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Investigation of the Pancreatin-Catalyzed Acylation of *cis*-Cyclopent-2-ene-1,4-diol with Various Trichloroethyl and Vinyl Alkanoates

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During the pancreatin-catalyzed acetylation of the *meso*-diol **1** with 2,2,2-trichloroethyl acetate (**2a**) in tetrahydrofuran/triethylamine, the enantiomeric monoacetates **3a** and *ent*-**3a** are formed at nearly equal rates. *ent*-**3a** is rapidly acetylated in a second enzyme-catalyzed step, forming **4a**, whereas **3a** resists further enzymatic acetylation. Thus, the monoacetate **3a** can be obtained in 48% yield with an enantiomeric excess (e.e.) of more than 99%. 2,2,2-Trichloroethyl propanoate and butanoate give the corresponding monoacylation products even in slightly better yield, whereas the octanoate affords the monoacylation product with a lower enantiomeric excess. 2,2,2-Trichloroethyl monochloroacetate provides the monoacylation product in a 40% yield with an e.e. of 90%. The dichloroacetate, however, affords the diacylation product exclusively in an enzyme-independent chemical reaction. With the 2,2,2-trichloroethyl esters of isobutyric, phenylacetic, and benzoic acid no transesterification could be achieved within 24 hours. The application of vinyl acetate, however, represents a significant improvement in the synthesis of enantiomerically pure monoacetate **3a** from *meso*-diol **1**.

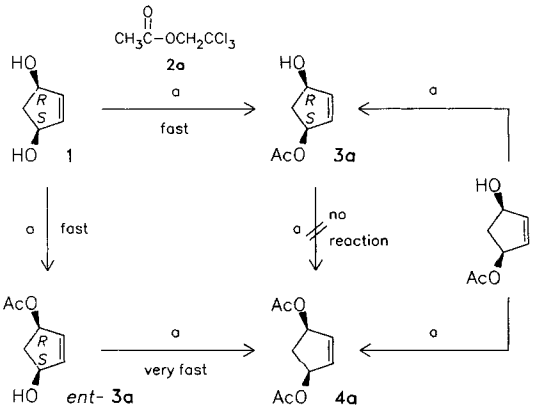
(1*S*,4*R*)-(−)-4-Hydroxycyclopent-2-enyl acetate (**3a**), its enantiomer *ent*-**3a**, and other related 1,4-disubstituted cyclopent-2-enes are attractive starting materials for prostaglandins[2-5] and other cyclopentanoid natural products[6]. Recently we have published a highly efficient method for the enantioselective synthesis of **3a** by an enzyme-catalyzed transesterification of the *meso*-diol **1** with 2,2,2-trichloroethyl acetate (**2a**) in the solvent system tetrahydrofuran/triethylamine[7]. This method, complemented in the meantime by Jommi et al.[8], proved to be a superior alternative to the microbial or enzymatic hydrolysis of the *meso*-diacetate **4a** yielding the monoacetates **3a**[9-12] or *ent*-**3a**[13-15].

Although the enantiomeric purity of **3a** obtained by enzyme-catalyzed transesterification of **1** with 2,2,2-trichloroethyl acetate (**2a**) was excellent, the chemical yield did not exceed 50%[7]. Therefore, we were interested in the mechanistic pathway and the influence of the structure of the acylating agent on the chemical and optical yield of this enzyme-catalyzed transesterifiction.

Reaction Path of the Pancreatin-Catalyzed Acetylation of *cis*-Cyclopent-2-ene-1,4-diol (1) Using 2,2,2-Trichloroethyl Acetate (2a)

During the pancreatin-catalyzed acetylation of the *meso*-diol **1**, 45% of the *meso*-diacetate **4a** is otained as a by-product, with 48% of the desired monoacetate **3a**[7]. It is of interest, for theoretical and practical reasons, to find out via which intermediate the diacetate **4a** is formed. Considering Scheme 1, at least two routes may be discussed. The first one could consist of the enzymatically catalyzed acetylation of the (*S*)-hydroxy group of the diol **1** affording the monoacetate **3a**, followed by an enzyme-catalyzed acetylation of the (*R*)-hydroxy group of **3a**, yielding the diacetate **4a**. The second route could start with an acetylation of the (*R*)-hydroxy group of **1**, affording *ent*-**3a**, followed by an acetylation of the (*S*)-hydroxy group of *ent*-**3a**, giving rise to the diacetate **4a**. Obviously, it depends on the individual reac-

Scheme 1. Mechanistic investigation of the formation of the *meso*-diacetate **4a** by the pancreatin-catalyzed acetylation of the *meso*-diol **1** using 2,2,2-trichloroethyl acetate (**2a**). a: $CH_3CO_2CH_2CCl_3$ (**2a**), pancreatin, THF, NEt_3, 23 °C



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tion rates whether these routes are equal in significance or to which extent one of them is preferred to the other. This question could be decided by two simple experiments. In the first experiment, enantiomerically pure monoacetate **3a** was subjected to the conditions of the pancreatin-catalyzed acetylation of the *meso*-diol **1**[7]. After workup, **3a** was recovered unchanged in quantitative yield without any loss of enantiomeric purity. In the second experiment, the same procedure was repeated using racemic monoacetate *rac*-**3a**. In this case, enantiomerically pure monoacetate **3a** and *meso*-diacetate **4a** were obtained in a chemical yield of 46 and 49%, respectively. Hence, this method represents a very efficient resolution procedure for *rac*-**3a**.

These two experiments clearly indicate that the formation of the *meso*-diacetate **4a** during the pancreatin-catalyzed acetylation of the *meso*-diol **1** with 2,2,2-trichloroethyl acetate (**2a**) in tetrahydrofuran/triethylamine proceeds via the monoacetate *ent*-**3a**, which is rapidly acetylated in a second enzyme-catalyzed reaction step at its (*S*)-hydroxy group, whereas monoacetate **3a** resists further enzymatic acetylation at its (*R*)-hydroxy group.

Pancreatin-Catalyzed Acylation of *cis*-Cyclopent-2-ene-1,4-diol (1) Using Various 2,2,2-Trichloroethyl Alkanoates

For a systematic investigation of the influence of the acylating agent on the outcome of the pancreatin-catalyzed acylation of the *meso*-diol **1** we used the trichloroethyl esters **2a**–**f** of various carboxylic acids. All transesterification experiments were carried out with 7 equivalents of **2a**–**f** in the presence of tetrahydrofuran and 0.7 equivalents of triethylamine as standard conditions. The results are presented in Table 1.

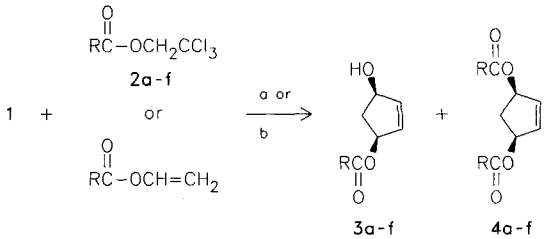
Table 1. Pancreatin-catalyzed acylation of *meso*-diol **1** with 2,2,2-trichloroethyl carboxylates **2a**–**f**

Entry	$RCO_2CH_2CCl_3$	Reaction time (h)	Reaction products (yield in %)[a] **3**	**4**	$[\alpha]_D^{20}$ [b] of **3**	e.e. (%)
1	**2a**	5	48	45	−66.3	>99[c]
2	**2b**	3	58	35	−56.7	>99[c]
3	**2c**	3	51	41	−59.2	>99[c]
4	**2d**	5	53	36	−41.3	80[c]
5	**2e**	1	39	51	−71.8	90[d]
6	**2f**	0.17	<5	74	–	–

[a] Yields were determined after flash chromatography and kugelrohr distillation. – [b] $c = 1$ in $CHCl_3$. – [c] Determined by ^{19}F-NMR spectroscopy of the (+)-Mosher ester. – [d] Determined on the basis of $[\alpha]_D^{20}$ of **6** from **3e** (Table 2).

Whereas the 2,2,2-trichloroethyl acetate (**2a**) affords the monoacetate **3a** in a chemical yield of 48% with an e.e. of more than 99%[16], the straight-chain trichloroethyl alkanoates **2b**–**d** furnish the monoalkanoates **3b**–**d** in a slightly higher yield, between 50 and 60%, in addition to the corresponding diacylated products **4b**–**d**. The enantiomeric excess of **3b** and **3c** was more than 99%, the e.e. of **3d**, however, was only 80%. The significantly diminished enantioselectivity obtained by using the octanoate **2d** is comparable to the observation that glycerol esters of long-chain fatty acids are not hydrolyzed enantioselectively by catalysis with porcine pancreatic lipase[17].

Scheme 2. Pancreatin-catalyzed acylation of the *meso*-diol **1** using the 2,2,2-trichloroethyl alkanoates **2a**–**f**, vinyl acetate or vinyl butanoate. a: $RCO_2CH_2CCl_3$ **2a**–**f**, pancreatin, THF, NEt_3, 23°C. – b: $CH_3CO_2CH{=}CH_2$ or n-C_3H_7-$CO_2CH{=}CH_2$, pancreatin, THF, NEt_3, 23°C

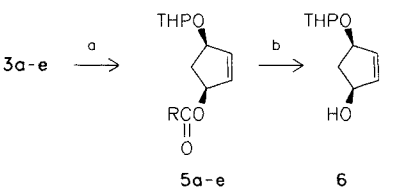


	R		R
a	Me	d	n-C_7H_{15}
b	Et	e	CH_2Cl
c	nPr	f	$CHCl_2$

As to the reaction rates, the highest rates were observed by using the chloroacetates **2e** and **2f**. Under standard conditions the diol **1** was completely converted after 1 hour using the monochloroacetate **2e** or even within 10 minutes using the dichloroacetate **2f**. With **2e** the monoacylation product **3e** was obtained in a chemical yield of 39% with an e.e. of 90%[18]. With the dichloroacetate **2f**, however, the bisacylation product **4f** was formed almost exclusively, in an isolated yield of 74%. This reaction proceeds at an extremely high reaction rate, and requires triethylamine as a catalyst, but no enzyme.

The absolute configuration of the monoalkanoates **3b**–**e** was determined by formation of the tetrahydropyranyl (THP) ethers **5b**–**e**, followed by basic methanolysis of the acyloxy group. Thus, in all four cases the known tetrahydropyranyloxy alcohol **6**[10] with a positive optical rotation was obtained (Table 2). This is a clear evidence for the fact that **3b**–**e** are (*S*)-acyloxy compounds. The same conclusion can be drawn from the ^{19}F-NMR spectra of the (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetates [(+)-Mosher esters] of **3b**–**e**.

Scheme 3. Conversion of the monoalkanoates **3a**–**e** into the THP ether **6**. a: Dihydropyran, pyridinium *p*-toluenesulfonate, CH_2Cl_2, 23°C, 2 h. – b) Basic ion-exchange resin Wofatit SPW (OH form), MeOH, 23°C, 16 h



	a	b	c	d	e
R	Me	Et	nPr	n-C_7H_{15}	CH_2Cl

Table 2. Determination of the absolute configuration of the monoalkanoates **3b–e** on the basis of the optical rotation of **6**

Starting material	$[\alpha]_D^{20}$ of **6** (*c* in $CHCl_3$)	Absolute configuration
3a	+31.5 (2.47)	*S*
3b	+30.6 (2.80)	*S*
3c	+32.0 (2.63)	*S*
3d	+25.5 (2.10)	*S*
3e	+27.8 (2.83)	*S*

Attempts to acylate the *meso*-diol **1** with the 2,2,2-trichloroethyl esters of 2-methylpropanoic, phenylacetic, and benzoic acid within 24 hours under standard conditions have failed. This means that these esters are not substrates for a pancreatin-catalyzed transesterification. However, it has been published only recently that a lipase of *Pseudomonas fluorescens* transfers the benzoyl group of benzoic anhydride onto a sugar derivative[19].

Pancreatin-Catalyzed Acylation of *cis*-Cyclopent-2-ene-1,4-diol (1) with Vinyl Alkanoates

Owing to the irreversible formation of the acyl enzyme[20] and the irreversibility of the acyl transfer, the application of enol esters has been shown to offer some advantages in enzyme-catalyzed transesterifications[21–23]. Therefore, it has also been of interest for us to investigate the pancreatin-catalyzed acylation of the *meso*-diol **1** with some enol esters under various conditions.

The acylation of **1** with 7 equivalents of isopropenyl acetate in the presence of pancreatin, tetrahydrofuran, and triethylamine under standard conditions proceeded very slowly. Within 24 hours, only 50% of **1** was converted. Compared with the described procedures[7,8], this result is of no preparative importance. The reaction of **1** with vinyl acetate, however, proceeded very rapidly under standard conditions, affording the monoacetate **3a** in 65% chemical yield with an enantiomeric excess of more than 99% (Table 3, entry 1). A higher excess of vinyl acetate (entries 2 and 3), the absence of triethylamine (entry 4) or tetrahydrofuran (entry 5) did not influence the reaction rate and the enantiomeric purity of the monoacetate **3a** formed in all cases in a yield of about 60%. In comparison with other observations[24,25], however, it is noteworthy that the reaction rate and the enantioselectivity were significantly diminished when the reaction was carried out in the absence of both triethylamine and tetrahydrofuran (Table 3, entry 6). In a final experiment, vinyl butanoate was shown to react under standard conditions even more rapidly than vinyl acetate. Unfortunately, however, the enantiomeric purity of the monobutanoate **3c** formed was slightly diminished (Table 3, entry 7).

In conclusion, it can be said that the yield of the monoacylated products **3a–e** can only be influenced slightly by lengthening the chain of the acid component of the trichloroethyl alkanoates **2a–e**. However, the use of vinyl alkanoates instead of 2,2,2-trichloroethyl alkanoates caused a significant improvement of the yield of **3a**, obviously because of the irreversibility of all reactions in Scheme 1. Having discussed the influence of the structure of the acylating agent on the pancreatin-catalyzed enantioselective monoacylation of the *meso*-diol **1**, the role of the solvent system tetrahydrofuran/triethylamine also deserves some comment. From earlier experiments we know that the pancreatin-catalyzed acylation of **1** in tetrahydrofuran using 2,2,2-trichloroethyl acetate (**2a**) is strongly accelerated by addition of triethylamine[7]. The experiments with the more reactive vinyl esters as acylating agent (Table 3) reveal that both tetrahydrofuran (entry 4) and triethylamine (entry 5) significantly enhance the reaction rate compared with the experiment without these components (entry 6).

Experimental

Tetrahydrofuran was dried with sodium wire. Triethylamine was distilled from and stored over potassium hydroxide. Pancreatin, qualified as 6 × NF, is a mixture of crude porcine pancreatic enzymes with protease, amylase, and lipase activities. The product purchased from Fa. Belger, Kleinmachnow, GDR, had a water content of 5.4% (Karl Fischer titration) and a lipase activity of 820 U/g (triolein as substrate). – TLC was carried out on plates precoated with silica gel 60 (E. Merck). For visualization the plates were treated with 5% sulfuric acid in ethanol and heated to 150 °C. Flash

Table 3. Results of the pancreatin-catalyzed acylation of diol **1** with vinyl acetate and vinyl butanoate

Entry	$RCO_2CH=CH_2$ R	Reaction conditions: $RCO_2CH=CH_2$ [mmol]	THF [ml]	NEt_3 [mmol]	Time [h]	Products (yield in %[a]) **3a**	**4a**	$[\alpha]_D^{20}$ (**3a**)[c]	e. e. (%)
1	CH_3	70	25	7	2.5	65	32	−65.1	>99[d] 99[e]
2	CH_3	140	25	7	2.5	58	39[b]	−66.4	99.8[e]
3	CH_3	350	25	7	2.5	62	48[b]	−63.4	99.8[e]
4	CH_3	70	25	–	2.5	60	31	−64.6	>99[d]
5	CH_3	350[f]	–	7	2.5	57	40	−64.4	>99[d]
6	CH_3	350[f]	–	–	24	55	31	−50.5	72[d]
7	n-C_3H_7	70	25	7	1.25	55	32	−56.7	93[d]

[a] Yields were determined after flash chromatography and kugelrohr distillation. – [b] Yield after flash chromatography. – [c] $c = 1$ in $CHCl_3$. – [d] Determined by ^{19}F-NMR spectroscopy of the (+)-Mosher ester. – [e] Determined by differential scanning microcalorimetry. – [f] The diol **1** could not be completely dissolved in a smaller amount of vinyl acetate.

chromatography was performed on silica gel 60 (0.040–0.063 mm), column dimensions 30 × 4 cm and solvent system hexane/ethyl acetate (2:1), followed by (1:1). – ^{1}H-NMR spectra were recorded at 80 MHz on a Tesla BS 587.4 instrument and ^{13}C-NMR spectra at 20 MHz on a Varian CFT 20 instrument in $CDCl_3$ with hexamethyldisiloxane as internal standard. ^{19}F-NMR spectra were measured at 376 MHz on a Bruker MSL 400 instrument in $CDCl_3$ with $CFCl_3$ as internal standard. All chemical shifts are reported in δ values[27]. – Electron impact mass spectra were obtained on the GC/MS-Datensystem HP 5985 B. – IR spectra were recorded on a Specord 75 IR spectrometer (Carl Zeiss, Jena). – Optical rotations were measured with the photoelectric polarimeter Polamat A (Carl Zeiss, Jena) at 546 and 578 nm and extrapolated to 589 nm. – Differential scanning microcalorimetry was carried out on a DSC-7 (Perkin-Elmer).

Synthesis of 2,2,2-Trichloroethyl Alkanoates **2**. – *General Procedure:* The 2,2,2-trichloroethyl esters of propanoic, butanoic, octanoic, monochloroacetic, dichloroacetic, isobutyric, phenylacetic, and benzoic acid were prepared in the usual manner[26] by reaction of one equivalent of 2,2,2-trichloroethanol with 1.1 equivalents of the corresponding acid chloride in the presence of triethylamine and 10 mg of 4-(dimethylamino)pyridine at 0 °C.

Synthesis of Vinyl Butyrate: This substance was prepared by transesterification of vinyl acetate with butanoic acid in the usual manner[22].

*Synthesis of the Racemic Monoalkanoates rac-***3a**–*rac-***3d**: These compounds were prepared in the usual manner by reaction of one equivalent of the corresponding acid chloride with one equivalent of diol **1** in pyridine at 0 °C. *rac-***3e** was prepared using the corresponding anhydride (prepared in situ from chloroacetic acid and dicyclohexylcarbodiimide) under the above-mentioned conditions.

Synthesis of the (R)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetic Acid Esters (Mosher Esters) of the Monoalkanoates **3a**–**e** *and rac-***3a**–*rac-***3e**: These compounds were prepared from the corresponding monoalkanoates by reaction with three equivalents of the (*R*)-(+)-Mosher acid anhydride (prepared in situ from the acid and dicyclohexylcarbodiimide) in the presence of triethylamine and 4-(dimethylamino)pyridine. The synthesis of the (+)-Mosher ester of **3e** failed because of side reactions. In the ^{19}F-NMR spectra of the obtained (+)-Mosher esters the signal at -72.17 ± 0.01 ppm corresponds to the (*S*)-acyl derivative. The signal at -72.23 ± 0.01 ppm corresponds to the (*R*)-acyl derivative.

*Pancreatin-Catalyzed Acetylation of rac-***3a**: A solution of *rac-***3a** (0.142 g, 1 mmol) in tetrahydrofuran (2.5 ml), triethylamine (0.071 g, 0.7 mmol), and 2,2,2-trichloroethyl acetate (**2a**) (1.34 g, 7 mmol) was treated with pancreatin (0.50 g) and stirred at room temperature for 5 h. The suspension was filtered through Celite. The filter cake was washed with ethyl acetate (3 × 5 ml) and the filtrate evaporated to dryness. The residue was purified by flash chromatography with hexane/ethyl acetate. The first fraction was diacetate **4a** (0.09 g, 49%) in the form of a colorless liquid. The second fraction was monoacetate **3a** (0.065 g, 46%), which solidified immediately after evaporation of the solvents, m.p. 46–48 °C, $[\alpha]_D^{20} = -65.8$ ($c = 1.0$ in $CHCl_3$) ⟨ref.[7] $[\alpha]_D^{20} = -66.3$ ($c = 1.0$ in $CHCl_3$)⟩, e.e. >99%.

Subjection of **3a** *to the Transesterification Conditions:* Enantiomerically pure monoacetate **3a**[7] ⟨0.142 g, 1 mmol, $[\alpha]_D^{20} = -66.3$ ($c = 1.0$ in $CHCl_3$)⟩ was treated under the same conditions and yielded unchanged **3a** ⟨0.135 g, 95%, $[\alpha]_D^{20} = -66.0$ ($c = 1.0$ in $CHCl_3$)⟩.

Pancreatin-Catalyzed Enantioselective Acylation of the meso-Diol **1** *with the 2,2,2-Trichloroethyl Alkanoates* **2b**–**e**. – *General Procedure* (Table 1, entries 2–5): Triethylamine (0.71 g, 7 mmol), the corresponding 2,2,2-trichloroethyl ester **2** (70 mmol), and pancreatin (5.0 g) were added to a solution of diol **1** (1.0 g, 10 mmol) in tetrahydrofuran (25 ml). The reaction mixture was stirred at room temperature and monitored by TLC control until **1** was completely consumed. Then the suspension was filtered and the filter cake washed with ethyl acetate (3 × 20 ml). The solvent and the excess of the 2,2,2-trichloroethyl ester **2** were distilled off under reduced pressure and the residue was separated in two homogeneous fractions by flash chromatography with hexane/ethyl acetate followed by kugelrohr distillation. The less polar fraction represents the corresponding dialkanoate **4**, the more polar one the corresponding monoalkanoate **3**. The analytical data of the individual compounds **3b**–**e** and **4b**–**e** are given below.

(1S,4R)-(–)-4-Hydroxycyclopent-2-enyl Propanoate (**3b**): Yield: 0.905 g (58%), b.p. 110–120 °C (bath temp.)/10 Pa, colorless liquid. – IR (film): $\tilde{\nu} = 1730\ cm^{-1}$ (C=O), 3410 (OH). – ^{1}H NMR[27]: δ = 1.08 (t, J = 8 Hz, 3H, 3′-H$_3$), 1.58 (dt, J = 15 and 4 Hz, 1H, 5α-H), 2.04 (s, 1H, OH), 2.28 (q, J = 8 Hz, 2H, 2′-H$_2$), 2.74 (dt, J = 15 and 8 Hz, 1H, 5β-H), 4.64 (m, 1H, 4-H), 5.44 (m, 1H, 1-H), 5.90 and 6.04 (2d, J = 6 Hz, 2H, 2-H and 3-H). – ^{13}C NMR: δ = 9.04 (C-3′), 27.70 (C-2′), 40.63 (C-5), 74.81 (C-4), 76.96 (C-1), 132.56 and 138.53 (C-2 and C-3), 174.22 (C-1′). – MS (70 eV): m/z (%) = 155 (0.1) [M$^+$ – 1], 139 (5), 82 (22), 57 (100).

$C_8H_{12}O_3$ (156.2) Calcd. C 61.52 H 7.74
Found C 61.52 H 8.21

(1S,4R)-(–)-4-Hydroxycyclopent-2-enyl Butanoate[15] (**3c**): Yield: 0.867 g (51%), b.p. 130–135 °C (bath temp.)/10 Pa, colorless liquid. – IR (film): $\tilde{\nu} = 1730\ cm^{-1}$ (C=O), 3410 (OH). – ^{1}H NMR: δ = 0.86 (t, J = 8 Hz, 3H, 4′-H$_3$), 1.36–1.82 (m, 3H, 5α-H and 3′-H$_2$), 2.18 (m, 3H, OH and 2′-H$_2$), 2.74 (dt, J = 15 and 8 Hz, 1H, 5β-H), 4.64 (m, 1H, 4-H), 5.44 (m, 1H, 1-H), 5.86 and 6.02 (2d, J = 6 Hz, 2H, 2-H and 3-H). – ^{13}C NMR: δ = 13.61 (C-4′), 18.43 (C-3′), 36.32 (C-2′), 40.64 (C-5), 74.81 (C-4), 76.90 (C-1), 132.56 and 138.48 (C-2 and C-3), 173.41 (C-1′). – MS (70 eV): m/z (%) = 170 (1.5) [M$^+$], 153 (10), 139 (12), 83 (70), 82 (100), 57 (40).

$C_9H_{14}O_3$ (170.2) Calcd. C 63.51 H 8.29
Found C 63.62 H 8.52

(1S,4R)-(–)-4-Hydroxycyclopent-2-enyl Octanoate (**3d**): Yield: 1.198 g (53%), b.p. 180–190 °C (bath temp.)/10 Pa, m.p. 24–25 °C, colorless crystals. – IR (film): $\tilde{\nu} = 1720\ cm^{-1}$ (C=O), 3400 (OH). – ^{1}H NMR: δ = 0.83 (br. t, J = 6 Hz, 3H, 8′-H$_3$), 1.23 [m, 10H, (CH_2)$_5$CH$_3$], 1.59 (dt, J = 15 and 4 Hz, 1H, 5α-H), 1.92 (br. s, 1H, OH), 2.24 (t, J = 7 Hz, 2H, CH_2CO$_2$), 2.76 (dt, J = 15 and 8 Hz, 1H, 5β-H), 4.66 (m, 1H, 4-H), 5.46 (m, 1H, 1-H), 5.90 and 6.04 (2d, J = 6 Hz, 2H, 2-H and 3-H). – ^{13}C NMR: δ = 14.04 (C-8′), 22.59, 24.07, 28.94, 29.12, and 31.68 (C-7′, C-6′, C-5′, C-4′, and C-3′), 34.49 (C-2′), 40.66 (C-5), 74.84 (C-4), 76.91 (C-1), 132.64 and 138.50 (C-2 and C-3), 173.59 (C-1′). – MS (70 eV): m/z (%) = 226 (0.5) [M$^+$], 127 (65), 83 (100), 57 (85), 57 (75).

$C_{13}H_{22}O_3$ (226.3) Calcd. C 68.99 H 9.80
Found C 68.87 H 9.81

(1S,4R)-(–)-4-Hydroxycyclopent-2-enyl Chloroacetate (**3e**): Yield: 0.689 g (39%), b.p. 185–190 °C (bath temp.)/10 Pa, colorless liquid. – IR (film): $\tilde{\nu} = 1730\ cm^{-1}$ (C=O), 3360 (OH). – ^{1}H NMR: δ = 1.66 (dt, J = 15 and 4 Hz, 1H, 5α-H), 1.86 (br. s, 1H, OH), 2.78 (dt, J = 15 and 8 Hz, 1H, 5β-H), 4.00 (s, 2H, 2′-H$_2$), 4.70 (m, 1H, 4-H), 5.54 (m, 1H, 1-H), 5.92 and 6.14 (2d, J = 6 Hz, 2H, 2-H and 3-H). – ^{13}C NMR: δ = 40.25 (C-5), 40.92 (C-

2′), 84.68 (C-4), 79.12 (C-1), 131.67 and 139.42 (C-2 and C-3), 167.06 (C-1′). – MS (70 eV): *m/z* (%) = 83 (40) [$M^+ - ClCH_2CO_2$], 82 (100), 77 (15).

$C_7H_9ClO_3$ (176.6) Calcd. C 47.61 H 5.14
Found C 47.57 H 5.63

cis-Cyclopent-2-ene-1,4-diyl Dipropanoate (**4b**): Yield: 0.742 g (35%), b.p. 100–110°C (bath temp.)/10 Pa, colorless liquid. – IR (film): $\tilde{\nu}$ = 1730 cm^{-1} (C=O). – ^1H NMR: δ = 1.07 (t, *J* = 8 Hz, 6H, 2 × 3′-H_3), 1.40 (dt, *J* = 15 and 4 Hz, 1H, 5α-H), 2.28 (q, *J* = 8 Hz, 4H, 2 × 2′-H_2), 2.82 (dt, *J* = 15 and 8 Hz, 1H, 5β-H), 5.49 (ddd, *J* = 8, 4, and 1.5 Hz, 2H, 1-H and 4-H), 6.01 (d, *J* = 1.5 Hz, 2H, 2-H and 3-H). – ^{13}C NMR: δ = 9.05 (C-3′), 27.64 (C-2′), 37.34 (C-5), 76.49 (C-1 and C-4), 134.64 (C-2 and C-3), and 174.03 (C-1′). – MS (70 eV): *m/z* (%) = 139 (38) [$M^+ - C_2H_5CO_2$], 82 (87), 57 (100).

$C_{11}H_{16}O_4$ (210.2) Calcd. C 62.25 H 7.60
Found C 62.85 H 7.83

cis-Cyclopent-2-ene-1,4-diyl Dibutanoate[15] (**4c**): Yield: 0.984 g (41%), b.p. 100–110°C (bath temp.)/7 Pa, colorless liquid. – IR (film): $\tilde{\nu}$ = 1730 cm^{-1} (C=O). – ^1H NMR: δ = 0.86 (t, *J* = 8 Hz, 6H, 2 × 4′-H_3), 1.36–1.82 (m, 5H, 5α-H and 2 × 3′-H_2), 2.20 (m, 4H, 2 × 2′-H_2), 2.82 (dt, *J* = 15 and 8 Hz, 1H, 5β-H), 5.50 (ddd, *J* = 8, 4, and 1.5 Hz, 2H, 1-H and 4-H), 6.02 (d, *J* = 1.5 Hz, 2H, 2-H and 3-H). – ^{13}C NMR: δ = 13.62 (C-4′), 18.45 (C-3′), 36.26 (C-2′), 37.37 (C-5), 76.37 (C-1 and C-4), 134.66 (C-2 and C-3), 173.23 (C-1′). – MS (70 eV): *m/z* (%) = 153 (22) [$M^+ - C_3H_7CO_2$], 83 (22), 71 (100).

$C_{13}H_{20}O_4$ (240.2) Calcd. C 64.98 H 8.39
Found C 65.46 H 8.21

cis-Cyclopent-2-ene-1,4-diyl Dioctanoate (**4d**): Yield: 1.267 g (36%), b.p. 240–250°C (bath temp.)/1 Pa, m.p. 30–31°C, colorless crystals. – IR (film): $\tilde{\nu}$ = 1730 cm^{-1} (C=O). – ^1H NMR: δ = 0.83 (br. t, *J* = 6 Hz, 6H, 2 × 8′-H_3), 1.24 [br. s, 20H, 2 × (CH_2)$_5$$CH_3$], 1.65 (dt, *J* = 15 and 4 Hz, 1H, 5α-H), 2.25 (t, *J* = 7 Hz, 4H, 2 × 2′-H_2), 2.82 (dt, *J* = 15 and 8 Hz, 1H, 5β-H), 5.50 (ddd, *J* = 8, 4, and 1.5 Hz, 2H, 1-H and 4-H), 6.02 (d, *J* = 1.5 Hz, 2H, 2-H and 3-H). – ^{13}C NMR: δ = 14.01 (C-8′), 22.56, 24.93, 28.90, 29.08, and 31.65 (C-7′, C-6′, C-5′, C-4′, and C-3′), 34.37 (C-2′), 37.33 (C-5), 76.38 (C-1 and C-4), 134.60 (C-2 and C-3), 173.42 (C-1′). – MS (70 eV): *m/z* (%) = 127 (85) [C_5H_5CO], 82 (10) [$M^+ - C_7H_{15}CO_2 - C_7H_{15}CO$], 57 (100).

$C_{21}H_{36}O_4$ (352.5) Calcd. C 71.55 H 10.29
Found C 71.66 H 10.52

cis-Cyclopent-2-ene-1,4-diyl Bis(chloroacetate) (**4e**): Yield: 1.290 g (51%), b.p. 175–180°C (bath temp.)/10 Pa, colorless liquid. – IR (film): $\tilde{\nu}$ = 1750 cm^{-1} (C=O). – ^1H NMR: δ = 1.78 (dt, *J* = 15 and 4 Hz, 1H, 5α-H), 2.88 (dt, *J* = 15 and 8 Hz, 1H, 5β-H), 4.00 (s, 4H, 2 × 2′-H_2), 5.58 (ddd, *J* = 8, 4, and 1.5 Hz, 2H, 1-H and 4-H), 6.10 (d, *J* = 1 Hz, 2H, 2-H and 3-H). – ^{13}C NMR: δ = 36.76 (C-5), 40.80 (C-2′), 78.26 (C-1 and C-4), 134.67(C-2 and C-3), 166.89 (C-1′). – MS (70 eV): *m/z* (%) = 83 (78) [$M^+ - ClCH_2CO_2 - ClCH_2CO$], 82 (100), 77 (55), 65 (18), 49 (35).

$C_9H_{10}Cl_2O_4$ (253.1) Calcd. C 42.71 H 3.98
Found C 43.33 H 4.11

cis-Cyclopent-2-ene-1,4-diyl Bis(dichloroacetate) (**4f**): Triethylamine (0.22 g, 0.21 mmol) and 2,2,2-trichloroethyl dichloroacetate (**2f**) (7.0 g, 21 mmol) were added to a solution of diol **1** (0.3 g, 3 mmol) in tetrahydrofuran (7.5 ml) and stirred for 10 min at room temperature. The solvent and the excess of the acylation agent were distilled off under reduced pressure. Flash chromatography with hexane/ethyl acetate as eluant and kugelrohr distillation afforded **4f** (0.705 g, 74%), b.p. 190–200°C (bath temp.)/10 Pa, slightly yellow liquid. – IR (film): $\tilde{\nu}$ = 1760 cm^{-1} (C=O). – ^1H NMR: δ = 1.88 (dt, *J* = 15 and 4 Hz, 1H, 5α-H), 2.92 (dt, *J* = 15 and 8 Hz, 1H, 5β-H), 5.62 (ddd, *J* = 8, 4, and 1.5 Hz, 2H, 1-H and 4-H), 5.87 (s, 2H, 2 × 2′-H), and 6.16 (d, *J* = 1.5 Hz, 2H, 2-H and 3-H). – ^{13}C NMR: δ = 36.74 (C-5), 64.14 (C-2′), 79.46 (C-1 and C-4), 134.76 (C-2 and C-3), 164.10 (C-1′). – MS (70 eV): *m/z* (%) = 193 (15) [$M^+ - Cl_2CHCO_2$], 83 (100), 65 (30).

$C_9H_8Cl_4O_4$ (321.9) Calcd. C 33.57 H 2.50
Found C 34.02 H 2.63

Conversion of the Monoalkanoates **3a–e** *into (1S,4R)-(+)-4-(Tetrahydro-2-pyranyloxy)cyclopent-2-enol* (**6**). – *General Procedure:* 3,4-Dihydro-2*H*-pyran (5 equivalents) and pyridinium *p*-toluenesulfonate (0.1 equivalents) were added to a solution of the monoalkanoates **3a–e** (0.70–0.44 mmol) in dichloromethane (2 ml). After 2 h the reaction was complete. The mixture was diluted with dichloromethane and washed with a saturated solution of sodium hydrogen carbonate and with water. The organic phase was dried ($MgSO_4$) and evaporated to dryness, affording the corresponding tetrahydropyranyl ether **5**. The crude product was then dissolved in dry methanol (3 ml) and stirred at room temperature with the ion-exchange resin Wofatit SPW (OH form) (200 mg). After 16 h the mixture was filtered and the solvent removed under reduced pressure. The remaining residue was purified by flash chromatography with hexane/ethyl acetate yielding **6** as a 1:1 mixture of diastereomers as a colorless oil[10]. – ^1H NMR: δ = 1.20–1.76 (m, 7H, 5α-H and 3 × CH_2), 2.20 (br. s, 1H, OH), 2.62 (dt, *J* = 15 and 8 Hz, 0.5H, 0.5 × 5β-H), 2.72 (dt, *J* = 15 and 8 Hz, 0.5H, 0.5 × 5β-H), 3.32–3.58 (m, 1H, 4-H), 3.68–3.96 (m, 1H, 1-H), 4.48–4.66 (m, 3H, 2′-H and 6′-H_2), 5.98 (br. s, 2H, 2-H and 3-H). The ^1H NMR spectra of **6** from **3a–e** were identical.

Pancreatin-Catalyzed Acylation of the meso-Diol **1** *with Vinyl Acetate.* – a) *In the Presence of Tetrahydrofuran and Triethylamine* (Table 3, entry 1): Triethylamine (0.71 g, 7 mmol), vinyl acetate (6.02 g, 70 mmol), and pancreatin (5.0 g) were added to a solution of diol **1** (1.0 g, 10 mmol) in tetrahydrofuran (25 ml) and stirred until **1** was completely consumed (2.5 hours). Workup following the general procedure for the synthesis of **3b–e** afforded the monoacetate **3a** (0.922 g, 65%) and the diacetate **4a** (0.589 g, 32%), which were identical in every respect with authentic material[7].

b) *In the Presence of a Higher Excess of Vinyl Acetate* (Table 3, entries 2 and 3): The reaction was performed as in a), but with 14 and 35 equivalents of vinyl acetate, respectively, starting from 10 mmol of diol **1** affording **3a** (0.820 g, 58% and 0.880 g, 62%) and **4a** (0.720 g, 39% and 0.880 g, 48%), respectively.

c) *In the Absence of Triethylamine* (Table 3, entry 4): Vinyl acetate (6.02 g, 70 mmol) and pancreatin (5.0 g) were added to a solution of diol **1** (1.0 g, 10 mmol) in tetrahydrofuran (25 ml) and stirred at room temperature for 2.5 h. Workup was performed as described above and afforded **3a** (0.852 g, 60%) and **4a** (0.570 g, 31%).

d) *In the Absence of Tetrahydrofuran* (Table 3, entry 5): Triethylamine (0.71 g, 7 mmol) and pancreatin (5.0 g) were added to a solution of diol **1** (1.0 g, 10 mmol) in vinyl acetate (30.1 g, 350 mmol) and stirred at room temperature for 2.5 h. Workup was performed as described above and afforded **3a** (0.809 g, 57%) and **4a** (0.736 g, 40%).

e) *In the Absence of Triethylamine and Tetrahydrofuran* (Table 3, entry 6): Pancreatin (5.0 g) was added to a solution of diol **1** (1.0 g, 10 mmol) in vinyl acetate (30.1 g, 350 mmol) and stirred at room temperature for 24 h. Workup performed as described above afforded **3a** (0.795 g, 56%) and **4a** (0.570 g, 31%).

Pancreatin-Catalyzed Acylation of the meso-Diol **1** *with Vinyl Butanoate* (Table 3, entry 7): Triethylamine (0.71 g, 7 mmol), vinyl butanoate (7.98 g, 70 mmol), and pancreatin (5.0 g) were added to a solution of diol **1** (1.0 g, 10 mmol) in tetrahydrofuran (25 ml). The reaction mixture was stirred under TLC control until **1** was completely consumed (1.25 h). Workup was performed as described above affording **3c** (0.935 g, 55%) and **4c** (0.768 g, 32%), which were identical in every respect with **3c** and **4c** prepared from 2,2,2-trichloroethyl butanoate.

CAS Registry Numbers

1: 29783-26-4 / **2a**: 625-24-1 / **2b**: 84443-43-6 / **2c**: 57392-44-6 / **2d**: 84443-53-8 / **2e**: 57691-12-0 / **2f**: 130670-42-7 / **2** (R = CH_2Ph): 75573-62-5 / **2** (R = Ph): 37934-99-9 / **2** (R = iPr): 57392-45-7 / **3a**: 60176-77-4 / **3b**: 103656-19-5 / **3c**: 130792-54-0 / **3d**: 130670-43-8 / **3e**: 130670-44-9 / *rac*-**3a**: 61740-26-9 / *rac*-**3b**: 130792-55-1 / *rac*-**3c**: 130792-56-2 / *rac*-**3d**: 130792-57-3 / *rac*-**3e**: 130792-58-4 / **3a** (*R*-Mosher ester): 130670-45-0 / **3b** (*R*-Mosher ester): 130851-96-6 / **3c** (*R*-Mosher ester): 130670-46-1 / **3d** (*R*-Mosher ester): 130670-47-2 / *ent*-**3a** (*R*-Mosher ester): 130792-59-5 / *ent*-**3b** (*R*-Mosher ester): 130670-48-3 / *ent*-**3c** (*R*-Mosher ester): 130792-60-8 / *ent*-**3d** (*R*-Mosher ester): 130792-61-9 / **4a**: 54664-61-8 / **4b**: 95645-86-6 / **4c**: 95645-87-7 / **4d**: 130670-49-4 / **4e**: 130670-50-7 / **4f**: 130670-51-8 / **6** (*S*-THP): 130792-62-0 / **6** (*R*-THP): 130792-63-1 / isopropenyl acetate: 108-22-5 / pancreatin: 8049-47-6 / vinyl acetate: 108-05-4 / vinyl butanoate: 123-20-6

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[164/90]