Enantioselective Hydrolysis of Dimethyl 2α,3α-[(Dimethylmethylene)dioxy]-5β-hydroxy-1β,4β-cyclopentanedicarboxylate with Pig Liver Esterase. Stereoselective Synthesis of Methyl 2(*R*),3(*S*)-[(Dimethylmethylene)dioxy]-5(*R*)-hydroxy-1(*S*)-carboxy-4(*R*)-cyclopentanecarboxylate. A Cyclopentane Synthone with All Ring Atoms Chiral[1]

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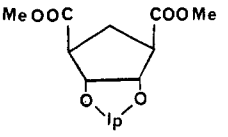
A synthesis of methyl 2(*R*),3(*S*)-[(dimethylmethylene)dioxy]-5(*R*)-hydroxy-1(*S*)-carboxy-4(*R*)-cyclopentanecarboxylate (**8**) is described. The protected dicarboxylic acid **4** was converted to the corresponding diester **5** by reaction with diazomethane. Deblocking of **5** with 90% CF_3COOH gave trihydroxy derivative **6**. Alternately, compound **6** was obtained in a single step from dicarboxylic acid **4** (esterification with a simultaneous deprotection) by using HCl in methanol. Reaction of **6** with acetone and $CuSO_4$ afforded diester **7**. The pig liver esterase catalyzed hydrolysis of **7** led to compound **8** with a *pro-S* stereoselectivity. The enantiomeric purity of **8** was determined by ^1H NMR spectroscopy of the respective salt with 1(*S*)-(1-naphthyl)ethylamine. The absolute configuration of **8** followed from an X-ray diffraction analysis. Fully protected ester **5** is resistant to both pig liver esterase and α-chymotrypsin. At pH 7, a slow elimination of a dimethyleneoxy group from **7** gave olefin **9** in a low yield. Racemic ester **8** was obtained by deprotection of **10** with 90% CF_3COOH to give compound **11** which was isopropylidenated in situ with acetone and $CuSO_4$. A partial deprotection of diester **5** with HCl in methanol gave compound **12**. The latter is not a substrate for pig liver esterase but derivative **6** is very slowly hydrolyzed. A virtual stereospecificity of hydrolysis of **7** starkly contrasts with 5-unsubstituted 1,3-cyclopentanedicarboxylates and related systems where enantiomeric enhancement was only 30–60%. A tentative binding site model for pig liver esterase is proposed.

In recent years chemicoenzymatic methodologies have become of increasing importance for organic synthesis.[2,3] Of the several enzymes used for such purposes pig liver esterase (PLE, EC 3.1.1.1) is of particular advantage because of its stability, lack of a need for cofactors, low cost, and the fact that a wide variety of substrates are amenable to hydrolysis. In addition, the PLE-catalyzed hydrolysis of meso diesters can be employed for generating a single enantiomer with high enantioselectivity. The procedure has a distinct advantage over the classical kinetic resolution which gives both enantiomers in equal amounts. The potential of the method was recently documented[4] by an enantioselective synthesis of the antibiotics aristeromycin and neplanocin A.

The most significant obstacle to the use of PLE is, in many cases, a lack of sufficient stereoselectivity. This is particularly apparent in the series of cyclopentanedicarboxylates where virtually no known meso diester exhibits enantioselectivity exceeding 60% ee. Thus, e.g., dimethyl 1,2-cyclopentanedicarboxylate is hydrolyzed with only 10–17% ee.[5,6] A higher but nonetheless insufficient optical purity was noted in a series of 1,3-cyclopentanedicarboxylates. Thus, compound **1** was hydrolyzed to the



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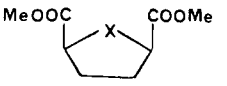

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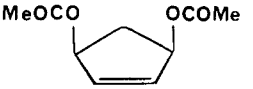
2a: X = CH_2
2b: X = O
2c: X = S

corresponding acid ester with ca. 60% ee.[4,7] The observed low enantioselectivity precluded the use of ester **1** for synthesis of aristeromycin and neplanocin A.[4] Likewise, monocyclic substrate **2a** gave an acid ester with only 34% ee.[8] A similar situation was encountered in 5-oxa and 5-thia analogues **2b** and **2c** where the ee values were 42% and 46%, respectively.[8] In striking contrast, diacetate **3**,



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which can be considered as an unsaturated retroanalogue[9] of **2a**, was hydrolyzed in a highly enantioselective fashion.[10,11] It is then obvious that substrates with a highly functionalized cyclopentane skeleton exhibiting sufficient stereoselectivity of hydrolysis are of interest for synthesis

(1) For nomenclature of cyclopentane derivatives, see: Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc.* **1969**, *91*, 3075. Abbreviations are as follows: Ip, isopropylidene (dimethylmethylene); Me, methyl; *t*-Bu, *tert*-butyl.
(2) Whitesides, G. M.; Wong, C.-H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 617.
(3) Jones, J. B. *Tetrahedron* **1986**, *42*, 3351.
(4) Arita, M.; Adachi, K.; Ito, Y.; Sawai, H.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 4049.
(5) Schneider, M.; Engel, N.; Honicke, P.; Heinemann, G.; Gorisch, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 67.
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(7) No experimental details were given.[4]
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(10) Wang, Y. I. F.; Chen, C. S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 3695.
(11) Laumen, K.; Schneider, M. *Tetrahedron Lett.* **1984**, *25*, 5875.

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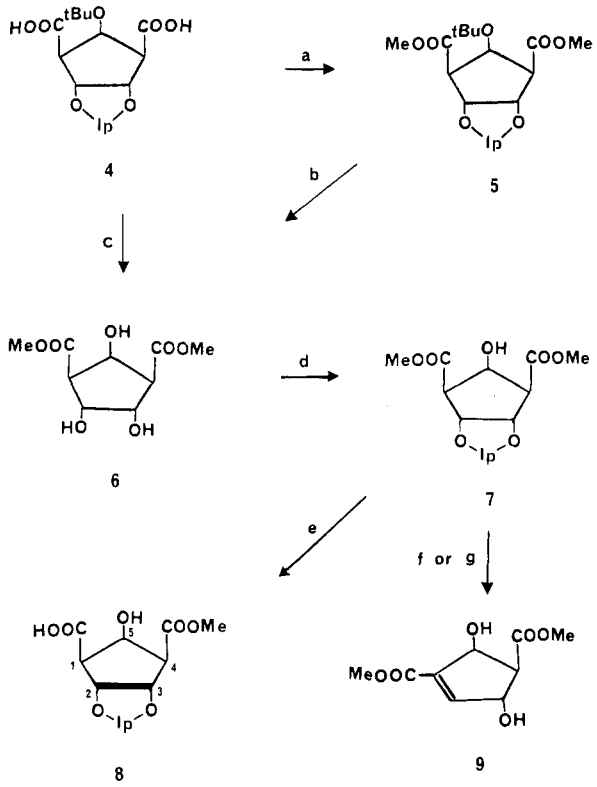
Scheme I[a]



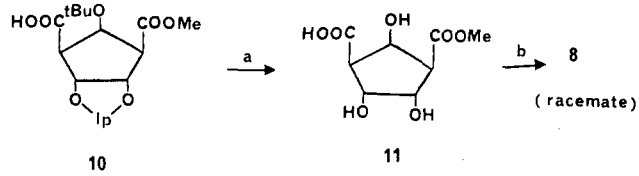
[a] (a) CH_2N_2, ether; (b) 90% CF_3COOH; (c) HCl, MeOH; (d) Me_2CO, $CuSO_4$; (e) PLE, pH 7.0; (f) α-chymotrypsin, pH 7.0; (g) pH 7.0.

of cyclopentanoid natural products[12,13] in general and carbocyclic nucleoside analogues[4,14] in particular.

Synthesis of Substrates. We have now synthesized the first of such substrates–diester **7**. Thus, the known[14] protected dicarboxylic acid **4** was transformed to the corresponding diester **5** by the action of diazomethane in 64% yield (Scheme I). Deprotection of **5** with 90% CF_3COOH gave compound **6** (90%). More conveniently, esterification and deprotection of dicarboxylic acid **4** can be achieved in a single step by using HCl in methanol to give **6** in almost quantitative yield. The isopropylidene group was then reintroduced[14] with acetone and $CuSO_4$ to give diester **7** in 90% yield. Compound **7** was then converted to **8** by PLE (see below). The synthesis of racemic **8**, necessary as a control for determination of optical purity of **8** obtained by PLE-catalyzed hydrolysis, was accomplished as follows (Scheme II). The known[14] racemic ester **10** was completely deprotected with 90% CF_3COOH to give compound **11** which was re-isopropylidenated in situ by using acetone–$CuSO_4$ reagent. The overall yield of racemic **8** was 35%. It is noteworthy that reaction of ester **11** with acetone–$CuSO_4$ was considerably more difficult than the corresponding transformation of diester **6**. Selective deprotection of the fully protected diester **5** with HCl in methanol then afforded compound **12** in 45% yield (Scheme III). The conditions were not optimized and it is likely that higher yields of **12** could be obtained.

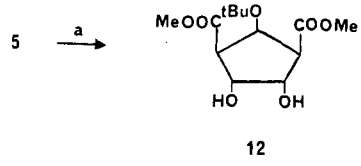
PLE Studies. The PLE-catalyzed hydrolysis of **7** at pH 7 and room temperature (450 units of PLE/mmol of **7** and ca. 0.2 M substrate concentration) to the monoester

Scheme II[a]



[a] (a) 90% CF_3COOH; (b) Me_2CO, $CuSO_4$.

Scheme III[a]



[a] (a) 0.75 M HCl, MeOH.

8 was 90% complete after 5 h as determined both by titration with NaOH and TLC. Compound **8** was isolated by extraction, after a careful acidification, in 40–80% yield depending on the workup conditions. Thus, at pH 2 (yield 42%) TLC showed partial deprotection whereas at pH 3 an 81% yield of **8** was obtained.

It is also apparent that diester **7** belongs to a class of substrates of lower reactivity. Thus, under the conditions approximating those[8] used for hydrolysis of diesters **2a–c** (50 units PLE/mmol, 0.2 M substrate, pH 7), no hydrolysis of **7** was observed during 1.5 h. By contrast, ethyl butyrate was readily hydrolyzed within 45 min. The fully protected diester **5** was completely resistant to PLE, probably because of a poor solubility and/or presence of a bulky (*tert*-butoxy) group in the vicinity of ester moieties. The latter factor may play a more important role as shown by the finding that the more hydrophilic diester **12** is also not a substrate. By contrast, trihydroxy diester **6** is a substrate of PLE but of a very low reactivity (complete hydrolysis in ca. 5 days at room temperature).

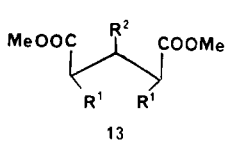
Neither **5** nor **7** are substrates for α-chymotrypsin. After a prolonged incubation of **7** at pH 7 (15 days), an elimination of the (dimethylmethylene)oxy function was observed to give olefin **9** in low (8%) yield. A similar elimination was reported previously with 2′,3′-*O*-isopropylideneribonucleoside 5′-uronates.[15]

The enantiomeric purity of **8** was determined by high-field ^1H NMR spectroscopy of the corresponding salts with 1(*S*)-phenylethylamine or 1(*S*)-(1-naphthyl)ethylamine. The salt of racemic **8** with 1(*S*)-phenylethylamine in CD_3COCD_3 gave a resolution of methoxy signals in the ^1H NMR spectra for both enantiomers of only 1.5 Hz (data not shown). By contrast, a similar resolution[8] of PLE-catalyzed hydrolysis products of **2c** was 3.6 Hz at 200 MHz in $CDCl_3$. Nevertheless, the use of 1(*S*)-(1-naphthyl)-ethylamine led, in conjunction with $CDCl_3$, to a markedly increased anisotropic effect on both methoxy and methyl (isopropylidene) signals of **8** (Figure 1). Thus, the separation of methoxy signals of racemic **8** was 7 Hz, almost twice the value observed[8] for the hydrolysis products of **2c**. It is significant that even greater differences of chemical shifts were observed for the isopropylidene methyl groups of both enantiomers of **8**, 16.1 and 20.4 Hz, respectively. It is, therefore, reasonable to expect that 1(*S*)-(1-naphthyl)ethylamine will find a wider use for determination of enantiomeric excess in the hydrolysis of esters catalyzed by PLE. It can then be concluded that

(12) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847.
(13) Harre, M.; Raddatz, P.; Walenta, R.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 480.
(14) Ben Cheikh, A.; Craine, L. E.; Recher, S. G.; Zemlicka, J. *J. Org. Chem.*, previous paper in this issue.
(15) Nagpal, K. L.; Horwitz, J. P. *J. Org. Chem.* **1971**, *36*, 3743.

PLE-catalyzed hydrolysis of diester **7** proceeds with >95% stereoselectivity.

Although the ^1H NMR studies have provided ample evidence for an enantioselective course of hydrolysis of **7** catalyzed by PLE, the question of the absolute configuration of product **8** remained. X-ray diffraction of a single crystal of **8** has shown that configurations at C1 through C5 are as follows: 1*S*, 2*R*, 3*S*, 4*R*, and 5*R* (see Crystallographic Results). We would like to add that the X-ray diffraction study of ester **8** also unambiguously confirms the structure of intermediary diacid **4** and thus of 6′β-hydroxyaristeromycin.[14] The hydrolysis of **7** then proceeds with a *pro-S* stereoselectivity observed[8] in diesters **2a–c**. By contrast, diester **1** which lacks the oxygen function at C5 was hydrolyzed in a *pro-R* fashion giving the product of different absolute configuration[4] and with a distinctly lower stereoselectivity. Consequently, in the series, **2a** → **1** → **7**, a double reversal of stereoselectivity was encountered; the first with introduction of a (dimethylmethylene)dioxy function and the second with substitution of C5. Abrupt reversals of stereoselectivity are the hallmark of PLE[8] although they are difficult to interpret. For example, substrate **7** has two oxygen functions in a β-position to a given carbomethoxy group. It is then difficult to decide which one will be more important for enzyme binding. In other words, can diester **7** be regarded as an analogue of 5-unsubstituted diester **1** or of dimethyl 3-hydroxyglutarate[16] (**13a**) which mimics the "top" (C1–C5–C4) portion of **7**?



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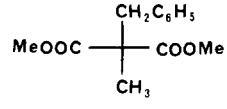

14

13a: $R^1 = H, R^2 = OH$
13b: $R^1 = Me, R^2 = H$
13c: $R^1 = Me, R^2 = OH$

PLE is a serine hydrolase[19] and a mixture of several molecular forms (isozymes).[20] The first working model[18] of its action summarized the available information in terms of a generalized substrate structure but it did not attempt to relate these findings to particular binding sites of PLE. The latter drawback was removed in an active-site model with defined hydrophobic and catalytic sites along with a pocket for the nonhydrolyzable ester group.[21] Somewhat surprisingly, binding sites for hydrophilic or charged groups have not been considered although several of such compounds, e.g. **13a** and **13c**, are excellent substrates. Loss and reversals of stereospecificity typical for meso diesters[8] can then be interpreted in terms of two different binding modes. Similar but less pronounced changes of stereoselectivity were noted in another serine hydrolase–chymotrypsin.[22]

Given the wide range of substrates that are amenable to PLE-catalyzed hydrolysis, it is reasonable to propose

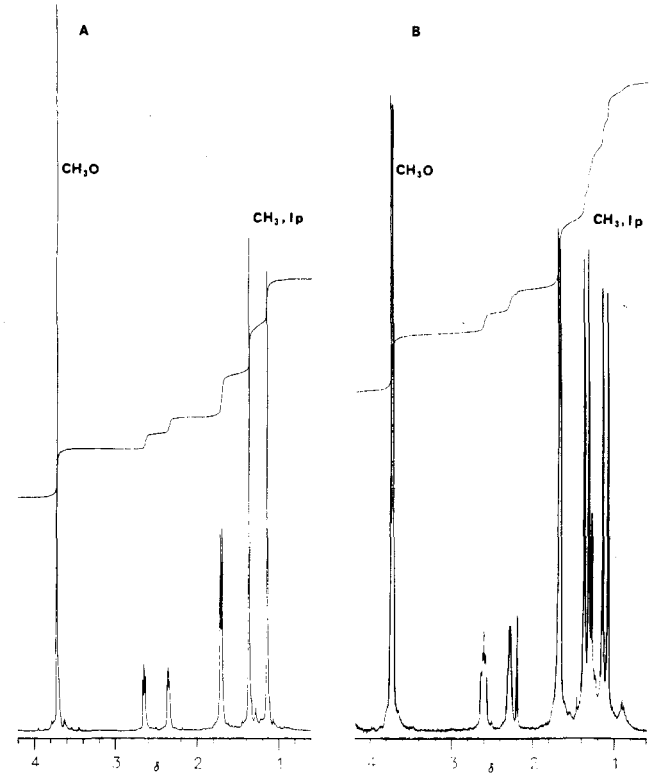

Figure 1. Determination of optical purity of ester **8**. Two molar equivalents of 1(*S*)-(1-naphtyl)ethylamine were added to the solution of optically active (A) or racemic (B) ester **8** in $CDCl_3$. For the corresponding reference spectrum of **8**, see the Experimental Section.

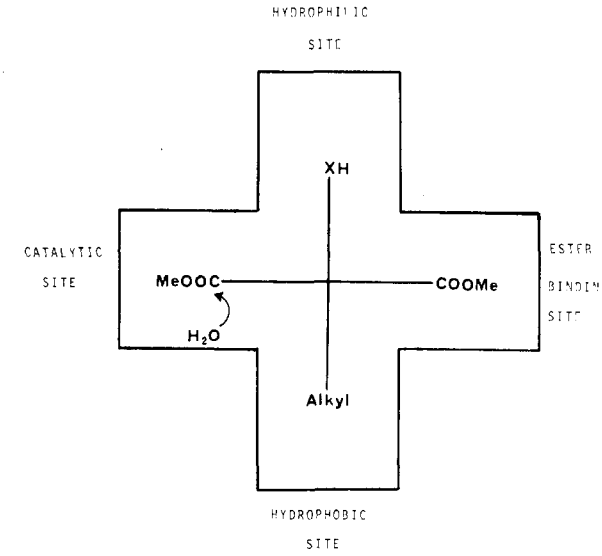

Figure 2. Hypothetical model of active site of pig liver esterase (PLE). Letter X implies a heteroatom (e.g. oxygen), alkyl residue also includes aralkyl and aryl substituents. Attack of one of the ester residues with a water molecule symbolizes function of the catalytic site not a mechanism (unknown) of the process.

both hydrophobic and hydrophilic binding sites in addition to a catalytic site and an alternate locus binding the nonhydrolyzable ester group (Figure 2). It is probable that there is still another binding site accommodating charged groups, e.g. NH_3^+. Such an arrangement will then resemble that of a synthetase, ribosomal peptidyltransferase,[23] which must also provide sites for different types of amino acids

(16) This compound was reported to be hydrolyzed by PLE with an *S* stereoselectivity[17] sufficiently high for the synthesis of natural products. This result sharply contrasts with only 12% ee obtained by another group.[18]

(17) Brooks, D. W.; Palmer, J. T. *Tetrahedron Lett.* **1983**, *24*, 3059.

(18) Mohr, P.; Waespe-Sarcevic, N.; Tamm, C.; Gawronska, K.; Gawronski, J. K. *Helv. Chim. Acta* **1984**, *66*, 2501.

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(22) Schwartz, H. M.; Wu, W.-S.; Marr, P. W.; Jones, J. B. *J. Am. Chem. Soc.* **1978**, *100*, 5199.

(23) Chladek, S.; Sprinzl, M. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 371.

Table I. Atomic Positional Parameters of Optically Active Ester 8

atom	x	y	z
O1	−0.0743 (4)	−0.83430	0.3315 (2)
O2	−0.1222 (3)	−1.0600 (4)	0.1894 (2)
O3	−0.3039 (3)	−0.5877 (4)	0.1215 (2)
O4	−0.2301 (3)	−0.3083 (4)	−0.0783 (3)
O5	−0.5029 (3)	−0.3899 (4)	−0.2077 (2)
O6	−0.3209 (3)	−0.9979 (4)	−0.1667 (2)
O7	−0.3760 (3)	−0.7790 (3)	−0.3224 (2)
C1	−0.1866 (4)	−0.6314 (5)	0.0621 (4)
C2	−0.1694 (4)	−0.8174 (4)	0.0546 (3)
C3	−0.3443 (4)	−0.8701 (5)	−0.0790 (3)
C4	−0.4000 (4)	−0.7229 (4)	−0.1912 (3)
C5	−0.2723 (4)	−0.5862 (4)	−0.1126 (3)
C6	−0.1165 (4)	−0.9016 (5)	0.2088 (4)
C7	−0.3497 (4)	−0.4186 (4)	−0.1387 (4)
C8	−0.3983 (4)	−0.9503 (5)	−0.3291 (3)
C9	−0.2939 (4)	−1.0188 (5)	−0.4040 (3)
C10	−0.5866 (4)	−0.9969 (5)	−0.4084 (3)
C11	−0.0722 (5)	−1.1588 (5)	0.3284 (4)

involved in the peptide bond formation process. As PLE, the latter enzyme accommodates two distinct ester groups, albeit in two separate substrates.[23,24]

A high stereoselectivity of the PLE-catalyzed hydrolysis of diester **7** is then probably a consequence of simultaneous binding of the 5-hydroxy and 2,3-dimethylmethylenedioxy groups to the hydrophilic and hydrophobic sites, respectively. Compounds **1**, **2a**, **2b**, and **2c**, lacking an extra binding (polar) group, then exhibit much lower enantioselectivity. In addition, these diesters can be bound to the hydrophobic site of PLE in two different binding modes which will also adversely affect the stereoselectivity. It is interesting to note that dialkylmalonate **14**, wherein both alkyl groups can be utilized for binding, is also hydrolyzed with a little enantioselectivity.[25] Comparison of diesters **1** and **7** with the corresponding open-chain analogues[18] **13b** and **13c** is particularly striking. Compound **13b** is hydrolyzed with a reversed stereoselectivity relative to **1** (60% ee in both cases).[18] By contrast, PLE-catalyzed hydrolysis of diester **13c** proceeds with the same stereochemistry as that of **7** (98% ee).[18] The fact that the ee values of pairs **1**, **13b** and **7**, **13c** coincide is probably fortuitous. It must be noted, however, that the configuration at carbon atoms carrying the hydroxy function (C3 of **13c** and C5 of **7**) is different. Assuming that hydroxy groups of diesters **7** and **13c** occupy the same locus on PLE, the observed stereochemistry of hydrolysis readily follows from an inspection of the respective space-filling models.

It is hoped that this model will be further refined after more information is obtained on the topography of the active site of PLE and structure–activity relationships.

Crystallographic Results. The results of an X-ray structural analysis of ester **8** are given in Table I and Figure 3.[26] Final R values are 0.045 and 0.035 (weighted). The molecule consists of a 2-dimethyl-1,3-dioxolane ring fused with a substituted cyclopentane ring. All bond distances and angles are normal for these ring systems. The configuration about the five chiral centers of the cyclopentane ring is R,R,S,R,S for C1 through C5, respectively.[27] Each five-membered ring is slightly but significantly puckered toward a half-chair conformation. The maximum deviation of an atom from the best least squares plane through its ring is 0.27 Å in cyclopentane and 0.20 Å in dioxolane. The dihedral angle between the two best ring planes is 43.9 (2)°. The torsion angles indicate that the C–C bond common to both rings is twisted 7.6° from an eclipsed arrangement. Two unique hydrogen bonds are present: one intermolecular O4–H···O6′ with 1.696 (3) Å for H···O6′, and the other intramolecular O3–H···O1 with 2.083 (3) Å for H···O1.

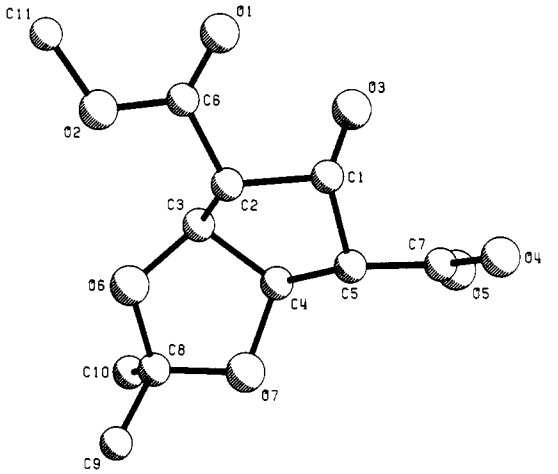

Figure 3. Molecular drawing of optically active ester **8**. The molecule is viewed down the a crystallographic axis. Note that numbering of the cyclopentane system different from that given in formula **8** was adopted in the crystallographic study. Only the C3 atoms are identical in both notations. Thus, C1 of Figure 3 corresponds to C5, C2 to C4, C4 to C2, and C5 to C1 in formula **8**.

Experimental Section

General Methods. See reference 14. Pig liver esterase, type I was a product of Sigma Chemical Co., St. Louis, MO, activity 260 units/mg protein. Thin layer chromatography (TLC) was performed in the following solvent systems: S_1, benzene–ethyl acetate (9:1); S_2, CH_2Cl_2–methanol (9:1); S_3, CH_2Cl_2–methanol (95:5); and S_4, CH_2Cl_2–methanol (4:1). ^1H NMR spectra were determined at 300 MHz by using a QE-300 spectrometer (General Electric) unless stated otherwise. Proton-decoupled ^{13}C NMR spectra were run at 75 MHz. Electron-impact and chemical ionization mass spectra (EI-MS and CI-MS) were obtained with a Kratos MS80 RFA high resolution spectrometer. 2-Methylpropane was used as an ionization gas. Infrared spectra were determined on a Perkin-Elmer 1330 spectrophotometer.

Dimethyl 2α,3α-[(Dimethylmethylene)dioxy]-5β-*tert*-butoxy-1β,4β-cyclopentanedicarboxylate (5). Diazomethane (ca. 32.2 mmol) generated[14] from Diazald by using ca. one-half of the recommended volume of solvents was introduced into a suspension of dicarboxylic acid **4** (3.59 g, 11.9 mmol)[14] in ether (15 mL) with stirring and ice-cooling. The acid went gradually

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(26) Nicolet R3 diffractometer, monochromated Mo Kα radiation, ambient temperature, cell constants: a = 8.582 (2), b = 8.286 (2), and c = 9.605 (4) Å, β = 116.35 (5)°, V = 612.0 (6) Å^3, Z = 2, space group $P2_1$, density(calcd) = 1.412 g cm^{-3}, $\theta/2\theta$ scans, $2\theta_{max}$ = 50°, 2–5° min^{-1}, μ = 1.27 cm^{-1}, anisotropic refinement on all non-hydrogen atoms. A complete description of the crystallographic experiment and all pertinent resulting tables are available as supplementary material.

(27) To determine the absolute configuration, a complete set of Friedel pairs was collected and for the intense reflections (F_o > 20) the ratios $F_o(hkl)/F_o(-h,-k,-l)$ and $F_c(hkl)/F_c(-h,-k,-l)$ were compared with F_c values from models consisting of x, y, z coordinates and the inverted set $-x, -y, -z$. When the F_o ratio was <1, the enantiomer which showed F_c < 1 was chosen; conversely when the F_o ratio was >1, then the enantiomer which showed F_c > 1 was chosen. Of those showing a clear preference, seven sets agreed better with the inverted coordinates while four agreed better with the initial coordinates. Further the R values were marginally increased by using the initial coordinates (cf. R, R_w = 0.046, 0.036 for the x, y, z model and 0.045, 0.035 for the $-x, -y, -z$ model). While the effects of anomalous dispersion are small in this molecule with Mo radiation, statistically the reported model (with the inverted coordinates) is more favored.

(28) Zadrazil, S. In *Synthetic Procedures in Nucleic Acid Chemistry*; Zorbach, W. W., Tipson, R. S., Eds.; Wiley-Interscience: New York, 1973; Vol. 2, p 632.

into solution and TLC (S_1) showed a strong spot of diester **5**. The excess of diazomethane was titrated with 10% acetic acid under ice-cooling and stirring. The resultant solution was evaporated to give a syrupy, partly crystalline, residue. This material was dissolved in warm benzene (15 mL), and the solution was decanted from the red-brown syrup which according to TLC did not contain any diester **5**. The solution was applied on silica gel column (50 g, 7 × 5 cm) which was eluted with benzene (400 mL), toluene (700 mL), and toluene–ethyl acetate (9:1, 600 mL). The appropriate fractions were pooled and they were evaporated to give 2.50 g (64%) of the title diester **5**, mp 100–102 °C (sinters from 90 °C), homogeneous on TLC (S_1). Recrystallization from cyclohexane (10 mL) afforded analytically pure diester **5**, 1.96 g (50%), mp 95–97 °C; ^{1}H NMR (100 MHz, $CDCl_3$) 5.21 (dd, 2, $H_2 + H_3$, $J_{2,3} = J_{3,2} = 4.4$, $J_{2,1} = J_{3,4} = 1.4$), 4.85 (t, 1, H_5, $J_{5,1} = J_{5,4} = 4.3$), 3.70 (s, 6, MeO), 2.97 (dt, 2, $H_1 + H_4$, $J_{1,5} = J_{4,5} = 4.4$, $J_{1,2} = J_{4,3} = 1.5$), 1.46 and 1.35 (2s, 6, Me of Ip), 1.03 (s, 9, Me of *t*-Bu); ^{13}C NMR 170.33 (CO), 113.55 (>(—O)CO— of Ip), 80.28 ($C_2 + C_3$), 78.50 (C_5), 75.21 (>CO of *t*-Bu), 57.27 ($C_1 + C_4$), 51.77 (MeO), 28.06 (Me of *t*-Bu), 27.27 and 24.89 (Me of Ip); EI-MS, *m/e* (relative intensity) 331 (11.7, M + 1), 315 (29.2, M – Me). The following fragments were also found in the spectrum of isopropylidene diester **7**: 275 (62.7), 259 (7.9), 243 (5.8), 217 (4.8), 199 (31.5), 185 (8.9), 167 (17.2), 139 (37.9), 111 (39.8). Other major peaks: 73 (*t*-BuO, 51.1), 57 (*t*-Bu, 100.0). Anal. Calcd for $C_{16}H_{26}O_7$: C, 58.17; H, 7.93. Found: C, 58.22; H, 8.09.

Dimethyl 2α,3α,5β-Trihydroxy-1β,4β-cyclopentanedicarboxylate (6). A. From Diester 5. Diester **5** (1.46 g, 4.63 mmol) was dissolved in cold 90% trifluoroacetic acid (25 mL) with stirring and ice-cooling. The resultant almost colorless solution was stirred for 55 min at room temperature. Trifluoroacetic acid was evaporated at room temperature and the residue was lyophilized. TLC (S_2) showed a single spot of the expected diester **6**. The residue was dissolved in water (20 mL) and the solution was lyophilized again. The residue was washed with ether (10 mL), petroleum ether was added (35 mL), and the white solid was filtered off, 0.98 g (91%), mp 105–110 °C, homogeneous on TLC (S_2). Analytical sample of **6** was obtained by crystallization of 0.1 g of the above compound from butanone, mp 112–115 °C: ^{1}H NMR (100 MHz, $CD_3COCD_3 + D_2O$) 4.59 (m, 3, $H_2 + H_3 + H_5$), 3.67 (s, 6, MeO), 2.97 (t, 2, $H_1 + H_4$). The spectrum without D_2O was much less resolved and it exhibited signals at 4.07 (br s, 1, OH) and 2.90 (br s overlapped with $H_1 + H_4$, 2 OH); ^{13}C NMR 171.44 (CO), 70.72 ($C_2 + C_3 + C_5$), 57.11 ($C_1 + C_4$), 51.14 (MeO); EI-MS, *m/e* (relative intensity) 235 (0.7, M + H), 203 (3.4, M – MeO), 103 (100.0), 71 (69.7); CI-MS, *m/e* (relative intensity) 235 (100.0, M + H), 203 (81.7, M – MeO), 185 (31.5), 167 (9.7), 103 (27.7), 71 (11.8). Anal. Calcd for $C_9H_{14}O_7$: C, 46.15; H, 6.03. Found: C 46.03; H, 5.80.

B. From Dicarboxylic Acid 4. Compound[14] **4** (5 g, 0.165 mmol) was dissolved in cold (4 °C) methanol saturated with HCl (100 mL). The solution was allowed to reach room temperature and the progress of the reaction was monitored by TLC (S_2). The esterification was complete in 4 h, the solvent and HCl were removed in vacuo, and the oily residue was repeatedly coevaporated with methanol (50-mL portions). The product gradually solidified to give 3.71 g (96%) of diester **6**, mp 109–112 °C, homogeneous on TLC (S_2) and identical with the compound obtained by method A.

Dimethyl 2α,3α-[(Dimethylmethylene)dioxy]-5β-hydroxy-1β,4β-cyclopentanedicarboxylate (7). A mixture of diester **6** (0.78 g, 3.33 mmol), acetone (dried with molecular sieves 4A, 65 mL), and anhydrous $CuSO_4$ (5.2 g, 32.6 mmol) was magnetically stirred for 5 days at room temperature. TLC (S_3) showed a single spot of the expected diester **7**. The $CuSO_4$ was filtered off with the aid of a Celite bed, it was washed with dry acetone, and the clear filtrate was evaporated to a slightly yellow syrup **7**. The latter crystallized after addition of petroleum ether (10 mL) and seeding, 0.82 g (90%), mp 77–83 °C. Recrystallization from benzene–cyclohexane (1:2, 7.5 mL) gave 0.55 g (55%), mp 81–82 °C: ^{1}H NMR ($CDCl_3$) 5.14 (dd, 2, $H_2 + H_3$, $J_{2,3} = J_{3,2} = 4.1$, $J_{2,1} = J_{3,4} = 1.4$), 4.86 (t, 1, H_5, $J_{5,1} = J_{5,4} = 3.8$), 3.80 (s, 6, MeO), 3.02 (t, 2, $H_1 + H_4$), 1.53 and 1.38 (2s, 6, Me of Ip); ^{13}C NMR 171.53 (CO), 114.06 (>CO of Ip), 80.89 ($C_2 + C_3$), 76.07 (C_5), 55.81 ($C_1 + C_4$), 52.37 (MeO), 27.33 and 24.70 (Me of Ip); EI-MS, *m/e* (relative intensity) 275 (M + 1, 20.9), 259 (M – Me, 40.0), 243 (4.2, M – MeO), 217 (4.6), 199 (7.2), 185 (10.5), 167 (14.3), 153 (5.9), 139 (30.7), 114 (30.2), 111 (26.8), 97 (5.8), 83 (10.9), 73 (18.6), 69 (13.7), 59 (33.6), 55 (11.6), 43 (100.0). Anal. Calcd for $C_{12}H_{18}O_7$: C, 52.55; H, 6.62. Found: C, 52.70; H, 6.45.

Methyl 1(*S*)-Carboxy-2(*R*),3(*S*)-[(dimethylmethylene)dioxy]-5(*R*)-hydroxy-4(*R*)-cyclopentanecarboxylate (8). Workup at pH 2. Diester **7** (0.27 g, 1 mmol) was incubated with pig liver esterase (PLE, 450 units) in 0.1 M Na_2HPO_4 (pH 6.9, 5 mL, 0.5 mmol) with magnetic stirring at room temperature under a continuous pH monitoring (pH meter). The pH was kept at 7 by addition of 1 M NaOH from a burette. A theoretical amount of NaOH (1 mL) was consumed in 3 h. TLC (S_3) showed still some unreacted diester **7**. The solution was stirred for 19 h at room temperature whereupon TLC indicated a complete absence of the starting material. The pH was adjusted to 2 by addition of 2 M HCl with ice-cooling and stirring and the mixture was extracted with CH_2Cl_2 (5 × 15 mL) after addition of some NaCl. After the first extraction a precipitated gel was removed by centrifugation. The organic layers were dried ($MgSO_4$) and evaporated to give a white solid, 0.11 g (42%), homogeneous on TLC (S_3 and S_4), mp 162–164 °C (hot stage), change of modification to a cluster of needles at 130–140 °C: $[\alpha]^{24}$ +5.49° (*c* 0.51, dioxane); ^{1}H NMR (CD_3COCD_3) 5.13 (qt, 2, $H_2 + H_3$), 4.88 (t, 1, H_5), 3.69 (s, 3, MeO), 3.06 (t, 2, $H_1 + H_4$), 1.38 and 1.27 (2s, 6, Me of Ip); ^{13}C NMR 171.81 and 171.20 (CO), 113.84 (>(—O)CO— of Ip), 81.54 and 81.24 ($C_2 + C_3$), 77.83 (C_5), 57.98 and 57.34 ($C_1 + C_4$), 51.97 (MeO), 27.48 and 24.77 (Me of Ip); EI-MS, *m/e* (relative intensity) 261 (5.9, M + H), 245 (17.5, M –Me), 203 (1.7, M + H – Me_2CO); peaks 185 (6.5), 167 (5.2), 139 (7.7) and 111 (5.9) were also found in the spectra of diester **5**. Other major fragments: 125 (9.4), 109 (6.2), 97 (7.3), 83 (10.1), 59 (35.6), and 43 (100.0). Anal. Calcd for $C_{11}H_{16}O_7$: C, 50.77; H, 6.20. Found: C, 50.72; H, 6.21. For determination of optical purity, see Figure 1; for an X-ray diffraction, Figure 3. Suitable crystals were obtained by a slow evaporation of the solution of **8** in $CHCl_3$.

B. Workup at pH 3. The experiment was performed as described in method A on a 2-mmol scale. After 5 h, 90% of the theoretical amount of NaOH was consumed. The mixture was stirred for a total of 24 h whereupon the pH was adjusted to 3 (at 0 °C) with H_3PO_4 and the solution was immediately extracted with ether (5 × 10 mL) and CH_2Cl_2 (5 × 10 mL). Evaporation of the organic phases gave ester **8**, 0.42 g (81%), identical (mp, TLC) with a sample obtained by method A.

(±)-Methyl 2α,3α-[(Dimethylmethylene)dioxy]-1β-carboxy-5β-hydroxy-4β-cyclopentanecarboxylate (8). Protected monoester **10** (0.63 g, 2 mmol)[14] was dissolved in an ice-cold 90% CF_3COOH (20 mL). The solution was kept for 10 min at 0 °C and then ca. 50 min at room temperature. TLC (S_2) showed that the deprotection was complete. The mixture was evaporated in vacuo and the crude residue was coevaporated several times with water and finally with ethanol to give gummy material **11**. The latter was dissolved in acetone (45 mL), anhydrous $CuSO_4$ (2 g, 12.5 mmol) was added, and the mixture was stirred for 18 h at room temperature. The isopropylidenation was incomplete as shown by TLC (S_2); therefore, the mixture was refluxed for 5.5 h. Additional $CuSO_4$ (1 g, 6.3 mmol) was added and the reflux was continued for 1 h whereupon the mixture was stirred for 16 h at room temperature. TLC (S_2) still showed some starting material **10**. The $CuSO_4$ was filtered off, it was washed with acetone (4 × 25 mL), and the filtrate was evaporated. The residue was dissolved in water (15 mL) and the solution (pH 2.5) was extracted with CH_2Cl_2 (3 × 15 mL). Citric acid (0.5 g, 2.6 mmol) was then added and the solution was extracted again with CH_2Cl_2 (7 × 15–25 mL). The dried (Na_2SO_4) organic phase was evaporated to give a white solid (0.18 g, 35%), mp 150–154 °C (modification change at 120–130 °C). Crystallization from cyclohexane–acetone (4:1) gave racemic compound, in three crops (0.15 g, 29%), mp 156–158 °C (second crop), identical according to ^{1}H and ^{13}C NMR, EI-MS, IR, and TLC (S_2) with the optically active material **8**.

Attempted Hydrolysis of Diester 7 with α-Chymotrypsin. Isolation of (±)-Dimethyl 2β,4α-Dihydroxy-1,3β-cyclopentenedicarboxylate (9). A solution of diester **7** (0.14 g, 0.51 mmol) in 0.1 M Na_2HPO_4 (pH 7, 2.5 mL, 0.25 mmol) and α-chymotrypsin (10 mg, 470 units) was stirred at room temperature for 15 days. TLC showed the presence of less mobile, UV ab-

sorbing, and $KMnO_4$-positive product in addition to the starting diester 7. The solution was extracted with CH_2Cl_2 (4 × 15 mL), and the extracts were dried ($MgSO_4$) and evaporated to give a syrup which was chromatographed on a loose layer of silica gel,[28] 2 mm thick, 2 × 20 cm in solvent system S_3. The strongly UV-absorbing band of **9** was eluted and the eluate was evaporated to give a syrup which soon crystallized, 9 mg (8%), mp 109–110 °C: UV max (ethanol) 204 nm (ε 6 250); ^1H NMR ($CDCl_3$) 6.84 (d, 1, H_2, $J_{2,3}$ = 2), 5.53 (dt, H_5, $J_{5,4}$ = 7), 5.24 (dd, 1, H_3, $J_{3,2}$ = 2, $J_{3,4}$ = 7), 3.793 and 3.787 (2s, 6, COOMe), 3.06 (t, 1, H_4, $J_{4,3}$ = $J_{4,5}$ = 7); EI-MS, *m/e* (relative intensity) 217 (0.2, M + 1), 199 (M - H_2O + 1, 2.7), 184 (4.9, M - MeOH), 166 (100.0, 184 - H_2O). Additional peaks: 155 (13.0), 139 (50.8), 123 (25.7), 111 (42.2), 97 (15.4), 83 (20.8), 69 (37.8), 59 (33.3). CI-MS, *m/e* (relative intensity) 217 (15.4, M + H), 199 (100.0, M + H - H_2O), 167 (96.3, M + H - H_2O - MeOH), 139 (14.0). Sample recovered from ^1H NMR was analyzed. Anal. Calcd for $C_9H_{12}O_6 \cdot {}^1/_4CDCl_3$: C, 45.11; H, 5.11 (includes 0.2% D). Found: C, 45.10; H, 5.42. The same product was obtained when α-chymotrypsin was omitted from the reaction mixture.

Dimethyl 2α,3α-Dihydroxy-5β-*tert*-butoxy-1β,4β-cyclopentanedicarboxylate (12). A solution of diester **5** (1.5 g, 4.5 mmol) in 0.75 M HCl in methanol (25 mL) was kept for 90 min at room temperature. TLC (S_3) showed the presence of a polar component (component **12**) and starting material **5**. Triethylamine (2.7 mL) was added with ice-cooling, the mixture was evaporated, and the residue was partitioned between water (25 mL) and CH_2Cl_2 (2 × 25 mL). The organic phase was dried (Na_2SO_4) and evaporated. The residue was chromatographed on a silica gel column (15 g) in solvent system S_3 to give compound **12** (0.59 g, 45%), mp 145–150 °C, homogeneous on TLC (S_3) in addition to starting material **5** (0.73 g, 49%). An analytical sample was obtained by crystallization from cyclohexane–ethanol (6:1), mp 145–150 °C: IR 3360 and 3250 (OH), 1735 (CO); ^1H NMR (C_3SOCD_3) 4.79 (d, 2, OH), 4.61 (t, 1, H_5), 4.32 (qt, 2, H_2 + H_3), 3.56 (s, 6, MeO), 2.93 (q, 2, H_1 + H_4), 0.97 (Me of *t*-Bu, s, 9); ^{13}C NMR 170.60 (CO), 74.19 (>CO of *t*-Bu), 72.37 (C_2 + C_3), 70.84 (C_5), 56.08 (C_1 + C_4), 51.00 (MeO), 27.54 (Me of *t*-Bu). Anal. Calcd for $C_{13}H_{22}O_7$: C, 53.78; H, 7.64. Found: C 54.02; H, 7.68.

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Note added in proof: An alternate binding model of PLE comprising two hydrophobic sites one of which is capable of interacting with a nonhydrolyzable ester group has been proposed: Lam, L. K. P.; Hui, A. H. F.; Jones, J. B. *J. Org. Chem.* **1986**, *51*, 2047. Sabbioni, G.; Jones, J. B. *Ibid.* **1987**, *52*, 4565. A possible hydrophilic site has not been considered.

Supplementary Material Available: A complete description of the crystallographic experiment and tables of pertinent crystallographic data for compound **8** (8 pages). Ordering information is given on any current masthead page.

On the Mechanism of the Thermal Decomposition of 1-Bromo-1-(trimethylstannyl)cyclopropanes

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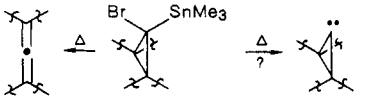
A mechanistic study of the thermolysis of compounds **4a** and **4b** is reported. In methanolic benzene, **4a** reacts entirely via formation of norcaranylidene (**8**), while **4b** gives no carbene but rather ring-opening to a cycloheptenyl ion. The pathway for carbene formation is discussed. Under less polar conditions (cyclohexene), carbene formation from **4a** and ionic ring-opening from **4b** still predominate. However, **4b** now gives some carbenic product.

Introduction

In 1975, Seyferth reported[1] that heating α-bromo-α-(trimethylstannyl)cyclopropanes **1** in solution provided a possible route to cyclopropylidenes **2**. Irrespective of mechanism, most of the variants of **1** tested gave ring-opening to allenes **3** (including all the monocyclic examples of **1**). Only the norcarane system **4** produced divalent



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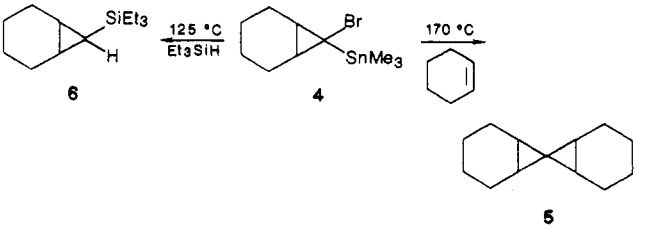
carbon transfer products (e.g., **5**, **6**) with olefins or Et_3SiH. Seyferth concluded that the mechanism of the divalent carbon transfer reaction was unclear, there being several disturbing features observed mitigating against a simple carbene mechanism (e.g., **6** was formed as a 1:1 mixture of epimers).



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Among the noteworthy observations of Seyferth were the differential reactivities of **4a** and **4b**, with the former considerably more reactive at 83 °C in refluxing cyclohexene. In refluxing cyclooctene (146 °C), **4a**, and **4b** both gave **7**, but in different yields. But whether both precursors gave **7** via a common carbene intermediate (**8**) was unclear. In addition, a 4:1 mixture of **4a**:**4b**, when heated at 170 °C in cyclohexene, gave a 33% isolated yield of **5**. Lastly, the same **4a**:**4b** mixture in chlorobenzene/Et_3SiH (125 °C) afforded, in addition to **6**, 12% of allene dimer **10**. Did **10** arise via the pathway **8** → **9** → **10**?

Despite the uncertainties, we had hoped to use this method as an entry to norcarenylidene (**11**). However,

(1) Seyferth, D.; Lambert, R. L., Jr. *J. Organomet. Chem.* **1975**, *91*, 31.

0022-3263/88/1953-0942$01.50/0