Absolute Configuration and Synthesis of β- and δ-Lactones Present in the Pheromone System of the Giant White Butterfly *Idea leuconoe*

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Males of the giant white butterfly *Idea leuconoe* release a complex mixture of compounds during courtship. Besides alkaloids, aromatics, terpenoids and hydrocarbons, several lactones have been identified in the pheromone bouquet. Two simple stereoselective methods to create the lactones in good enantiomeric excesses have been developed. The generation of the stereocenters of the β-lactones **1a** and **1b** is based on a controlled C–C coupling by a Horner–Wadsworth–Emmons approach, followed by asymmetric dihydroxylation, whereas the synthesis of the δ-lactone **3b** uses an enantioselective hydrogenation of a dioxoalkanoate precursor. The absolute configurations of the natural lactones **1a**, **1b** and **3b** were determined by gas chromatography on a chiral stationary phase. Both **1a** and **1b** are of (*S*,*S*) configuration, suggesting their biosynthetic origin from (–)-viridifloric acid (**7a**) or (–)-norviridifloric acid (**7b**), respectively. In contrast, natural **3b** is a mixture of all enantiomers, in which the (5*S*,7*S*) enantiomer dominates.
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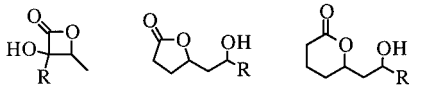
Introduction

Males of the giant white butterfly *Idea leuconoe* (Danainae) possess evertible scent glands, so-called hairpencils, on the end of their abdomen and use them preferentially during courtship. Investigation of these hairpencils showed that several substance classes, such as dihydropyrrolizines, terpenoids, aromatics, lactones, hydrocarbons and others, constitute the scent bouquet, which consists of over 100 components.[1] At least three of these compounds − danaidone, geranyl methyl thioether and viridifloric β-lactone (**1a**) − act as courtship pheromone.[2] The effect can be enhanced by additional hairpencil components to these three substances, such an artificial mixture evoking the same courtship behavior as the crude hairpencil extract. Besides their courtship function, hairpencil components are probably involved in male−male interactions and may have a function as a warning signal against predators.[2]

All lactones identified in the hairpencil extract are hydroxyalkanolides containing two chiral centers. The ring size varies from four to six. So far, two β-lactones − 2-hydroxy-2-(1-methylethyl)-3-butanolide (viridifloric β-lactone) (**1a**) and its nor derivative 2-ethyl-2-hydroxy-3-butanolide (**1b**) − have been identified, but their absolute configurations have not been reported. Major components of the hairpencil secretion, acting as synergists, are 6-hydroxy-4-alkanolides **2**, accompanied by smaller amounts of the respective δ-lactones, the 7-hydroxy-5-alkanolides **3** (Scheme 1).[1] The chain lengths of the two lactone types vary between C_{10} and C_{13}. While the absolute configurations of the γ-lactones have been determined to be exclusively (4*S*,6*S*)[3] the configurations of the δ-lactones remained unknown. In this work the syntheses of enantiomers of the β- and δ-lactones are presented, and the determination of the absolute configurations of the natural lactones is reported.



1a: R = $CH(CH_3)_2$ **2a**: R = C_4H_9 **3a**: R = C_4H_9
1b: R = CH_2CH_3 **2b**: R = C_5H_{11} **3b**: R = C_5H_{11}
2c: R = C_6H_{13} **3c**: R = C_6H_{13}
2d: R = C_7H_{15}

Scheme 1. Hydroxyalkanolides of *Idea leuconoe*

Results and Discussion

Synthesis of Viridifloric β-Lactone (1a) and Its nor Derivative 1b

Natural **1a** has been shown to possess the (*R**,*R**) configuration.[4] In our retrosynthetic analysis (Scheme 2), the lactones are disconnected into the respective dihydroxy acid derivatives **4**. In the case of **4a** the compound has been syn-

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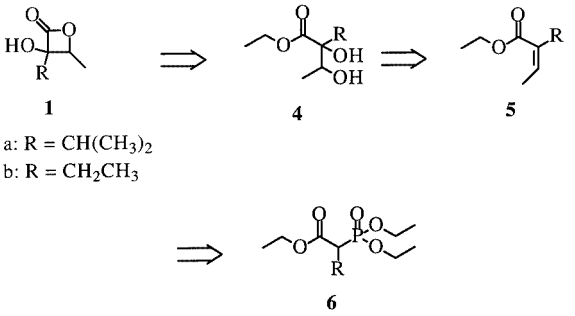
thesized before, because the respective acids occur in many pyrrolizidine alkaloids as necic acids.[5]

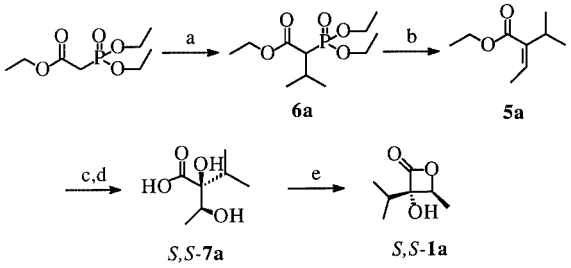


Scheme 2. General strategy for the synthesis of butanolides **1**

The earliest synthesis of the enantiomers of both viridifloric [(*R**,*R**)- or *anti*-**7a**] and trachelantic [(*R**,*S**)- or *syn*-**7a**] acids was performed by Kochetkov.[6] His strategy was based on diastereoselective dihydroxylations of (*Z*)- and (*E*)-isopropylcrotonic acid, furnishing either (±)-*anti*-**7a** or (±)-*syn*-**7a**. The (*E*)-isopropylcrotonic acid was synthesized in poor yield from ethyl 3-hydroxy-2-isopropylbutyrate. Racemic *anti*-**7a** and *syn*-**7a** were then resolved by fractional crystallization of their respective salts with (+)- or (−)-α-phenylethylamine. A similar strategy was adopted by Nambu and White,[7] who used Sharpless dihydroxylation to obtain the enantiomers of *syn*-**4** (trachelantic acid esters) directly from (*E*)-crotonates. The α-alkylation of 1,3-dioxolanones derived from enantiomerically pure α-hydroxy acids offers another way to synthesize enantiomers of *anti*- or *syn*-**7a**. This was used by Seebach et al.,[8] Ladner[9] and Niwa et al.[10] Fujisawa and co-workers[11] obtained (−)-trachelantic acid [(2*R*,3*S*)-**7a**] by nucleophilic addition of organometallic reagents to (*S*)-2-alkoxy-1-(1,3-dithian-2-yl)-1-propanone, starting from (*S*)-lactate. Finally, a multistep procedure from carbohydrates as chiral starting materials affording (+)- or (−)-*syn*-**7a** was performed by Nishimura et al.[12]

For the synthesis of the dihydroxy esters **4** we chose to use the Sharpless dihydroxylation, as had Nambu and White,[7] but with (*Z*)-crotonic acid derivatives **5** instead of the (*E*)-crotonates used by them, thus arriving at the *anti*-dihydroxy series of compounds. These crotonates should be accessible through Horner−Wadsworth−Emmons (HWE) reactions with suitable phosphonoacetates.

For the synthesis of **1a**, the key component **5a** was obtained by treatment of acetaldehyde with the alkylated phosphonoacetate **6a** at −78 °C in the presence of LHMDS as base, the highest (*Z*)/(*E*) selectivity being obtained under these conditions (88:12, see Table 1, Scheme 3). Subsequent asymmetric dihydroxylation in the presence of AD-mix-α or AD-mix-β at 0 °C furnished the two viridifloric acid ethyl esters (*R*,*R*)-**4a** and (*S*,*S*)-**4a** in only three steps. According to the Sharpless mnemonic,[13] dihydroxylation with AD-mix-α generated the (*S*,*S*) enantiomer, whereas dihydroxylation with AD-mix-β produced the (*R*,*R*) enantiomer. In both cases an *ee* of about 85% was observed by GC on a chiral heptakis(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (DAT) phase, while the *dr* was 95:5 after purification. Saponification with KOH in methanol, followed by lactonization by Adam's procedure but with mesyl chloride instead of tosyl chloride[14] furnished the β-lactones (+)-(*R*,*R*)-**1a** and (−)-(*S*,*S*)-**1a** in 65% yield and with the same *ee*. The mesyl chloride activates the acid group by forming a mixed anhydride, which is internally trapped by the hydroxy group to form the lactone.[14] The configurations at C-2 and C-3 thus remain unchanged during the lactonization process.



Scheme 3. Synthesis of viridifloric β-lactone (**1a**); a: $(CH_3)_2CH_2I$, KO*t*Bu, DMSO; b: LHMDS, CH_3CHO, THF, −78 °C; c: AD-mix-α, H_2O/*t*BuOH, 0 °C; d: KOH, H_2O/EtOH; e: MesCl, py, 0 °C; the (*R*,*R*) enantiomer of **1**a was obtained by the same reaction sequence, but with AD-mix-β

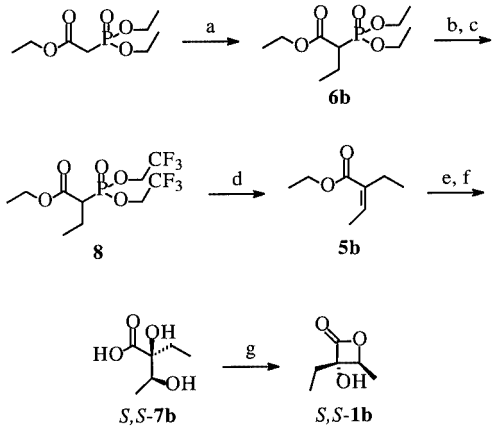
The same strategy was used for the synthesis of the ethyl butanolide **1b**. Surprisingly, application of the HWE reaction conditions reported above resulted in inverted selectivity [(*Z*)/(*E*) = 27:73]. Several other sets of conditions were

Table 1. (*E*)/(*Z*) selectivity in HWE reactions between different phosphorylacetates and acetaldehyde

$R'OP(OR)_2$ R =	Conditions	(*Z*)/(*E*), **5a**	(*Z*)/(*E*), **5b**
CH_2CH_3	LHMDS, −78 °C, THF	88:12	27:73
CH_2CH_3	NHMDS, −78 °C, THF	80:20	
CH_2CH_3	KHMDS, −78 °C, THF	63:37	
CH_2CH_3	NaH, 0 °C, THF	36:64	
CH_2CH_3	KHMDS, 18-crown-6, −78 °C, THF		40:60
o-Tolyl	KHMDS, 18-crown-6, −78 °C, THF		39:61
o-Tolyl	NaI, DBU, −78 °C, THF		80:20
CH_2CF_3	NHMDS, 18-crown-6, −78 °C, THF	55:45	93:7

then investigated, as shown in Table 1. A change in the base did not improve the (*Z*)/(*E*) ratio, while the modified HWE method of Ando et al.,[15] which uses diarylphosphonoacetate in the presence of NaI and DBU, furnished an isomeric mixture of the ethyl crotonate **5b** in a promising 80:20 (*Z*)/(*E*) ratio. The best result, however, was obtained by the Still−Gennari[16] procedure, in which electrophilic bis(trifluoroethyl)phosphonoacetates were used. A good (*Z*) selectivity of 93:7 was achieved in this way. Surprisingly, these conditions resulted in complete loss of selectivity when applied to the synthesis of **5a**.

The required fluorinated phosphonoacetate **8** was obtained by alkylation of ethyl phosphonoacetate, followed by a two-step transesterification.[16] Asymmetric dihydroxylation of **5b** under the conditions reported above produced the ethyl dihydroxybutanoates (*S*,*S*)-**4b** and (*R*,*R*)-**4b**, with *ee*s > 93% and *dr*s of 98:2, according to GC analysis on a chiral DAT phase. The acids **7b** were then obtained by saponification of **4b** with LiOH in 2-propanol (use of KOH in methanol resulted in degradation). Again, lactonization with mesyl chloride in pyridine furnished the crude β-lactones (*R*,*R*)-**1b** and (*S*,*S*)-**1b** (Scheme 4). Attempts to purify the unstable lactones by chromatography on silica gel or alumina or by low-temperature distillation failed, but samples pure enough for characterization could be obtained. This lactone is far less stable than **1a**, presumably due to its reduced steric hindrance.



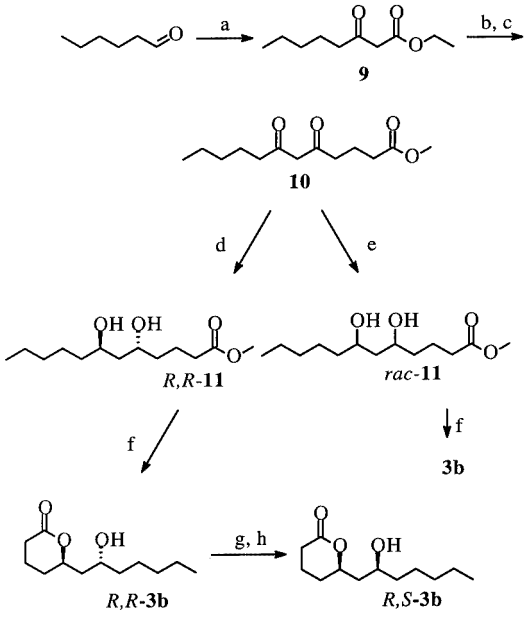
Scheme 4. Synthesis of β-lactone **1b**; a: EtI, KO*t*Bu, DMSO; b: PCl_5, 75 °C; c: CF_3CH_2OH, TolH, Et_3N; d: NHMDS, 18-crown-6, CH_3CHO, THF, −78 °C; e: AD-mix-α, H_2O/*t*BuOH, 0 °C; f: LiOH, H_2O/2-propanol; g: MesCl, py, 0 °C; the enantiomer (*R*,*R*)-**1**a was obtained by the same reaction sequence, but with use of AD-mix-β

Gas chromatographic analysis of the synthetic β-lactones and crude hairpencil extract on a chiral heptakis(2,6-*O*-dimethyl-3-*O*-pentyl)-β-cyclodextrin (DMP) phase showed that both natural β-lactones **1a** and **1b** were of (*S*,*S*) configuration. Lactonization of natural (−)-viridifloric acid [(*S*,*S*)-**7a**], obtained by saponification of pyrrolizidine alkaloids,[4] also furnished (*S*,*S*)-**1a**. The validity of the Sharpless model in the dihydroxylation of **5** was thus established. Both the isopropyl and the ethyl group must play the role of the bulky group with regard to the ethoxycarbonyl group, because we would otherwise have arrived at the unwanted *syn* series.

While the acid **7a** occurs naturally as necic acid in many pyrrolizidine alkaloids,[5] the nor derivative **7b** is so far known only from the pyrrolizidine alkaloids ideamine A and B[4] and 14-deoxyparsonsianidine,[17] which occur both in *I. leuconoe* and in its food plant *Parsonsia laevigata*. Chiral GC comparison of methylated samples of (−)-**7b** obtained by hydrolysis of ideamine A[4] with our synthetic material showed that the natural acid also has the (*S*,*S*) configuration. It can safely be assumed that the butterflies produce **1b** from **7b** present in the alkaloids that they sequester or store.

Synthesis of 7-Hydroxy-5-dodecanolide (3b)

We have shown that the γ-lactones (*S*,*S*)- and (*R*,*R*)-**2** can be synthesized by a highly enantioselective hydrogenation of a dioxo ester in the presence of a commercially available Ru−BINAP catalyst.[3] These compounds allowed the unambiguous identification of (*S*,*S*)-**2b** as the only naturally occurring enantiomer. We reasoned that the corresponding δ-lactones **3** should be synthesizable by the same method (Scheme 5).



Scheme 5. Synthesis of 7-hydroxy-5-dodecanolides **3b**; a: $SnCl_2$, N_2CH_2COOEt, CH_2Cl_2; b: $Mg(OEt)_2$, $ClCO(CH_2)_3COOMe$, Et_2O; c: NaCl, Δ, DMSO/H_2O; d: H_2, (*R*)-Ru−BINAP, MeOH; e: $NaBH_4$, MeOH, Δ; f: *p*TSA, $CHCl_3$; g: PPh_3, $(EtCO_2N)_2$, HOBz, CH_2Cl_2; h: NaOMe, MeOH

The key component **10** was obtained by acylation of **9** (synthesized by treatment of hexanal with ethyl diazoacetate) with methyl 4-(chloroformyl)butanoate, followed by Krapcho deethoxycarbonylation.[18] This dioxo ester was then hydrogenated in the presence of [(*S*)-(−)-2,2′-bis-(diphenylphosphanyl)-1,1′-binaphthyl]chloro(*p*-cumene)-ruthenium chloride, furnishing the (*S*,*S*)-diol (*S*,*S*)-**11**, while

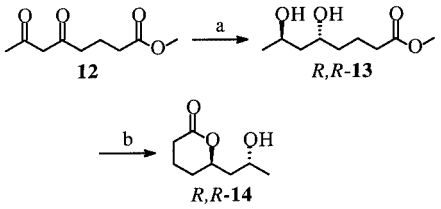
the use of the corresponding (*R*)-Ru−BINAP catalyst provided the (*R*,*R*)-diol (*R*,*R*)-**11.**[3,19] In addition, a mixture of all stereoisomers needed for comparison was synthesized by reduction of **10** with $NaBH_4$. All esters were then transformed to the corresponding δ-lactones **3b** by stirring with a catalytic amount of *p*-TsOH in $CHCl_3$. Finally, the lactone (*R*,*R*)-**3b** was epimerized by means of a Mitsunobu reaction[20] to give (5*R*,7*S*)-7-hydroxy-5-dodecanolide [(*R*,*S*)-**3b**] (Scheme 5). These compounds allowed the unambiguous assignment of all stereoisomers in the following GC experiment.

The *dr*s and *ee*s were determined by GC on a chiral DMP phase, which allowed separation of all enantiomers; *ee*s higher than 98% and *dr*s of better than 95:5 were obtained for the *anti*-δ-lactones (*R*,*R*)- and (*S*,*S*)-**3b**, with an *ee* of 81% and a *dr* of 92:8 for the *syn* enantiomer (*R*,*S*)-**3b**.

Analysis of hairpencil extracts of *I. leuconoe* showed that, contrary to the γ-lactones **2**, the δ-lactones **3** occur as mixtures of diastereomers in varying compositions. While **3a** shows a *syn*/*anti* ratio of 85:15, this changes to 8:92 in **3b** and to 4:96 in **3c**. Both diastereomers can readily be distinguished by their mass spectra; in the *anti* isomers the ion peak at $m/z = 114$ is more intense than that at $m/z = 125$, while this ratio is reversed in the *syn* isomers. Analysis by chiral GC showed that all enantiomers of **3b** occur naturally. The (*S*,*S*)/(*R*,*R*) ratio is about 7:3, while the minor *syn* enantiomers occur in roughly equal amounts, as do the lactones *syn*-**3a**. Ratios of 1:1 and 3:2 were found in two other samples. This result is surprising in comparison with the enantiomeric purity of the lactones **2** in all samples investigated. It probably shows that the lactones **3** are only byproducts formed by the same enzymes used to produce **2**, but in a less selective manner because of their slight structural difference from the target compounds.

To confirm the stereochemical course in the enantioselective hydrogenation of **10** we performed a chemical correlation of **3b** with 5-dodecanolide by removal of the 7-OH group. Thus, (*R*,*R*)-**3b** was treated with *N*,*N*′-thiocarbonyldiimidazole in CH_2Cl_2, followed by reduction with nBu$_3$SnH and AIBN[21] in toluene to obtain (*R*)-5-dodecanolide. This lactone eluted later as the (*S*) enantiomer from the DMP GC phase, as has been shown previously,[22] thus confirming our assignments.

We also investigated whether the size of the alkyl side chain has any influence on the sense of induction in the enantioselective reduction of the dioxo esters. The hydrogenation of methyl 5,7-dioxooctanoate (**12**) with the (*S*)-Ru−BINAP catalyst afforded the δ-lactone (*S*,*S*)-**14** after lactonization of the methyl dihydroxyoctanoate intermediate **13**, with an *ee* of 98% and a *dr* of 99.5:0.5 (Scheme 6). So far we have investigated the reduction of 4,6-[3] or 5,7-dioxoalkanoates with 6- or 7-alkyl chains ranging from methyl to hexyl. In all cases the (*S*)-Ru−BINAP catalyst generates the (*S*,*S*) enantiomer. This may point to recognition of the ester function by the catalysts determining the stereochemical outcome of the reduction, regardless of the length of the side chain.



Scheme 6. Synthesis of (5*R*,7*R*)-7-hydroxy-5-octanolide [(*R*,*R*)-**14**]; a: (*R*)-Ru−BINAP, MeOH; b: *p*TSA, $CHCl_3$

Conclusion

In this work we have been able to devise a simple stereoselective syntheses of the lactones **1** and **3** with good to excellent *ee*s, by use either of Sharpless dihydroxylation or of the hydrogenation of dioxoalkanoates as key steps. These lactones are part of the hairpencil volatiles disseminated from the male danaine butterfly *Idea leuconoe*. Chiral-phase gas chromatographic analysis of the synthetic and natural products allowed the absolute configuration of the β-lactones to be determined as (*S*,*S*), whereas the δ-lactones occur as mixtures of all enantiomers. The major part of this mixture is made up of *anti* enantiomers in which the (*S*,*S*) enantiomer predominates, but variation between samples occurs. In contrast, and as previously shown, the related lactones **2** are enantiomerically pure and occur in the (*S*,*S*) configuration.[3]

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were obtained with Bruker AC 200 and AMX 400 instruments. For NMR experiments, $CDCl_3$ at 25 °C was used if not mentioned otherwise; the internal standard was tetramethylsilane or solvent (CD_2Cl_2: δ = 5.32 ppm and δ = 53.7 ppm; CD_3OD: δ = 3.31 ppm and 49.0 ppm). GC-MS was carried out with a Hewlett−Packard model 5973 mass-selective detector connected to a Hewlett−Packard model 6890 gas chromatograph. Analytical GLC analyses were carried out with a CE instruments GC 8000 gas chromatograph with a flame ionization detector and split or splitless injection. The following phases were used for chiral GC separations: DAT: heptakis(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin, 15 m, 0.25 mm i.d. (LS-hydrodex-β-6TBDM, Macherey−Nagel);[23] DMP: 50% heptakis(2,6-*O*-dimethyl-3-*O*-pentyl)-β-cyclodextrin and 50% OV1701, 50 m, 0.32 mm i.d.[23] Optical rotary powers were measured with a Dr Kernchen Propol Digital Automatic polarimeter. All reactions were carried out under nitrogen in oven-dried glassware. Dry solvents: THF was distilled from sodium/benzophenone, Et_2O from $LiAlH_4$, dichloromethane from CaH_2, pyridine from KOH. All other chemicals were commercially available (Fluka, Aldrich) and used without further treatment. All reactions were monitored by thin layer chromatography (TLC) carried out on Macherey−Nagel Polygram SIL G/UV_{254} silica plates visualized with heat gun treatment with 10% molybdatophosphoric acid in ethanol or $KMnO_4$ in aqueous KOH. Column chromatography was performed with Merck silica gel 60 (70−200 mesh). PE: light petroleum ether, b.p. 40−60 °C.

Ethyl 2-(Diethoxyphosphoryl)-3-methylbutyrate (6a): Yield: 6.2 g, 93%, oil. Potassium *tert*-butoxide (3.08 g, 27.5 mmol) was added at 0 °C to a stirred solution of ethyl (diethoxyphosphoryl)acetate (5 mL, 25 mmol) in DMSO (25 mL). After the mixture had been stirred at room temperature until the potassium *tert*-butoxide was dissolved, 2-iodopropane (2.75 mL, 27.5 mmol) was added. The solution was then stirred for 1 h at 60 °C. Finally, the mixture was poured into saturated NH_4Cl solution and extracted three times with diethyl ether. The combined extracts were washed with brine, dried with $MgSO_4$, and concentrated to afford a pale yellow oil, sufficiently pure for use in the next step. ^{1}H NMR: δ = 1.00 (dd, *J* = 7.6, *J* = 1.3 Hz, 3 H, CH_3CH), 1.14 (d, *J* = 6.7 Hz, 3 H, CH_3CH), 1.27−1.34 (m, 9 H, CH_3CH$_2$), 2.32−2.43 [m, 1 H, CH(CH$_3$)$_2$], 2.72 (dd, *J* = 9.3, *J* = 20.2 Hz, 1 H, CH, PCH), 4.10−4.24 (m, 4 H, POCH$_2$), 4.20 (q, 2 H, OCH$_2$, *J* = 7.1 Hz) ppm. ^{13}C NMR: δ = 14.1 (q), 16.3 (q, *J* = 6.1 Hz), 21.6 (q, *J* = 11.8 Hz), 21.7 (q, *J* = 1.8 Hz), 28.3 (d, *J* = 4.5 Hz), 53.4 (d, *J* = 132.9 Hz), 61.1 (t), 62.3 (t, *J* = 3.0 Hz), 62.4 (t, *J* = 2.4 Hz), 169.3 (s, *J* = 4.1 Hz) ppm. NMR spectroscopic data are congruent with those reported by Allen et al.[24] MS (70 eV): *m*/*z* (%) = 41 (11), 55 (11), 81 (20), 83 (19), 88 (13), 105 (18), 109 (12), 111 (11), 122 (15), 123 (55), 125 (20), 129 (11), 137 (20), 138 (14), 151 (38), 152 (62), 169 (24), 179 (45), 180 (13), 193 (28), 197 (78), 221 (52), 221 (52), 224 (100).

Ethyl (*Z*)-2-(1-Methylethyl)but-2-enoate (5a): Yield: 2.54 g, 81%, liquid. A solution of (diethoxyphosphoryl)acetate **6a** (5.8 g, 20 mmol) in anhydrous THF (60 mL) was cooled to −78 °C under nitrogen and treated with LHMDS (23 mL, 23 mmol, 1 N solution in hexane). Acetaldehyde (1.27 mL, 22 mmol) was added in one batch and the resulting mixture was stirred at −78 °C for 90 min. The reaction was quenched by addition of saturated NH_4Cl. The product was isolated by threefold extraction with diethyl ether. The combined extracts were dried with $MgSO_4$, the solvent was removed, and the product was isolated by flash chromatography (pentane/diethyl ether, 19:1). The (*Z*)/(*E*) ratio was 88:12 as determined by GC. The two diastereomers can be identified by their NMR spectroscopic data.[25] ^{1}H NMR: δ = 0.80 (d, *J* = 6.6 Hz, 3 H, CH_3CH), 0.99 (d, *J* = 6.9 Hz, 3 H, CH_3CH), 1.25 (t, *J* = 7.1 Hz, 3 H, CH_3CH$_2$), 1.80 (dd, *J* = 7.1, *J* = 1.1 Hz, 3 H, CH_3CH=C), 2.62 [m, *J* = 6.9, *J* = 1.1 Hz, 1 H, CH(CH$_3$)$_2$], 4.17 (q, *J* = 7.2 Hz, 2 H, OCH_2CH$_3$), 5.76 (dq, *J* = 7.1, *J* = 1.2 Hz, 1 H, C=CHCH$_3$) ppm. ^{13}C NMR: δ = 14.3 (q), 15.4 (q), 21.8 (2 q), 31.5 (d), 60.0 (t), 129.6 (d), 140.0 (s), 169.1 (s) ppm. MS (70 eV): *m*/*z* (%) = 39 (23), 41 (44), 43 (20), 53 (13), 55 (64), 59 (15), 67 (43), 69 (18), 81 (13), 82 (12), 83 (100), 95 (49), 109 (12), 110 (18), 111 (65), 113 (40), 141 (25).

Ethyl (2*S*,3*S*)-2,3-Dihydroxy-2-(1-methylethyl)butyrate [(*S*,*S*)-4a]: Yield: 0.67 g, 69%, oil. According to the procedure of Nambu and White,[7] a solution of AD-mix-α (6.92 g) in a mixture of *tert*-butyl alcohol and water (50 mL, 1:1) was stirred at room temperature for 5 min. Methanesulfonamide (460 mg, 5.2 mmol) and **5a** (790 mg, 5.1 mmol) were added, and the solution was stirred at 0 °C for 42 h. Sodium sulfite (7.3 g, 57.5 mmol) was added in portions, and the solution was stirred at room temperature for an additional 30 min. Water (50 mL) was then added, the solution was extracted four times into ethyl acetate, and the combined organic extracts were washed with 1 N NaOH and brine. The solvent was removed after drying with $MgSO_4$ and the product was purified by flash chromatography (PE/diethyl ether, 1:1). The *dr* and *ee* were determined by GC on a DAT chiral phase at 70 °C, isothermal, $t_{r,R,R\text{-}\mathbf{4a}}$ = 30.3 min, $t_{r,S,S\text{-}\mathbf{4a}}$ = 31.6 min, $t_{r,R^*,S^*\text{-}\mathbf{4a}}$ = 32.9 min. *ee* = 87%, *dr* 95:5. ^{1}H NMR: δ = 0.90 (d, *J* = 6.9 Hz, 3 H, CH_3CH), 0.93 (d, *J* = 6.8 Hz, 3 H, CH_3CH), 1.31 (t, *J* = 7.1 Hz, 3 H, CH_3CH$_2$O), 2.01−2.08 [m, 1 H, CH(CH$_3$)$_2$], 2.22 (d, *J* = 5.9 Hz, 3 H, CH_3CHOH), 4.28 (q, *J* = 3.8 Hz, 1 H, CHOH), 4.34 (q, *J* = 7.1 Hz, 2 H, CH$_2$O) ppm. ^{13}C NMR: δ = 14.2 (q), 16.1 (q), 17.5 (q), 17.2 (q), 32.3 (d), 62.1 (t), 70.3 (d), 82.9 (s) ppm. MS (70 eV): *m*/*z* = 41 (12), 43 (61), 44 (13), 45 (25), 55 (11), 56 (18), 57 (22), 71 (27), 73 (16), 85 (19), 99 (11), 117 (100), 132 (73).

Ethyl (2*R*,3*R*)-2,3-Dihydroxy-2-(1-methylethyl)butyrate [(*R*,*R*)-4a]: Yield: 270 mg, 89%, oil. See (*S*,*S*)-**4a** for reaction details, NMR spectroscopic and MS data. AD-mix-β was used in place of AD-mix-α. The *dr* and *ee* were determined as described for the (*S*,*S*) enantiomer. *ee* = 83%, *dr* = 93:7.

(2*S*,3*S*)-2,3-Dihydroxy-2-(1-methylethyl)butyric Acid [(−)-Viridifloric Acid, (*S*,*S*)-7a]: Yield: 0.39 g, 85%, solid. Potassium hydroxide (490 mg, 8.7 mmol) was added to a solution of the ester (*S*,*S*)-**4a** (560 mg, 2.9 mmol) in an ethanol/water mixture (7 mL, 1:1) and the mixture was stirred at 50 °C for 36 h. The solvent was then evaporated, and the residue was acidified with 1 N HCl to pH = 2 and saturated with NaCl. The concentrated mixture was extracted five times with diethyl ether. The product was purified by recrystallization from ethyl acetate, which could not improve the *ee* (checked by chiral GC of respective methyl esters). ^{1}H NMR (CD$_3$OD): δ = 0.93 (d, *J* = 6.8 Hz, 3 H, CH_3CH), 0.96 (d, *J* = 6.8 Hz, 3 H, CH_3CH), 1.22 (d, *J* = 6.4 Hz, 3 H, CH_3CHOH), 2.14 [sept, *J* = 6.8 Hz, 1 H, CH(CH$_3$)$_2$], 3.99 (q, *J* = 6.4 Hz, 1 H, CHOH) ppm. ^{13}C NMR (CD$_3$OD): δ = 16.8 (q), 17.9 (q), 18.1 (q), 33.7 (d), 71.1 (d), 84.1 (s), 177.1 (s) ppm. NMR spectroscopic data are congruent with those reported by Ladner.[9]

(2*R*,3*R*)-2,3-Dihydroxy-2-(1-methylethyl)butyric Acid [(+)-Viridifloric Acid, (*R*,*R*)-7a]: Yield: 68 mg, 82%, solid. See (*S*,*S*)-**7a** for reaction details and NMR spectroscopic data. $[\alpha]_D^{20}$ = +4.1 (*c* = 2.1, H_2O) {ref.[9] $[\alpha]_D^{20}$ = +1.8 (*c* = 2.73, H_2O)}.

(−)-(2*S*,3*S*)-2-Hydroxy-2-(1-methylethyl)-3-butanolide [(*S*,*S*)-1a]: Yield: 95 mg, 65%, oil. In a modification of the procedure of Adam et al.,[14] viridifloric acid [(*S*,*S*)-**7a**], 165 mg, 1 mmol] was dissolved at 0 °C in anhydrous pyridine (2 mL), and methanesulfonyl chloride (0.09 mL, 1.2 mmol) was added. The reaction vessel was kept at 4 °C overnight. The solution was then quenched with ice and extracted three times with diethyl ether. The combined organic extracts were washed with aqueous $CuSO_4$ solution until the aqueous phase stayed pale blue. The organic extract was dried with $MgSO_4$, and the solvent was evaporated. No further purification was necessary. The *dr* and *ee* were determined by GC on a chiral DMP phase, programmed from 50 °C to 180 °C with 3 °C/min, $t_{r,R^*,S^*\text{-}\mathbf{1a}}$ = 22.0 min, $t_{r,S,S\text{-}\mathbf{1a}}$ = 24.0 min, $t_{r,R,R\text{-}\mathbf{1a}}$ = 24.4 min. *ee* = 88%, *dr* = 90:10. $[\alpha]_D^{20}$ = −69.0 (*c* = 2.5, diethyl ether). ^{1}H NMR: δ = 0.91 (d, *J* = 6.8 Hz, 3 H, CH_3CH), 1.08 (d, *J* = 6.8 Hz, 3 H, CH_3CH), 1.46 (d, *J* = 6.6 Hz, 3 H, CH_3CHOH), 2.18 [sept, *J* = 6.8 Hz, 1 H, CH(CH$_3$)$_2$], 4.57 (q, *J* = 6.6 Hz, 1 H, CHO) ppm. ^{13}C NMR: δ = 15.4 (q), 15.4 (q), 16.1 (q), 28.3 (d), 82.5 (d), 88.6 (s), 172.2 (s) ppm. MS (70 eV): *m*/*z* = 39 (21), 41 (34), 43 (100), 45 (49), 55 (23), 57 (99), 67 (29), 71 (38), 72 (24), 85 (57), 100 (51). HRMS: calcd. for $C_6H_{12}O$ [M^+ ($C_7H_{12}O_3$) − CO_2] 100.0888, found 100.0891.

(+)-(2*R*,3*R*)-2-Hydroxy-2-(1-methylethyl)-3-butanolide [(*R*,*R*)-1a]: Yield: 63 mg, 67%, oil. See (*S*,*S*)-**1a** for reaction details, NMR spectroscopic data and MS data. The *dr* and *ee* were determined as described for the (*S*,*S*) enantiomer. *ee* = 84%, *dr* = 90:10. $[\alpha]_D^{20}$ = +70.6 (*c* = 2.0 diethyl ether). HRMS: calcd. for $C_6H_{12}O$ [M^+ ($C_7H_{12}O_3$) − CO_2] 100.0888, found 100.0892.

Ethyl 2-(Diethoxyphosphoryl)butyrate (6b): Yield: 4.0 g, 88%, oil. Potassium *tert*-butoxide (2.42 g, 21.5 mmol) was added at 0 °C to

a stirred solution of ethyl (diethoxyphosphoryl)acetate (4 mL, 18 mmol) in DMSO (12 mL). Iodoethane (1.7 mL, 21.5 mmol) was added after the mixture had been stirred at room temperature until the potassium *tert*-butoxide dissolved. The solution was then stirred for 50 min at 50 °C. Finally, the mixture was poured into saturated NH_4Cl solution and extracted three times with diethyl ether. The combined extracts were washed with brine, dried with $MgSO_4$, and concentrated to a pale yellow oil, sufficiently pure for the next step. ^{1}H NMR: δ = 0.98 (dt, *J* = 7.4, *J* = 0.9 Hz, 3 H, C*H*$_3$CH$_2$), 1.25−1.37 (m, 9 H, 2 × C*H*$_3$CH, C*H*$_3$CH$_2$O), 1.90−1.99 (m, 2 H, CH$_2$), 2.81−2.90 (m, 1 H, CH), 4.11−4.25 (m, 6 H, OC*H*$_2$CH$_3$) ppm. ^{13}C NMR: δ = 12.7 (q, *J* = 15.9 Hz), 13.9 (q), 16.1 (q, *J* = 16.1 Hz), 16.1 (q, *J* = 16.1 Hz), 20.4 (t, *J* = 5.0 Hz), 47.2 (d, *J* = 131.4 Hz), 61.0 (t), 62.3 (t, *J* = 6.5 Hz), 62.4 (t, *J* = 6.9 Hz), 168.9 (s, *J* = 4.6 Hz) ppm. NMR spectroscopic data are congruent with those reported by Wiemer et al.[26] MS (70 eV): *m*/*z* (%) = 41 (18), 55 (21), 65 (20), 69 (23), 81 (41), 88 (13), 91 (19), 99 (25), 105 (21), 109 (50), 122 (11), 123 (83), 125 (16), 127 (18), 137 (13), 138 (56), 151 (51), 152 (45), 155 (30), 165 (16), 169 (16), 179 (91), 197 (55), 207 (100), 224 (84), 225 (13), 237 (37).

Ethyl 2-[Bis(2,2,2-trifluoroethoxy)phosphoryl]butyrate (8): Yield: 2.5 g, 43% over 2 steps, oil. By a procedure developed by Gennari and Still,[16] the (diethoxyphosphoryl)acetate **6b** (4.0 g, 16 mmol) was cooled to 0 °C and stirred, while PCl_5 (12.8 g, 62 mmol) was added in portions. This mixture was stirred at room temperature for 1 h and then at 75 °C for 3 h. Distillation under reduced pressure removed the byproduct $POCl_3$ and excess PCl_5. The crude dichloride was used without further purification. It was dissolved in 50 mL of anhydrous toluene and treated at 0 °C with a solution of trifluoroethanol (3 mL, 41 mmol) and triethylamine (5.96 mL, 41 mmol) in 50 mL of anhydrous toluene. The solvent was evaporated after the mixture had been stirred for 1 h at room temperature. The crude product was purified by flash chromatography (PE/diethyl ether, 2:1). ^{1}H NMR: δ = 1.04 (t, *J* = 7.4 Hz, 3 H, C*H*$_3$CH$_2$), 1.30 (t, *J* = 7.2 Hz, 3 H, C*H*$_3$CH$_2$O), 1.95− 2.05 (m, 2 H, C*H*$_2$CH$_3$), 3.03 (dq, *J* = 4.9, *J* = 21.6 Hz, 1 H, CH), 4.24 (q, *J* = 7.2 Hz, 2 H, OC*H*$_2$CH$_3$), 4.43 (q, *J* = 8.2 Hz, 4 H, OCH$_2$CF$_3$) ppm. ^{13}C NMR: δ = 12.4 (q), 13.9 (q), 20.6 (t, *J* = 5.9 Hz), 47.1 (d, *J* = 136.9 Hz), 62.0 (t), 62.3 (t, *J* = 6.2, *J* = 38.1 Hz), 62.6 (t, *J* = 5.6, *J* = 38.1 Hz), 121.0 (s, *J* = 7.5, *J* = 8.4 Hz), 123.8 (s, *J* = 7.5, *J* = 8.3 Hz), 167.9 (s, *J* = 3.5 Hz) ppm. NMR spectroscopic data are congruent with those reported by Jackson and Ciszewski.[27] MS (70 eV): *m*/*z* = 41 (19), 87 (10), 115 (21), 243 (18), 260 (27), 273 (100), 274 (11), 287 (64), 288 (24), 295 (11), 305 (12), 315 (66), 332 (27).

Ethyl (*Z*)-2-Ethylbut-2-enoate (5b): Yield: 0.7 g, 89%, liquid. A solution of (phosphoryl)butyrate **8** (5.8 g, 20 mmol) and 18-crown-6 (1.46 g, 5.5 mmol) in anhydrous THF (100 mL) was cooled to −78 °C and treated with an NHMDS solution (2.8 mL, 5.5 mmol, 2 N in THF). Acetaldehyde (0.31 mL, 5.5 mmol) was added and the mixture was stirred at −78 °C for 90 min. Saturated NH_4Cl was added and the product was extracted three times with diethyl ether. The combined extracts were dried with $MgSO_4$, the solvent was evaporated, and the product was isolated by flash chromatography (pentane/diethyl ether, 19:1). The two diastereomers can be identified by their NMR spectroscopic data.[25] (*Z*)/(*E*) = 93:7. ^{1}H NMR: δ = 1.03 (t, *J* = 7.4 Hz, 3 H, C*H*$_3$CH$_2$), 1.31 (t, *J* = 7.2 Hz, 3 H, C*H*$_3$CH$_2$O), 1.95 (dt, *J* = 7.2, *J* = 1.2 Hz, 3 H, CH$_3$CH), 2.27 (tq, *J* = 7.4, *J* = 1.2 Hz, 2 H, C*H*$_2$CH$_3$), 4.22 (q, *J* = 7.1 Hz, 2 H, OC*H*$_2$CH$_3$), 5.96 (tq, *J* = 7.1, *J* = 1.2 Hz, 1 H, C*H*CH$_3$) ppm. ^{13}C NMR: δ = 13.6 (q), 14.3 (q), 15.6 (q), 27.5 (t), 59.9 (t), 134.6 (d), 135.0 (s), 167.8 (s) ppm. MS (70 eV): *m*/*z* (%) = 39 (26), 41 (83), 53 (22), 43 (11), 55 (10), 67 (30), 68 (17), 69 (100), 81 (27), 95 (11), 96 (28), 97 (93), 99 (84), 114 (56), 127 (16), 142 (80).

Ethyl (2*S*,3*S*)-2-Ethyl-2,3-dihydroxybutyrate [(*S*,*S*)-4b]: Yield: 0.29 g, 73%, oil. The reaction was performed as described for **4a**. The *dr* and *ee* were determined by GC on chiral DAT phase, operated isothermally at 65 °C, $t_{r,R,R\text{-}\mathbf{4b}}$ = 29.6 min, $t_{r,S,S\text{-}\mathbf{4b}}$ = 33.2 min, at room temp. $t_{r\,R^*,S^*\text{-}\mathbf{4b}}$ = 36.0 min, *ee* = 95%, *dr* 90:10. $[\alpha]_D^{20}$ = −0.9 (*c* = 3.1, diethyl ether). ^{1}H NMR: δ = 0.86 (t, *J* = 6.9 Hz, 3 H, C*H*$_3$CH$_2$), 1.15 (d, *J* = 6.4 Hz, 3 H, C*H*$_3$CH), 1.32 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$CH$_2$O), 1.81 (m, 2 H, C*H*$_2$CH$_3$), 3.82 (m, 1 H, C*H*OH), 4.28 (q, *J* = 7.2 Hz, 1 H, CH$_2$O) ppm. ^{13}C NMR: δ = 7.7 (q), 14.2 (q), 17.7 (q), 28.2 (t), 62.1 (t), 71.8 (d), 80.6 (s), 174.9 (s) ppm. MS (70 eV): *m*/*z* = 43 (39), 45 (30), 57 (100), 47 (16), 58 (11), 85 (16), 89 (36), 103 (56), 104 (58), 132 (77).

Ethyl (2*R*,3*R*)-2-Ethyl-2,3-dihydroxybutyrate [(*R*,*R*)-4b): Yield: 145 mg, 74%, oil. See **4a** for reaction details, see (*S*,*S*)-**4b** above for NMR spectroscopic data and MS data. AD-mix-β was used in place of AD-mix-α. The *dr* and *ee* were determined by GC on chiral phase as described above. *ee* = 93%, *dr* = 97:3. $[\alpha]_D^{20}$ = +1.1 (*c* = 1.4, diethyl ether).

(2*S*,3*S*)-2-Ethyl-2,3-dihydroxybutyric Acid [(*S*,*S*)-7b]: Yield: 90 mg, 56%, solid. Lithium hydroxide (130 mg, 5.5 mmol) in water (4 mL) was added at 0 °C to a solution of (*S*,*S*)-**4b** (200 mg, 1.1 mmol) in 2-propanol (10 mL). The reaction mixture was allowed to warm to room temperature and stirred for 5 h (TLC monitoring). After removal of the solvent, the residue was acidified to pH = 2 with 1 N HCl, saturated with NaCl, concentrated, and extracted five times with diethyl ether. The combined organic extracts were dried with $MgSO_4$, and the solvent was evaporated. The acid was purified by recrystallization from ethyl acetate, which did not improve the *ee*. ^{1}H NMR (CD_3OD): δ = 0.90 (t, *J* = 7.5 Hz, 3 H, C*H*$_3$CH$_2$), 1.15 (d, *J* = 6.5 Hz, 3 H, C*H*$_3$CH), 1.80 (m, 2 H, C*H*$_2$CH$_3$), 3.83 (q, *J* = 6.4 Hz, 1 H, C*H*OHCH$_3$) ppm. ^{13}C NMR (CD_3OD): δ = 8.3 (q), 17.9 (q), 29.7 (t), 72.5 (d), 81.9 (s), 177.5 (s) ppm. NMR spectroscopic data are congruent with those reported by Irie et al.[28]

(2*R*,3*R*)-2-Ethyl-2,3-dihydroxybutyric Acid [(*R*,*R*)-7b]: Yield: 62 mg, 56%, solid. See (*S*,*S*)-**7b** for reaction details and NMR spectroscopic data. $[\alpha]_D^{20}$ = +1.4 (*c* = 1.0, H_2O).

(2*S*,3*S*)-2-Ethyl-2-hydroxy-3-butanolide [(*S*,*S*)-1b]: Yield: 24 mg, 68%, oil. The reaction was performed as described for **1a**. Attempts to purify the product by chromatography or distillation resulted in decomposition. The *dr* and *ee* were determined by GC on chiral DMP phase, programmed from 50 °C to 180 °C with 3 °C/min, $t_{r,R^*,S^*\text{-}\mathbf{1b}}$ = 20.5 min, $t_{r,R^*,S^*\text{-}\mathbf{1b}}$ = 20.6 min $t_{r,S,S\text{-}\mathbf{1b}}$ = 22.2 min, $t_{r,R,R\text{-}\mathbf{1b}}$ = 23.1 min; *ee* > 95%, *dr* = 96:4. ^{1}H NMR (CD_2Cl_2): δ = 1.08 (t, *J* = 7.5 Hz, 3 H, C*H*$_3$CH$_2$), 1.46 (d, *J* = 6.5 Hz, 3 H, C*H*$_3$CH), 1.78 (dq, *J* = 7.5, *J* = 15.0 Hz, 1 H, C*H*$_2$CH$_3$), 1.89 (dq, *J* = 7.5, *J* = 15.0 Hz, 1 H, C*H*$_2$CH$_3$), 4.62 (q, *J* = 6.5 Hz, 1 H, C*H*OH). ^{13}C NMR: δ = 6.8 (q), 15.1 (q), 23.9 (t), 82.2 (d), 86.7 (s) ppm. MS (70 eV): *m*/*z* = 41 (14), 43 (25), 45 (26), 53 (10), 57 (100), 86 (31). HRMS: calcd. for $C_4H_6O_2$ [M^+ ($C_6H_{10}O_3$) − C_2H_4O] 86.0368, found 86.0388; calcd. for $C_5H_{10}O$ [M^+ ($C_6H_{10}O_3$) − CO_2] 86.0732, found 86.0748.

(2*R*,3*R*)-2-Ethyl-2-hydroxy-3-butanolide [(*R*,*R*)-1b]: Yield: 45 mg, 68%, oil. See (*S*,*S*)-**1b** above for reaction details, NMR spectroscopic and MS data. The *dr* and *ee* were determined as described. *ee* = 93%, *dr* = 97:3. HRMS: calcd. for $C_4H_6O_2$ [M^+ ($C_6H_{10}O_3$)

− C_2H_4O] 86.0368, found 86.0382; calcd. for $C_5H_{10}O$ [M^+ ($C_6H_{10}O_3$) − CO_2] 86.0732, found 86.0742.

Ethyl 3-Oxooctanoate (9): Yield: 1.87 g, 72%, oil. By the procedure of Holmquist and Roskamp,[29] a solution of freshly distilled hexanal (1.6 mL, 14 mmol) in anhydrous dichloromethane (8 mL) was added to a mixture of anhydrous $SnCl_2$ (0.26 g, 1.4 mmol) and ethyl diazoacetate (1.5 mL, 15 mmol) in anhydrous dichloromethane (30 mL). After 1 h of stirring, the mixture was washed with brine and extracted three times with diethyl ether. The solvent was evaporated after drying with $MgSO_4$ and the residue was purified by flash chromatography (PE/diethyl ether, 6:1). ^{1}H NMR (keto form): δ = 0.89 (t, J = 6.9 Hz, 3 H, 8-H), 1.27−1.32 (m, 4 H, 6-H, 7-H), 1.28 (t, J = 7.3 Hz, 3 H, 2′-H), 1.61 (quint, J = 7.4 Hz, 2 H, 5-H), 2.53 (t, 2 H, 4-H), 3.43 (s, 2 H, 2-H), 4.19 (q, J = 7.2 Hz, 2 H, 1′-H) ppm. ^{13}C NMR: δ = −13.8 (q), 14.1 (q), 22.4 (t), 23.1 (t), 31.1 (t), 43.0 (t), 49.3 (t), 61.3 (t), 167.3 (s), 203.0 (s) ppm. NMR spectroscopic data are congruent with those reported by Turner and Jacks.[30] MS (70 eV): *m*/*z* = 41 (18), 42 (15), 43 (64), 55 (18), 56 (10), 69 (21), 70 (10), 71 (52), 84 (48), 87 (11), 88 (51), 97 (16), 99 (99), 102 (16), 115 (24), 130 (100), 131 (13), 143 (23), 144 (10).

Methyl 5,7-Dioxododecanoate (10): Yield: 1.13 g, 70%, oil. Magnesium ethoxide was prepared according to Krapcho,[18] by means of the reaction between magnesium turnings (165 mg, 6.8 mmol) and anhydrous ethanol (0.4 mL), catalyzed by a small amount of tetrachloromethane. A solution of **9** (1.26 g, 6.8 mmol) in anhydrous ethanol (0.7 mL) and anhydrous diethyl ether (2.7 mL) was carefully added. The mixture was stirred until the turnings were completely dissolved. A solution of methyl 4-(chlorocarbonyl)butyrate (1.12 g, 6.8 mmol) in anhydrous diethyl ether (0.7 mL) was then added dropwise, and the solution was stirred overnight. Ice/water (3 mL) and concentrated sulfuric acid (0.15 mL) were added, and the organic layer was separated and washed neutral with water. The combined aqueous layers were extracted three times with diethyl ether and dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was dissolved in water (0.3 mL) and DMSO (4.4 mL), and NaCl (0.34 g) was added. The mixture was heated to reflux for 8 h. Finally, water (30 mL) was added at 0 °C and the layers were separated. The aqueous layer was extracted three times with diethyl ether, the combined organic phases were washed with brine and dried with $MgSO_4$, and the solvent was evaporated. The crude product was purified by flash chromatography (PE/diethyl ether, 6:1, 0.5% Et_3N). The product undergoes a keto−enol equilibrium during the NMR measurement. ^{1}H NMR: δ = 0.89 (t, J = 6.6 Hz, 3 H, CH_3), 0.90 (t, J = 6.6 Hz, 3 H, CH_3), 1.18−1.43 (m, 12 H, CH_2), 1.61 (m, 2 H, CH_2), 1.94 (quint, J = 7.1 Hz, 2 H, CH_2), 1.95 (quint, J = 6.9 Hz, 2 H, CH_2), 2.27 (t, J = 7.7 Hz, 2 H, CH_2), 2.35 (t, J = 7.4 Hz, 2 H, CH_2), 2.38 (t, J = 7.4 Hz, 2 H, CH_2), 2.50 (t, J = 7.2 Hz, 2 H, CH_2), 2.60 (t, J = 7.1 Hz, 2 H, CH_2), 3.56 (s, OCH_3), 3.67 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 5.49 (s, 1 H, CH) ppm. ^{13}C NMR: δ = 13.9 (q), 14.2 (q), 18.5 (t), 20.1 (t), 20.7 (t), 22.3 (t), 23.0 (t), 25.4 (t), 31.3 (t), 32.7 (t), 33.0 (t), 33.1 (t), 33.3 (t), 37.3 (t), 38.2 (t), 42.5 (t), 43.8 (t), 51.5 (q), 57.0 (t), 99.2 (d), 173.4 (s), 193.4 (s), 194.2 (s) ppm. MS (70 eV): *m*/*z* (%) = 41 (15), 43 (30), 55 (32), 59 (23), 69 (27), 71 (29), 84 (16), 97 (13), 99 (51), 101 (44), 111 (31), 112 (19), 113 (54),129 (100), 139 (51), 141 (59), 154 (36),169 (14), 171 (17), 186 (47). $C_{13}H_{22}O_4$ (242.2): calcd. C 64.42, H 9.16; found C 64.73, H 9.19.

Methyl (5*S*,7*S*)-5,7-Dihydroxydodecanoate [(*S*,*S*)-11]: Yield: 0.34 g, 56%, oil. The dioxo ester **10** (600 mg, 2.5 mmol) was dissolved in anhydrous methanol (18 mL), and a catalytic amount of [(*S*)-(−)-2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl]chloro(*p*-cumene)]-ruthenium chloride was added.[3] The mixture was stirred at 80 °C and 40 bar hydrogen pressure for 5 d. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (PE/diethyl ether, 1:1). ^{1}H NMR: δ = 0.89 (t, J = 6.7 Hz, 3 H, 12-H), 1.21−1.78 (m, 14 H, CH_2), 2.17 (br. s, 1 H, OH), 2.56 (br. s, 1 H, OH), 2.36 (dt, J = 7.3, J = 1.9 Hz, 2 H, 6-H), 3.68 (s, 3 H, CH_3O), 3.94 (m, 2 H, 5-H and 7-H) ppm. ^{13}C NMR: δ = 13.8 (q), 20.8 (t), 22.4 (t), 25.2 (t), 31.6 (t), 33.6 (t), 36.6 (t), 37.3 (t), 42.1 (t), 51.4 (q), 68.6 (d), 69.3 (d), 174.1 (s) ppm. MS (70 eV): *m*/*z* (%) = 41 (28), 42 (14), 43 (36), 55 (58), 56 (13), 57 (19), 59 (14), 67 (17), 68 (43), 69 (26), 70 (14), 71 (38), 73 (10), 74 (77), 79 (12), 81 (12), 83 (29), 95 (10), 96 (24), 97 (39), 98 (13), 99 (100), 101 (10), 102 (17), 107 (11), 109 (27), 114 (44), 125 (94), 127 (15), 128 (40), 131 (61), 143 (32), 145 (12), 157 (58). $C_{13}H_{26}O_4$ (246.4): calcd. C 63.38, H 10.64; found C 63.23, H 10.79.

Methyl (5*R*,7*R*)-5,7-Dihydroxydodecanoate [(*R*,*R*)-11]: Yield: 0.36 g, 60%, oil. See (*S*,*S*)-**11** for reaction details, NMR and MS data. Instead of [(*S*)-(−)-2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl]chloro(*p*-cumene)ruthenium chloride the corresponding (*R*) catalyst was used.

Methyl 5,7-Dihydroxydodecanoate (*rac*-11): Yield: 0.19 g, 46%, oil. The dioxo ester **10** (410 mg, 1.7 mmol) was dissolved in anhydrous methanol (6 mL) and added at 0 °C to a solution of sodium borohydride (80 mg, 2.1 mmol) in anhydrous methanol (2 mL). The solution was stirred for 15 min at room temperature and then heated under reflux for 90 min. Several drops of saturated NH_4Cl solution was added after the mixture had cooled to room temperature, and the solvent was evaporated. Finally, water (10 mL) was added to the residue. The mixture was extracted three times with diethyl ether. The combined organic extracts were dried with $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by flash chromatography with PE/diethyl ether (1:1). See (*S*,*S*)-**11** for NMR spectroscopic data for the *anti* product; *syn*-**11**: ^{13}C NMR: δ = 15.1 (q), 20.3 (t), 24.8 (t), 30.7 (t), 38.1 (t), 42.6 (d), 72.2 (d), 73.0 (d), 174.1 (s) ppm.

General Method for the Lactonization of Methyl 5,7-Dihydroxydodecanotes (11): The respective methyl dihydroxydodecanoate (**11**) (100 mg, 0.4 mmol) was dissolved in $CHCl_3$ (5 mL), and a catalytic amount of 4-methylbenzenesulfonic acid was added. The mixture was stirred for 3 d. After removal of the solvent, water (2 mL) and a few drops of saturated $NaHCO_3$ solution were added. The mixture was extracted three times with diethyl ether, the organic extract was dried with $MgSO_4$, and the solvent was evaporated. No further purification was necessary. The *dr* and *ee* were determined by GC on chiral DMP phase, operated isothermally at 110 °C, which allowed separation of all enantiomers. $t_{r,5R,7S\text{-}\mathbf{3}}$ = 83.5 min, $t_{r,5S,7S\text{-}\mathbf{3}}$ = 86.4 min, $t_{r,5S,7R\text{-}\mathbf{3}}$ = 89.7 min, $t_{r,5R,7R\text{-}\mathbf{3}}$ = 97.2 min.

(5*S*,7*S*)-7-Hydroxy-5-dodecanolide [(*S*,*S*)-3b]: Yield: 75 mg, 90%, oil. *ee* > 98%, *dr* = 99:1. $[\alpha]_D^{20}$ = +29.0 (*c* = 5.9, diethyl ether). ^{1}H NMR: δ = 0.89 (t, J = 6.7 Hz, 3 H, CH_3), 1.30 (m, 6 H, CH_2), 1.44 (m, 2 H, CH_2), 1.54−1.78 (m, 2 H, CH_2), 1.81−1.93 (m, 4 H, CH_2), 2.45 (m, 1 H, CH_2), 2.61 (m, 1 H, CH_2), 3.99 (m, 1 H, CH), 4.62 (m, 1 H, CH) ppm. ^{13}C NMR: δ = 13.7 (q), 18.2 (t), 22.3 (t), 24.9 (t), 28.0 (t), 29.1 (t), 31.4 (t), 37.6 (t), 42.9 (t), 67.3 (d), 77.1 (d), 172.0 (s) ppm. MS (70 eV): *m*/*z* = 41 (63), 42 (32), 43 (68), 44 (50), 45 (15), 55 (76), 56 (49), 57 (39), 58 (17), 60 (19), 67 (19), 68 (44), 69 (28), 70 (16), 71 (42), 72 (17), 73 (19), 79 (13), 81 (14), 82 (17), 83 (23), 96 (30), 97 (34), 98 (13), 99 (63), 107 (11), 114 (100), 115 (11), 125 (84), 143 (40), 196 (1). HRMS: calcd. for $C_{12}H_{20}O_2$ [M^+ − H_2O] 196.1463, found 196.1459.

(5*R*,7*R*)-7-Hydroxy-5-dodecanolide [(*R*,*R*)-3b]: Yield: 55 mg, 90%, oil. *ee* > 98%, *dr* = 98:2. $[\alpha]_D^{20}$ = −26.5 (*c* = 2.4, diethyl ether).

For NMR and MS data, see (*S*,*S*)-**3**. HRMS: calcd. for $C_{12}H_{20}O_2$ [M^+] 196.1463, found 196.1462.

(5*R*,7*S*)-7-Hydroxy-5-dodecanolide [(*R*,*S*)-3b]: Yield: 21 mg, 47%, oil. According to Mitsunobu,[20] (*R*,*R*)-**3** (45 mg, 0.21 mmol), benzoic acid (26 mg, 21 mmol) and triphenylphosphane (55 mg, 0.21 mmol) were dissolved at 0 °C in anhydrous dichloromethane (2 mL). Diethyl azocarboxylate (37 mg, 0.21 mmol) was added, and the solution was allowed to warm to room temperature. After 16 h of stirring, the solvent was evaporated, and the residue was filtered through a 5-cm silica plug (PE/diethyl ether, 2:1) and concentrated. The residue was dissolved in methanol (10 mL) containing sodium methoxide (0.85 mmol) and stirred for 24 h. The solvent was evaporated, water (10 mL) was added, and the mixture was neutralized with 1 N HCl. The mixture was then extracted three times with dichloromethane, the combined organic extracts were dried with $MgSO_4$, and the solvent was removed. The crude product was purified by flash chromatography (diethyl ether). *ee* > 81%, *dr* = 85:15. ^{1}H NMR: δ = 0.89 (t, *J* = 6.7 Hz, 3 H, CH_3), 1.25 (m, 6 H, CH_2), 1.31 (m, 2 H, CH_2), 1.48−1.57 (m, 2 H, CH_2), 1.71−1.97 (m, 4 H, CH_2), 2.46 (m, 1 H, CH_2), 2.59 (m, 1 H, CH_2), 3.84 (m, 1 H, CH), 4.54 (m, 1 H, CH) ppm. ^{13}C NMR: δ = 14.0 (q), 18.5 (t), 22.6 (t), 25.1 (t), 28.0 (t), 29.4 (t), 31.8 (t), 37.7 (t), 43.1 (t), 69.5 (d), 79.6 (d), 172.1 (s) ppm. MS (70 eV): *m*/*z* = 41 (33), 42 (23), 43 (35), 55 (63), 68 (39), 71 (38), 99 (60), 114 (87), 125 (100), 143 (56), 196 (1). HRMS: calcd. for $C_{12}H_{20}O_2$ [$M^+ - H_2O$] 196.1463, found 196.1455.

(*S*)-5-Dodecanolide: A small amount of *N*,*N*′-thiocarbonyldiimidazole was added to (*S*,*S*)-**3** (< 1 mg) in dichloromethane (2 mL).[21] The vial was sealed and heated to 65 °C for a week. The solvent was then evaporated and the residue was filtered through a silica plug (pentane/diethyl ether, 2:1). The solvent was again removed, and the crude product was dissolved in toluene (1 mL) and heated at reflux in a microreaction vessel. *n*Bu_3SnH (10 μL) and a catalytic amount of AIBN in toluene (0.5 mL) were then slowly added over a period of 30 min. The reaction mixture was heated at reflux for 4 h, the solvent was removed, and the residue was purified by chromatography (gradient pentane to pentane/diethyl ether, 2:1). The product was analyzed by GC/MS. The product and the commercially available racemic 5-dodecanolide were investigated by GC on chiral DAT phase programmed from 50 °C to 180 °C with 3 °C/min, $t_{r,R,\mathbf{12}}$ = 37.1 min, $t_{r,S\text{-}\mathbf{12}}$ = 37.5 min. MS (70 eV): *m*/*z* = 39 (11), 41 (34), 42 (29), 43 (27), 55 (35), 56 (13), 57 (10), 69 (15), 70 (27), 71 (43), 99 (100), 114 (13).

Methyl 5,7-Dioxooctanoate (12): Yield: 1.92 g, 69%, oil. For reaction details see **10**. Instead of methyl 3-oxooctanoate (**9**) methyl acetoacetate was used. The product under goes a keto−enol equilibrium during the NMR measurement. ^{1}H NMR: δ = 1.94 (quint, *J* = 7.3 Hz, 2 H, CH_2), 2.06 (s, 3 H, CH_3), 2.24 (s, 3 H, CH_3), 2.34 (t, *J* = 7.4 Hz, 2 H, CH_2), 2.37 (t, *J* = 7.4 Hz, 2 H, CH_2), 2.51 (t, 2 H, CH_2, *J* = 7.2 Hz), 2.60 (t, *J* = 7.1 Hz, 2 H, CH_2), 3.58 (s, CH_2), 3.67 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 5.50 (s, 1 H, CH) ppm. ^{13}C NMR: δ = 20.6 (t), 24.8 (q), 33.1 (t), 37.2 (t), 51.6 (q), 57.8 (t), 99.9 (d), 173.4 (s), 191.1 (s), 193.2 (s) ppm. MS (70 eV): *m*/*z* (%) = 43 (47), 69 (13), 74 (13), 85 (99), 101 (18), 111 (18), 113 (100), 129 (17), 154 (31), 186 (29).

Methyl 5,7-Dihydroxyoctanoate [(*S*,*S*)-13 and (*R*,*R*)-13]: Yield: 38−50%, oil. For reaction details see (*S*,*S*)-**11** and (*R*,*R*)-**11**. Methyl 5,7-dioxooctanoate was used instead of **10**. ^{1}H NMR: δ = 1.24 (d, *J* = 6.3 Hz, 3 H, CH_3), 1.43−1.91 (m, CH_2, 6 H), 2.36 (t, *J* = 7.1 Hz, 2 H, CH_2), 3.01 (br. s, OH, 1 H), 3.23 (br. s, OH, 1 H), 3.68 (s, CH_3O, 3 H), 3.93 (m, CH, 1 H), 4.14 (m, CH, 1 H) ppm. ^{13}C NMR: δ = 21.0 (t), 23.5 (q), 33.7 (t), 36.6 (t), 44.1 (t), 51.5 (q), 65.2 (d), 68.5 (d), 174.3 (s) ppm. MS (70 eV): *m*/*z* = 42 (14), 43 (33), 45 (27), 55 (19), 59 (11), 68 (19), 71 (39), 74 (100), 97 (15), 99 (72), 102 (28), 128 (16), 131 (31).

Methyl 5,7-Dihydroxyoctanoate (*rac*-13): Yield: 40 mg, 10%, oil. For reaction details, see *rac*-**11**. Methyl 5,7-dioxooctanoate was used instead of **10**. For NMR spectroscopic data of the *anti* enantiomers, see (*S*,*S*)-**13**. *syn*-**13:** ^{1}H NMR: δ = 1.21 (d, *J* = 6.2 Hz, 3 H, CH_3), 1.43−1.91 (m, CH_2, 6 H), 2.34 (dt, *J* = 7.3, *J* = 1.9 Hz, CH_2, 2 H), 3.67 (s, CH_3O, 3 H), 3.86 (m, CH, 1 H), 4.29 (m, CH, 1 H) ppm. ^{13}C NMR: δ = 21.0 (t), 23.5 (q), 33.8 (t), 36.6 (t), 44.0 (t), 44.1 (t), 65.2 (d), 68.5 (d), 174.4 (s) ppm.

Lactonization of Methyl 5,7-Dihydroxyoctanoates (14): Lactonization was performed as described for compounds **11**. The *dr* and *ee* were determined by GC on chiral DMP phase operated isothermally at 110 °C, which allowed separation of all enantiomers ($t_{r,R^*,S^*\text{-}\mathbf{3}}$ = 63.1 min, $t_{r,5S,7S\text{-}\mathbf{3}}$ = 63.4 min, $t_{r,S^*,R^*\text{-}\mathbf{3}}$ = 63.8 min, $t_{r,5R,7R\text{-}\mathbf{3}}$ = 64.9 min).

(5*S*,7*S*)-7-Hydroxy-5-octanolide [(*S*,*S*)-14]: 70 mg, 89%. *ee* > 98%, *dr* 99.5:0.5. $[\alpha]_D^{20}$ = +42.4 (*c* = 1.3, diethyl ether). ^{1}H NMR: δ = 1.16 (d, *J* = 6.2 Hz, 3 H, C*H*$_3$CH$_2$), 1.43−1.88 (m, CH_2, 6 H), 2.34 (m, CH_2, 1 H), 2.51 (m, CH_2, 1 H), 4.10 (m, C*H*OH, 1 H), 4.52 (m, CH, 1 H) ppm. ^{13}C NMR: δ = 18.4 (t), 24.1 (q), 28.3 (t), 29.3 (t), 44.8 (t), 63.5 (d), 77.3 (d), 171.9 (s) ppm. MS (70 eV): *m*/*z* = 41 (44), 42 (73), 45 (86), 55 (82), 60 (53), 68 (56), 69 (28), 70 (31), 71 (80), 73 (20), 97 (30), 99 (71), 102 (24), 114 (100), 125 (16).

(5*R*,7*R*)-7-Hydroxy-5-octanolide [(*R*,*R*)-14]: 65 mg, 87%. *ee* > 98%, *dr* 99.5:0.5. $[\alpha]_D^{20}$ = −52.7 (*c* = 0.6, diethyl ether). For NMR and MS data, see (*S*,*S*)-**14**.

Supporting Information: Gas chromatographic separations of **1a**, **1b** and **3b** on chiral phases are presented, together with mass spectra of **3b** and ^{13}C NMR spectra of **1a**, **1b** and **3b**. For Supporting Information see also the footnote on the first page of this article

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