline{H}_3)_2$), 2.05 (2H, q, J=7 Hz, $-C\underline{H}_2CH_3$), 3.30 (1H, br, -OH), 3.83 (3H, s, $-CO_2CH_3$), and 4.57 (1H, br, $W_{1/2}$=8 Hz, $-C\underline{H}$(OH)-). Found: C, 57.67; H, 8.03%. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88%.

c): Anhydrous tin(IV) chloride (1.0 ml) was added dropwise to a stirred solution of **18b** (990 mg) and acetone (3.0 ml) in carbon tetrachloride (10 ml) with cooling in an ice-water bath. The mixture was stirred at this temperature for 30 min and then at room temperature for 34 h. After the work-up described in **a)**, the crude product was chromatographed on silica gel (100 g), using ether–benzene (1 : 99) as an eluent, to give an oily acetonide (**20b**) (651 mg: 53% yield), $[\alpha]_D$ −17.1° (c 5.14), Found: C, 59.53; H, 8.84%. Calcd for $C_{15}H_{26}O_6$: C, 59.58; H, 8.67%. The IR and ^1H NMR spectra of **20b** were identical with those of **20a**. Further elution with ether–benzene (5 : 95) afforded the starting **18b** (301 mg: 30% yield).

d): Anhydrous tin(IV) chloride (0.6 ml) was added dropwise to a stirred solution of **19b** (548 mg) and acetone (1.7 ml) in carbon tetrachloride (6.0 ml) with cooling in an ice-water bath. The mixture was stirred at this temperature for 30 min and then at room temperature for 24 h. After the work-up described in **a)**, the crude product was chromatographed on silica gel (50 g), using ether–benzene (1 : 99) as an eluent, to give an oily acetonide (**21b**) (536 mg: 79% yield), $[\alpha]_D$ −7.7° (c 3.66), Found: C, 59.28; H, 8.92%. Calcd for $C_{15}H_{26}O_6$: C, 59.58; H, 8.67%. The IR and ^1H NMR spectra of **21b** were identical with those of **21a**.

Conversions of Acetonides (20a, 21a, 20b, and 21b) into γ-Lactone Esters (22a, 23a, 22b, and 23b). a): A stirred solution of **20a** (1.064 g) in formic acid (85%, 16 ml) was heated at 60 °C for 4 h. The solution was cooled, diluted with ether, and then neutralized with aqueous sodium hydrogencarbonate. The mixture was extracted with ether. The ether extract was washed with brine, dried, and evaporated in vacuo. The residue was chromatographed on silica gel (50 g), using ether–benzene (1 : 9) as an eluent, to give an oily (2*S*,3*S*,4*S*)-γ-lactone ester (**22a**) (634 mg: 78% yield), $[\alpha]_D$ −15.6° (c 5.72), IR 3600, 3410, 1775, and 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.98 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 1.02 and 1.09 (each 3H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.94 (2H, q, J=7 Hz, $-C\underline{H}_2CH_3$), 2.53 (1H, dd, J=7 and 6 Hz, 2-H), 3.42 (1H, d, J=5 Hz, -OH), 3.84 (3H, s, $-CO_2CH_3$), and 4.47 (1H, dd, J=7 and 5 Hz, 3-H). Found: C, 57.09; H, 8.10%. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88%.

b): A stirred solution of **21a** (96.6 mg) in formic acid (85%, 3.0 ml) was heated at 60 °C for 4 h. After the work-up described in **a)**, the crude product was chromatographed on silica gel (10 g), using ether–benzene (1 : 9) as an eluent, to give a (2*S*,3*R*,4*R*)-γ-lactone ester (**23a**) (63.0 mg: 86% yield), mp 82—83 °C (from acetone–hexane). The IR and ^1H NMR spectra and $[\alpha]_D$ of **23a** were identical with those of the above-mentioned authentic sample.

c): A stirred solution of **20b** (650 mg) in formic acid (85%, 10 ml) was heated at 60 °C for 4 h. After the work-up described in **a)**, the crude product was chromatographed on silica gel (50 g), using ether–benzene (1 : 9) as an eluent, to give a (2*R*,3*R*,4*R*)-γ-lactone ester (**22b**) (387 mg: 78% yield), $[\alpha]_D$ +16.7° (c 5.26). Found: C, 57.56; H, 7.80%. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88%. The IR and ^1H NMR spectra of **22b** were identical with those of **22a**.

d): A stirred solution of **21b** (504 mg) in formic acid (85%, 15 ml) was heated at 60 °C for 4 h. After the work-up described in **a)**, the crude product was chromatographed on silica gel (50 g), using ether–benzene (1 : 9) as an eluent, to give a (2*R*,3*S*,4*S*)-γ-lactone ester (**23b**) (332 mg: 86% yield). This was recrystallized from acetone–hexane, mp 82—84 °C, $[\alpha]_D$ −29.5° (c 4.04). Found: C, 57.44; H, 8.01%. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88%. The IR and ^1H NMR spectra of **23b** were identical with those of **23a**.

Hydrolyses of γ-Lactone Esters (22a, 23a, 22b, and 23b). a): A mixture of **22a** (905 mg) and aqueous barium hydroxide (4%, 55 ml) in methanol (55 ml) was refluxed for 1 h. After removing the methanol in vacuo, the residue was acidified with dilute hydrochloric acid and continuously extracted with ether for 2 h. The ether extract was dried and evaporated in vacuo. The crude product was chromatographed on silica gel (Mallinckrodt CC-4, 40 g), using acetone–benzene (1 : 9) as an eluent, to give a (2*R*,3*S*,4*S*)-γ-lactone acid (**5b**) (606 mg: 71% yield). This was recrystallized from ether–petroleum benzine, mp 152—153 °C, $[\alpha]_D$ −27.4° (MeOH, c 2.85), CD (H_2O): $[\theta]_{205}$ +12180, $[\theta]_{228}$ −1070; IR (KBr) 3360, 1787, and 1715 cm^{-1}; ^1H NMR (90 MHz, acetone-d_6) δ=0.98 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 1.04 and 1.22 (each 3H, d, J=6 Hz, $-CH(C\underline{H}_3)_2$), 2.01 (2H, q, J=7 Hz, $-C\underline{H}_2CH_3$), 2.25 (1H, dd, J=9 and 5 Hz, 2-H), and 4.59 (1H, d, J=5 Hz, 3-H). Found: C, 55.84; H, 7.72%. Calcd for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46%.

Further elution with acetone–benzene (1 : 9) afforded a (2*S*,3*S*,4*S*)-γ-lactone acid (**4a**) (59 mg: 7% yield). This was recrystallized from ether–petroleum benzine, mp 132—133 °C, $[\alpha]_D$ −11.1° (MeOH, c 1.18), CD (H_2O): $[\theta]_{206}$ +15580, IR (KBr) 3390, 1775, and 1710 cm^{-1}; ^1H NMR (90 MHz, acetone-d_6) δ=0.98 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 1.01 and 1.08 (each 3H, d, J=6 Hz, $-CH(C\underline{H}_3)_2$), 2.44 (1H, t, J=6 Hz, 2-H), and 4.48 (1H, d, J=6 Hz, 3-H). Found: C, 55.83; H, 7.66%. Calcd for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46%.

Esterifications of the acids, **4a** and **5b**, with diazomethane produced the corresponding methyl esters, **22a** and **23b**, respectively.

b): A mixture of **23a** (102 mg) and aqueous barium hydroxide (4%, 10 ml) in methanol (10 ml) was refluxed for 1 h. After the work-up described in **a)**, the crude product was chromatographed on silica gel (Mallinckrodt CC-4, 10 g), using acetone–benzene (1 : 9) as an eluent, to give a (2*S*,3*R*,4*R*)-γ-lactone acid (**5a**) (83 mg: 86% yield). This was recrystallized from ether–petroleum benzine, mp 151—153 °C, $[\alpha]_D$ +27.1° (MeOH, c 1.37), CD (H_2O): $[\theta]_{205}$ −11150, $[\theta]_{228}$ +683. Found: C, 55.81; H, 7.62%. Calcd for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46%. The IR and ^1H NMR spectra of **5a** were identical with those of **5b**.

Esterification of the acid **5a** with diazomethane produced the corresponding methyl ester **23a**.

c): A mixture of **22b** (865 mg) and aqueous barium hydroxide (4%, 50 ml) in methanol (50 ml) was refluxed for 1 h. After the work-up described in **a)**, the crude product was chromatographed on silica gel (Mallinckrodt CC-4, 80 g), using

acetone–benzene (1 : 9) as an eluent, to give a (2*S*,3*R*,4*R*)-γ-lactone acid (515 mg: 63% yield), mp 152—154 °C (from ether–petroleum benzine), $[\alpha]_D$ +27.2° (MeOH, *c* 3.78), the IR and ^{1}H NMR spectra of which were identical with those of the above authentic **5a**.

Further elution with acetone–benzene (1 : 9) afforded a (2*R*,3*R*,4*R*)-γ-lactone acid (**4b**) (196 mg: 24% yield), mp 134—136 °C (from ether–petroleum benzine), $[\alpha]_D$ +10.4° (MeOH, *c* 1.83), CD (H_2O): $[\theta]_{206}$ − 13870. Found: C, 55.73; H, 7.68%. Calcd for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46%. The IR and ^{1}H NMR spectra of **4b** were identical with those of **4a**.

d): A mixture of **23b** (294 mg) and aqueous barium hydroxide (4%, 17 ml) in methanol (17 ml) was refluxed for 1 h. After the work-up described in **a)**, the crude product was chromatographed on silica gel (Mallinckrodt CC-4, 30 g), using acetone–benzene (1 : 9) as an eluent, to give a (2*R*,3*S*,4*S*)-γ-lactone acid (202 mg: 73% yield), mp 151—153 °C (from ether–petroleum benzine), $[\alpha]_D$ −25.9° (MeOH, *c* 2.63), the IR and ^{1}H NMR spectra of which were identical with those of the above authentic **5b**.

Dehydrations of γ-Lactone Esters (22a, 23a, 23b, and 27a).

a): A mixture of **22a** (104 mg) and phosphoryl chloride (0.2 ml) in pyridine (2.0 ml) was refluxed for 30 min. The mixture was cooled, diluted with a mixture of ice and dilute hydrochloric acid, and then extracted with ether. The ether extract was washed with brine, dried, and evaporated in vacuo. The residue was chromatographed on silica gel (10 g), using ether–benzene (2 : 98) as an eluent, to give (*S*)-4-ethyl-2-isopropyl-4-methoxycarbonyl-2-buten-4-olide (**24**) as an oil (67 mg: 70% yield), $[\alpha]_D$ −155° (*c* 1.82), IR 1763 and 1735 cm^{-1}, ^{1}H NMR δ=0.91 (3H, t, *J*=7 Hz, $-CH_2C\underline{H}_3$), 1.19 (6H, d, *J*=7 Hz, $-CH(C\underline{H}_3)_2$), 2.00 (2H, m, $-C\underline{H}_2CH_3$), 2.65 (1H, m, $-C\underline{H}(CH_3)_2$), 3.77 (3H, s, $-CO_2CH_3$), and 6.78 (1H, d, *J*=2 Hz, 3-H). Found: C, 62.51; H, 7.55%. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60%.

b): A mixture of **23a** (135 mg) and phosphoryl chloride (0.25 ml) in pyridine (2.0 ml) was refluxed for 30 min. After the work-up described in **a)**, the crude product was chromatographed on silica gel (10 g), using ether–benzene (2 : 98) as an eluent, to give (*R*)-4-ethyl-2-isopropyl-4-methoxycarbonyl-2-buten-4-olide (**25**) as an oil (85 mg: 68% yield), $[\alpha]_D$ +156° (*c* 2.70), the IR and ^{1}H NMR spectra of which were identical with those of **24**. Found: C, 62.49; H, 7.51%. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60%.

c): A mixture of **23b** (101 mg) and phosphoryl chloride (0.2 ml) in pyridine (1.5 ml) was refluxed for 30 min. After the work-up described in **a)**, the crude product was chromatographed on silica gel (10 g), using ether–benzene (2 : 98) as an eluent, to give an oil (65 mg: 70% yield), $[\alpha]_D$ −147° (*c* 0.93), the IR and ^{1}H NMR spectra of which were identical with those of **24**.

d): A mixture of **27a** (181 mg) and phosphoryl chloride (0.35 ml) in pyridine (2.0 ml) was refluxed for 30 min. After the work-up described in **a)**, the crude product was chromatographed on silica gel (15 g), using ether–benzene (2 : 98) as an eluent, to give an oil (97 mg: 58% yield), $[\alpha]_D$ −153° (*c* 1.70), the IR and ^{1}H NMR spectra of which were identical with those of **24**.

Esterifications of Dioic Acids (13a and 13b) with Chloromethyl Methyl Ether. a): Chloromethyl methyl ether (3.19 ml) was added to a stirred solution of the dioic acid (**13a**) (2.799 g) and triethylamine (5.86 ml) in *N*,*N*-dimethylformamide (14 ml) with coolig in an ice-water bath. The mixture was stirred at this temperature for 1 h, poured into ice-dilute hydrochloric acid, and extracted with ether. The ether extract was washed with brine, dried, and evaporated in vacuo to give a crude bis(methoxymethyl) ester (**26a**) (3.726 g), $[\alpha]_D$ +61.4° (*c* 3.18).^{1}H NMR δ=0.94 and 1.00 (each 3H, d, *J*=6.5 Hz, $-CH(C\underline{H}_3)_2$), 1.07 (3H, t, *J*=6.5 Hz, $-CH_2C\underline{H}_3$), 2.36 (2H, q, *J*=6.5 Hz, $-C\underline{H}_2CH_3$), 3.05 (1H, dd, *J*=10 and 8 Hz, $-C\underline{H}(CO_2CH_2OCH_3)-$), 3.40 and 3.43 (each 3H, s, 2 $-OCH_3$), 5.18 and 5.26 (each 2H, s, $2-OC\underline{H}_2OCH_3$), and 6.62 (1H, d, *J*=10 Hz, =CH–). The crude ester **26a** was used, without purification, in the next reaction.

b): Chloromethyl methyl ether (2.28 ml) was added dropwise to a stirred solution of the dioic acid (**13b**) (2.00 g) and triethylamine (4.18 ml) in *N*,*N*-dimethylformamide (10 ml) for 2 min. The mixture was stirred at room temperature for 1 h. Work-up as described in **a)** afforded a crude bis(methoxymethyl) ester (**26b**) (2.900 g), $[\alpha]_D$ −55.8° (*c* 5.95). This was used, without purification, in the next reaction.

Oxidations of 26a and 26b with Potassium Permanganate. a): A solution of potassium permanganate (2.85 g) and magnesium sulfate heptahydrate (4.77 g) in water (180 ml) was added dropwise at −45 to −40 °C into a stirred solution of the crude **26a** (3.726 g) in methanol (260 ml) for 30 min. The mixture was further stirred at this temperature for 30 min, and sodium hydrogensulfite was then added. The mixture was diluted with ethyl acetate and filtered. The filtrate was extracted with ethyl acetate. The ethyl acetate extract was washed with brine, dried, and evaporated in vacuo. The residue was dissolved in methanol (32 ml) containing dilute hydrochloric acid (10%, 2.0 ml), stirred at room temperature for 3 h, and then extracted with ethyl acetate. The extract was washed with brine, dried, and evaporated in vacuo. The residue was repeatedly chromatographed on silica gel (Mallinckrodt CC-4), using acetone–benzene (5 : 95 and 1 : 9) as eluents, to give the following two γ-lactone acids. Acetone–benzene (5 : 95) eluate afforded an oily (2*S*,3*S*,4*R*)-γ-lactone acid (**7a**) (103 mg: 3.7% yield from **13a**), $[\alpha]_D$ −11.7° (MeOH, *c* 5.14), CD (H_2O): $[\theta]_{207}$ −7710, $[\theta]_{228}$ +963; IR (KBr) 3390, 1750, and 1715 cm^{-1}. ^{1}H NMR (90 MHz, acetone-d_6) δ=0.99 (3H, t, *J*=7 Hz, $-CH_2C\underline{H}_3$), 1.01 and 1.07 (each 3H, d, *J*=7 Hz, $-CH(C\underline{H}_3)_2$), 2.69 (1H, dd, *J*=9 and 5 Hz, 2-H), and 4.29 (1H, d, *J*=9 Hz, 3-H). Found: C, 55.78; H, 7.39%. Calcd for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46%. Acetone–benzene (1 : 9) eluate afforded a (2*S*,3*R*,4*S*)-γ-lactone acid (**6a**) (1237 mg: 44.3% yield from **13a**), mp 171—173 °C (from acetone–benzene), $[\alpha]_D$ −17.4° (MeOH, *c* 2.65), CD (H_2O): $[\theta]_{218}$ +3140, IR (KBr) 3560, 3480, 1760, and 1700 cm^{-1}. ^{1}H NMR (90 MHz, acetone-d_6) δ=0.93 (3H, t, *J*=7 Hz, $-CH_2C\underline{H}_3$), 1.06 and 1.24 (each 3H, d, *J*=6 Hz, $-CH(C\underline{H}_3)_2$), 2.55 (1H, dd, *J*=9 and 5 Hz, 2-H), and 4.49 (1H, d, *J*=5 Hz, 3-H). Found: C, 55.31; H, 7.55%. Calcd for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46%.

b): A solution of potassium permanganate (2.21 g) and magnesium sulfate heptahydrate (3.70 g) in water (150 ml) was added dropwise at −35 to −40 °C into a stirred solution of the crude **26b** (2.900 g) in methanol (200 ml) for 50 min. The mixture was further stirred at this temperature for 30 min. After the work-up described in a), the crude product was repeatedly chromatographed on silica gel (Mallinckrodt CC-4), using acetone–benzene (5 : 95 and 1 : 9) as eluents, to give the following two γ-lactone acids. Acetone–benzene (5 : 95) eluate afforded a (2*R*,3*R*,4*S*)-γ-lactone acid (**7b**) (69 mg: 3.2%

yield from **13b**), $[\alpha]_D$ +10.0° (MeOH, *c* 3.00), CD (H_2O): $[\theta]_{207}$ +6070, $[\theta]_{228}$ −877; the IR and ^1H NMR spectra were identical with those of **7a**. Found: C, 55.25; H, 7.28%. Calcd for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46%. Acetone–benzene (1 : 9) eluate afforded a (2*R*, 3*S*, 4*R*)-γ-lactone acid (**6b**) (1107 mg: 51.2% yield from **13b**), mp 171—173°C (from acetone–benzene), $[\alpha]_D$ +17.3° (MeOH, *c* 3.65), CD(H_2O): $[\theta]_{218}$ −3690, the IR and ^1H NMR spectra of which were identical with those of **6a**. Found: C, 55.64; H, 7.60%. Calcd for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46%.

Esterifications of γ-Lactone Acids (6a, 7a, 6b, and 7b) with Diazomethane. a): A solution of **6a** (430 mg) in ether (5.0 ml) was esterified with an ethereal diazomethane solution at room temperature for 2 h. After the usual work-up, the crude product was chromatographed on silica gel (30 g), using ether–benzene (1 : 4) as an eluent, to give a (2*S*,3*R*,4*S*)-γ-lactone ester (**27a**) (448 mg: 98% yield), mp 130—132°C (from acetone–hexane), $[\alpha]_D$ −6.1° (MeOH, *c* 2.80), IR 3520, 1780, and 1728 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.98 (3H, t, *J*=7 Hz, $-CH_2C\underline{H}_3$), 1.06 and 1.26 (each 3H, d, *J*=7 Hz, $-CH(C\underline{H}_3)_2$), 3.03 (1H, d, *J*=5 Hz, 3-OH), 3.87 (3H, s, $-CO_2CH_3$), and 4.49 (1H, t, *J*=5 Hz, 3-H). Found: C, 57.47; H, 8.00%. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88%.

b): γ-Lactone acid **7a** (93 mg) was esterified with an ethereal diazomethane solution to give a (2*S*,3*S*,4*R*)-γ-lactone ester (**28a**) (82 mg: 83% yield), $[\alpha]_D$ −22.8° (MeOH, *c* 4.03), IR 3585, 3455, 1777, and 1740 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.00 (3H, t, *J*=7 Hz, $-CH_2C\underline{H}_3$), 1.02 and 1.10 (each 3H, d, *J*=7 Hz, $-CH(C\underline{H}_3)_2$), 2.69 (1H, dd, *J*=9 and 5 Hz, 2-H), 3.35 (1H, bs, 3-OH), 3.83 (3H, s, $-CO_2CH_3$), and 4.28 (1H, d, *J*=9 Hz, 3-H). Found: C, 57.61; H, 7.73%. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88%.

c): γ-Lactone acid **6b** (268 mg) was esterified with an ethereal diazomethane solution to give a (2*R*,3*S*,4*R*)-γ-lactone ester (**27b**) (260 mg: 91% yield), mp 131—132°C (from acetone–benzene), $[\alpha]_D$ +6.5° (MeOH, *c* 1.07), the IR and ^1H NMR spectra of which were identical with those of **27a**.

d): γ-Lactone acid **7b** (63 mg) was esterified with an ethereal diazomethane solution to give a (2*R*,3*R*,4*S*)-γ-lactone ester (**28b**) (53 mg: 79% yield), $[\alpha]_D$ +17.0° (MeOH, *c* 1.65), the IR and ^1H NMR spectra of which were identical with those of **28a**.

Hydrolyses of γ-Lactone Esters (27a and 28a). a): A mixture of **27a** (301 mg) and aqueous barium hydroxide (4%, 20 ml) in methanol (20 ml) was refluxed for 1 h. After removing the methanol in vacuo, the residue was acidified with dilute hydrochloric acid and continuously extracted with ether for 2 h. The ether extract was dried and evaporated in vacuo. The crude product was chromatographed on silica gel (Mallinckrodt CC-4, 50 g), using acetone–benzene (1 : 9) as an eluent, to give a γ-lactone acid (186 mg: 66% yield), mp 170—172°C (from acetone–benzene), $[\alpha]_D$ −17.0° (MeOH, *c* 1.76), the IR and ^1H NMR spectra of which were identical with those of **6a**.

b): A mixture of **28a** (54 mg) and aqueous barium hydroxide (4%, 5.0 ml) in methanol (6.0 ml) was refluxed for 1 h. After the work-up described in **a)**, the crude product was chromatographed on silica gel (Mallinckrodt CC-4, 10 g), using acetone–benzene (1 : 9) as an eluent, to give a γ-lactone acid (23 mg: 45% yield), $[\alpha]_D$ +16.9° (MeOH, *c* 1.10), the IR and ^1H NMR spectra of which were identical with those of **6b**.

Single-Crystal X-Ray Diffraction Analysis of 4-Ethyl-3-hydroxy-2-isopropyl-4-methoxycarbonyl-4-butanolide (23b). The crystal data for **23b** are as follows: orthorthombic; space group $P2_12_12_1$ with *a*=7.577 (4), *b*=8.982 (3), *c*=17.953 (7) Å; *V*=1222 $Å^3$; *Z*=4; empirical formula $C_{11}H_{18}O_5$; molecular weight 230.26; D_{calcd} 1.25 g cm^{-3}; D_{obsd} 1.25 g cm^{-3} by floatation in an aqueous $ZnCl_2$ solution. Three-dimensional X-ray data were collected by the use of graphite-monochromated Mo *Kα* radiation (λ=0.71073 Å) on a Syntex R3 automatic four-circle diffractometer up to a maximum 2θ of 50.0°. The structure was solved by the direct method (MULTAN). The intensity data of 849 reflections with $|F_o|>3\sigma|F_o|$ were used in the present X-ray analysis. All non-hydrogen atoms were located on the E synthesis, and the hydrogen atoms were included in the calculated positions (C–H, 1.08 Å). A block-diagonal least-squares refinements with anisotropic 16 non-hydrogen atoms and 18 isotropic hydrogens have converged to a conventional R factor of 0.098. All of the calculations were performed on a mini-computer of the Syntex R3 using a structure-determination program.

References

1) D. H. G. Crout, *J. Chem. Soc. C*, **1969**, 1379
2) H. Wiedenfeld, E. Roeder, and E. Anders, *Phytochemistry*, **24**, 376 (1985).
3) H. J. Bestmann and H. Schulz, *Chem. Ber.*, **95**, 2921 (1962).
4) M. Miyazaki, C. Mizuno, and S. Umie, *Yakugaku Zasshi*, **77**, 415 (1957).
5) T. Matsumoto, M. Takahashi, and Y. Kashihara, *Bull. Chem. Soc. Jpn.*, **52**, 3329 (1979).
6) C. Aaron, D. Dull, J. L. Schmiegel, D. Jaeger, Y. Ohashi, and H. S. Masher, *J. Org. Chem.*, **32**, 2797 (1967).
7) D. R. Clark and H. S. Masher, *J. Org. Chem.*, **35**, 1114 (1970).
8) M. S. Malinovskii, V. I. Avramenko, V. G. Dryuk, and A. F. Kurochkin, *J. Org. Chem. USSR*, **8**, 2375 (1972).
9) M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, **1968**, 2199.
10) A. B. A. Jansen and T. J. Russell, *J. Chem. Soc.*, **1965**, 2127.