Reagent-Controlled Addition of (*R*)- and (*S*)-2-Hydroxy-1,2,2-triphenylethyl Acetate to Chiral Aldehydes

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The enantiomeric enolates (*R*)- and (*S*)-**2**, generated by double deprotonation of (*R*)- and (*S*)-2-hydroxy-1,2,2-triphenylethyl acetate (**1**) ("HYTRA"), are added to chiral aldehydes **4**. It turnes out, that in this aldol reaction, the stereochemistry is largely determined by the configuration of the enolate **2** ("reagent control"). Depending on the enantiomer of the reagent **1**, which is combined with one of the enantiomerically pure aldehydes **4**, either *anti* or *syn* adducts **11** and **12** are formed predominantly. The basic hydrolysis of the crude adducts **11/12** affords *anti* and *syn* carboxylic acids **5** and **6** in the corresponding diastereomeric ratios. By recrystallization of some of the mixtures **11/12**, the esters **11c**, **11e**, and **11g** are available in high diastereomeric and enantiomeric purity. Scope and limitations of the method are discussed.

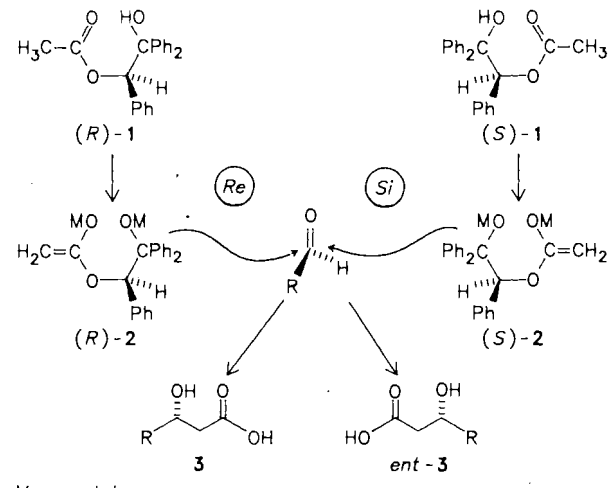
Reagenskontrolle bei der Addition von (*R*)- und (*S*)-(2-Hydroxy-1,2,2-triphenylethyl)acetat an chirale Aldehyde

Die durch Zweifachdeprotonierung von (*R*)- und (*S*)-(2-Hydroxy-1,2,2-triphenylethyl)acetat (**1**) („HYTRA") erhältlichen enantiomeren Enolate (*R*)- und (*S*)-**2** werden an chirale Aldehyde **4** addiert. Es zeigt sich, daß in dieser Aldolreaktion die Stereochemie weitgehend durch die Konfiguration des Enolats **2** bestimmt wird. Je nachdem, welches Enantiomer des Reagens **1** mit einem der enantiomerenreinen Aldehyde **4** kombiniert wird, bilden sich bevorzugt *anti*- oder *syn*-Addukte **11** und **12**. Alkalische Hydrolyse der Rohaddukte **11/12** liefert *anti*- und *syn*-Carbonsäuren **5** und **6** in entsprechenden Diastereomerenverhältnissen. Durch Umkristallisation einiger der Gemische **11/12** lassen sich die Ester **11c**, **11e** und **11g** in hoher Diastereomeren- und Enantiomerenreinheit erhalten. Möglichkeiten und Grenzen der Methode werden diskutiert.

An impressive progress was made in the field of directed and stereoselective aldol reactions during the past two decades[3]. However, the aldol addition with α-unsubstituted chiral enolates was for many years a serious problem for synthetic chemists because of its unsufficient stereoselectivity[4]. In the enolates (*R*)- and (*S*)-**2**, generated from the corresponding enantiomer of 2-hydroxy-1,2,2-triphenylethyl acetate (**1**) ("HYTRA"), we found a useful acetic acid derivative, which adds stereoselectively to achiral aldehydes[5,6]. Subsequent basic hydrolysis affords the β-hydroxycarboxylic acids **3** or *ent*-**3**, depending on whether (*R*)- or (*S*)-ester **1** was the starting material. In all cases studied so far[5-7], a *lk*-topicity[8] was observed: (*R*)-reagent **2** attacks the aldehyde RCHO predominantly from the *Re* side, the (*S*)-enolate correspondingly from the *Si* side.

Now we report the extension of this aldol reaction to chiral aldehydes. If the enantiomerically pure α- and β-alkoxy-substituted aldehydes **4a–e** are allowed to react with both enantiomers of the acetate enolate **2**, one should expect that the diastereofacial selectivities of aldehyde and enolate will cooperate in one of the combinations ("matched pair"), but will be antagonistic in the other ("mismatched pair")[3d]. Thus, unequal product ratios **5**:**6** could be obtained in the two cases: the matched pair gives a higher, the mismatched pair a smaller diastereomeric excess. If, however, the reagent selectivity of the enolate (*R*)- or (*S*)-**2** dominates, so that it is able to overcompensate the diastereofacial ("inherent") selectivity of the aldehydes **4a–e**, a possibility of a controlled and predictable synthesis of both the *anti* and the *syn* carboxylic acids **5** or **6** is opened.

Obviously, the success of this method depends on a low inherent selectivity of α- and β-alkoxy aldehydes towards lithium and magnesium enolates. Therefore, we have studied the addition of the deprotonated methyl acetate (with lithium and/or magnesium as counterions) to the aldehydes **4**. The ratios of the diastereomeric esters **7**:**8**, shown in Table 1, clearly demonstrate, that the aldehydes **4a–d** are unable to exhibit a significant inherent selectivity. This is not surprising, since the addition of lithiated ethyl acetate was found to give the esters **7c**:**8c** (R = C_2H_5) in a 1:1 ratio[9]. On the other hand, (*R*)-isopropylideneglyceraldehyde **4e** distinctly forces the lithium enolate of methyl acetate to a *Si* side attack[10].



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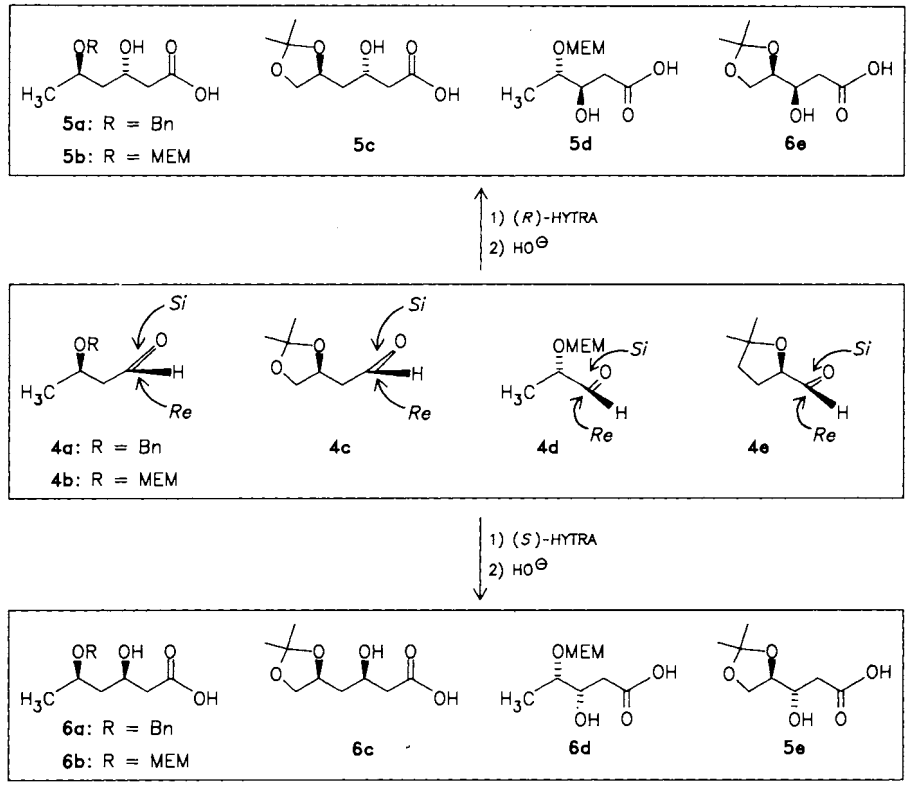
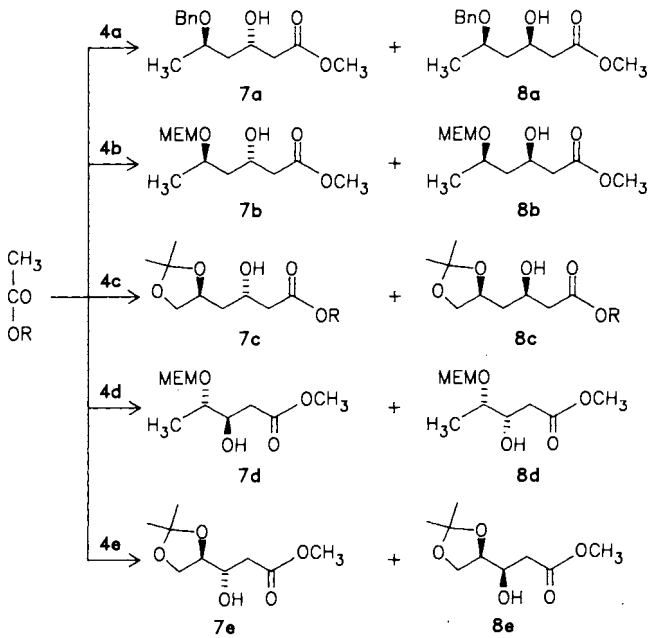


Bn = CH_2Ph; MEM = $CH_2OCH_2CH_2OCH_3$



R = CH_3, C_2H_5; Bn = CH_2Ph; MEM = $CH_2OCH_2CH_2OCH_3$

Aldol Reactions of (*R*)- and (*S*)-HYTRA 1 with Chiral Aldehydes 4

The aldehydes (*S*)-**4c**, (*S*)-**4d**, and (*R*)-**4e** are prepared according to known procedures[11–13] from malic acid, ethyl lactate, and mannitol, respectively. Polyhydroxybutyric acid (PHB) is depolymerized to the ethyl ester **9**[14], which serves as starting material for both **4a** and **4b**: The hydroxy group in **9** is protected by treatment with benzyl bromide or with (2-methoxyethoxy)methyl chloride (MEM chloride)[15] to give the butyric esters **10a** and **10b**, whose reduction with diisobutyl aluminum hydride (DIBAL) affords the aldehydes **4a** and **4b**, respectively.

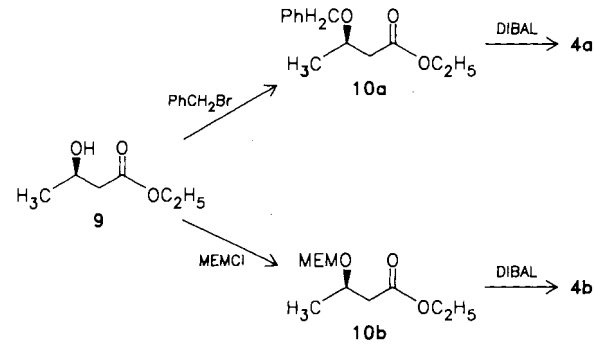
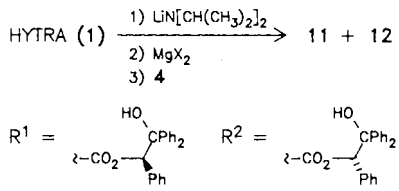


Table 1. Diastereomeric ratios **7**:**8**, obtained in the reaction of methyl acetate with the aldehydes **4**

Experiment No.	Counterion in the enolate	Aldehyde **4**	Esters **7**/**8**	Ratio **7**:**8**
1.1	Li^+	**4a**	**7a**/**8a**	50:50
1.2	Li^+	**4b**	**7b**/**8b**	56:44
1.3	$MgBr^+$	**4b**	**7b**/**8b**	63:37
1.4	Li^+	**4c**	**7c**/**8c**[a]	50:50
1.5	Li^+	**4d**	**7d**/**8d**	54:46
1.6	Li^+	**4e**	**7e**/**8e**	80:20[b]
1.7	Li^+	**4e**	**7e**/**8e**	85:15[c]

[a] R = CH_3; see also ref.[9a]. – [b] This work. – [c] Ref.[10].

(*R*)- and (*S*)-HYTRA is deprotonated with two equivalents of lithium diisopropylamide in tetrahydrofuran (THF). The lithium enolates (*R*)- or (*S*)-**2** (M = Li), generated in this way, are either added directly to the chiral aldehydes **4** or – in order to improve the diastereoselectivity – are transmetallated with magnesium bromide or magnesium iodide prior to the reaction with the aldehydes **4**. In the case of the magnesium enolates **2** (M = MgBr or MgI), the aldol addition is performed at −125°C to −135°C, using dimethyl ether or 2-methylbutane as cosolvents. The crude adducts **11/12** are hydrolyzed with potassium hydroxyde in aqueous methanol to afford in 63 to 85% overall yield mixtures of the carboxylic acids **5/6**, which are characterized by transformation into the corresponding methyl esters **7/8**. ^{13}C-NMR spectroscopy is known to be a reliable method for the structure evaluation of acyclic compounds with hydroxy or alkoxy groups in 1,2- or 1,3-distance[16]. Thus, the ratios of diastereomers **11**:**12**, generated by aldol reactions of (*R*)- and (*S*)-HYTRA **1** are determined not only by the ^{1}H- and ^{13}C-NMR spectra of the adducts **11/12** themselves, but also of the methyl esters **7/8**. The results are shown in Table 2.



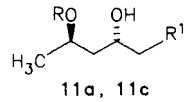
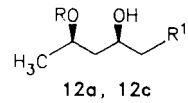
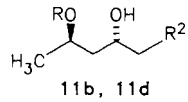
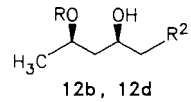
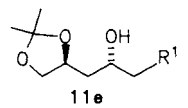
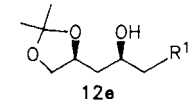
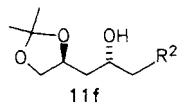
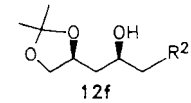
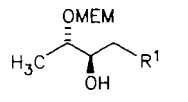
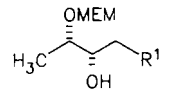
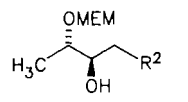
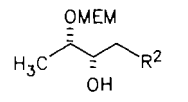
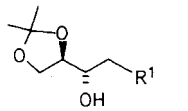
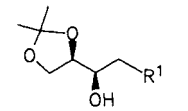
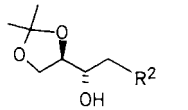
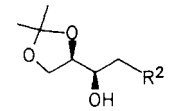
Ace-tate	Alde-hyde	Adducts 11/12
(*R*)−1	**4a** bzw. **4b**	 **11a, 11c**
		 **12a, 12c**
(*S*)−1	**4a** bzw. **4b**	 **11b, 11d**
		 **12b, 12d**
		11a, 11b, 12a, 12b: R = Bn **11c, 11d, 12c, 12d**: R = MEM
(*R*)−1	**4c**	 **11e**
		 **12e**
(*S*)−1	**4c**	 **11f**
		 **12f**
(*R*)−1	**4d**	 **11g**
		 **12g**
(*S*)−1	**4d**	 **11h**
		 **12h**
(*R*)−1	**4e**	 **11i**
		 **12i**
(*S*)−1	**4e**	 **11k**
		 **12k**

Table 2. Ratios of adducts **11**:**12**, prepared by addition of (*R*)- and (*S*)-HYTRA **1** to chiral aldehydes **4**

Exp. No.	Aldehyde **4**	Configuration of **1**	Addition of equivalents MgX_2	Solvent	Adducts **11/12**	Ratio **11**:**12**
2.1	**4a**	*R*	1 MgI_2	[a]	**11a/12a**	90:10
2.2	**4a**	*S*	1 MgI_2	[b]	**11b/12b**	5:95
2.3	**4b**	*R*	2 $MgBr_2$	[b]	**11c/12c**	91: 9
2.4	**4b**	*S*	1 MgI_2	[b]	**11d/12d**	11:89
2.5	**4c**	*R*	1 MgI_2	[a]	**11e/12e**	87:13
2.6	**4c**	*S*	1 MgI_2	[b]	**11f/12f**	8:92
2.7	**4d**	*R*	1 MgI_2	[b]	**11g/12g**	92: 8
2.8	**4d**	*S*	1 MgI_2	[b]	**11h/12h**	13:87
2.9	**4e**	*R*	–	THF	**11i/12i**	50:50
2.10	**4e**	*R*	1 $TiCl_3$	THF	**11i/12i**	38:62
2.11	**4e**	*R*	1 MgI_2	[a]	**11i/12i**	30:70
2.12	**4e**	*S*	–	THF	**11k/12k**	84:16
2.13	**4e**	*S*	1 MgI_2	[a]	**11k/12k**	>97:<3

[a] THF/dimethyl ether. – [b] THF/2-methylbutane.

It becomes evident, that a selective synthesis of *anti* and *syn* diastereomers **11a–h** and **12a–h** (and thus of *anti* and *syn* carbocylic acids **5a–d** and **6a–d**) is actually possible. As in the case of achiral aldehydes, the enolate (*R*)-**2** here also attacks predominantly from the *Re* side (→**11a–h**), while the (*S*)-reagent **2** adds preferably from the *Si* side (→**12a–h**). By recrystallization, the adducts **11c**, **11e**, and **11g** are obtained in high diastereomeric purity (d.e. >98% for **11c**, d.e. >96% for **11g** and **11e**), as shown by their ^{1}H- and ^{13}C-NMR spectra. Since the aldehydes **4a–d** have been used in optically pure form, the enantiomeric excess of the adducts **11c**, **11e**, and **11g** reaches 99% e.e.

In contrast to the aldehydes **4a–d**, the isopropylideneglyceraldehyde **4e** exhibits a significant inherent selectivity with respect to organolithium compounds[17], whereby the formation of *anti* adducts is favoured (see Table 1, exp. 1.6 and 1.7). The application of the (*S*)-enolate **2**, which here also prefers the approach from the *Si* side, leads to a considerable improvement of the *anti* selectivity (see Table 2, exp. 2.12 and 2.13). The topicity in the addition of (*R*)-**2** is also *lk*, but in this mismatched pair, the preference for the *syn* isomer **12i** is only low (exp. 2.9–2.11).

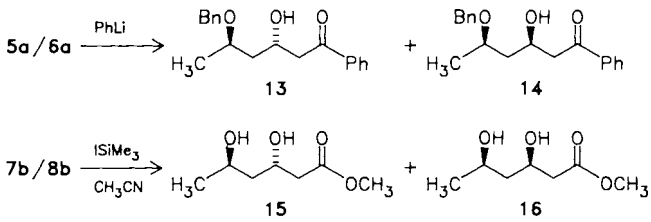
Evidently, this is a limitation of our method. An alternative is offered by the Lewis acid-mediated addition of silyl enol ethers or by the reaction with several organometallic reagents (particularly those containing boron and titanium). Thereby, the stereochemistry is determined by the chirality of the substrate in the sense of "chelate control" or in more special cases of "non chelate control"[18]. However, the "rea-

gent-controlled" method turns out to be advantageous for aldehydes with a remote chiral center.

Assignments of the Relative Configurations

Since the crude adducts **11/12** containing unequal amounts of diastereomers are convertible into the methyl esters **7/8** via the carboxylic acids **5/6**, the assignment of the configuration of one of these species also proves the structures of the two remaining pairs.

In order to determine the configuration of the carboxylic acids **5a** and **6a**, the crude adduct, prepared from (*S*)-HYTRA **1** and aldehyde **4a**, is hydrolyzed and subsequently treated with phenyllithium. Thus, the phenyl ketones **13** and **14** were obtained, which are known to differ in their ^{13}C-NMR spectra: Reetz and coworkers have demonstrated, that the chemical shifts of C-3 and C-5 appear at higher field in the *syn* isomer **14** than in the *anti* ketone **13**[16a,b]. The comparison of the ^{13}C-NMR data (see Table 3 and Experimental) clearly shows that the predominant isomer in the mixture of acids **5a/6a**, prepared with (*S*)-HYTRA **1**, has the *syn* configuration **6a**. Thus, structure **12b** has to be assigned to the main product, arising from (*S*)-HYTRA **1**. It becomes evident, that (*R*)-HYTRA **1** leads preferably to the formation of **11a**, since the hydrolysis of the crude mixture **11a/12a** affords the *anti* carboxylic acid **5a** in excess. Furthermore, the methyl esters **7a** and **8a** show characteristic ^{13}C-NMR data, too: *anti* and *syn* diastereomer are easily distinguishable by the C-5 high-field shift of the former (see Table 3).

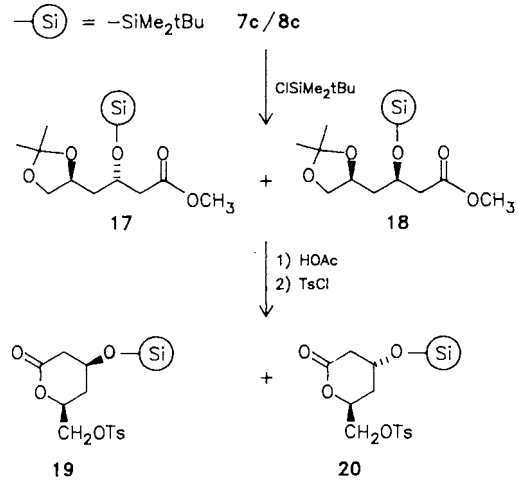


By analogy, the configuration of the MEM-protected methyl esters **7b** and **8b** is assigned. Here again, the chemical shift values of C-5 differ in a characteristic way, as shown in Table 3. Since the addition of (*R*)-HYTRA **1** affords predominantly the *anti* ester **7b**, whereas *syn* isomer **8b** is the main product when (*S*)-HYTRA **1** has been used, the structures **11c** and **12d**, respectively, are elucidated for the diastereomers formed in excess. An unambiguous proof is given by removing the MEM-protecting group in a 85:15 mixture of the methyl esters **7b** and **8b**: The ^{13}C-NMR data of the diols **15** and **16** (see Table 3 and Experimental) are comparable with those of a mixture **15/16**, which is prepared by hydrogenation of the benzyl-protected esters **7a** and **8a** (90:10).

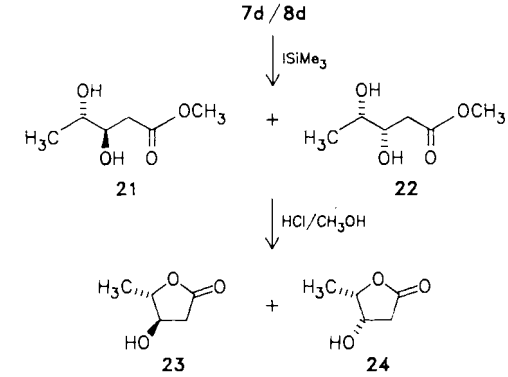
Table 3. Some characteristic chemical shifts in the ^{13}C-NMR spectra of the ketones **13** and **14** and of the esters **7a–c**, **8a–c**, **15**, and **16** (solvent $CDCl_3$)

Carbon atom	Compound	δ [ppm]	Compound	δ [ppm]
C-3	**13**	65.28	**14**	67.18
C-5	**13**	72.39	**14**	74.46
C-5	**7a**	71.23	**8a**	73.85
C-5	**7b**	70.00	**8b**	72.38
C-5	**7c**	73.20	**8c**	74.44
C-3, C-5	**15**	67.43; 68.08	**16**	72.33; 72.75

The ^{13}C-NMR spectra of the methyl esters **7c** and **8c** also differ in a significant manner. Here again, a characteristic high-field shift of the C-5 signal in the *anti* isomer **7c** with respect to the *syn* product **8c** is observed (see Table 3). An unambiguous proof of the structures **7c** and **8c** has been found by the transformation[9a] of a **7c/8c** mixture (8:92), arising from an addition of (*S*)-HYTRA **1** to the aldehyde **4c**, into the lactone moiety **19** of compactin[19]. According to Heathcocks procedure[9a], the hydroxy group in the carboxylic esters **7c/8c** is protected by silylation to **17/18**. Subsequent cyclization and tosylation deliver the mixture of lactones **19** and **20**. The minor isomer **19** is removed by column chromatography. The spectroscopic data of the major product are in accordance with those described[9a] for **20**.



Significant differences are found in both the ^{1}H- and the ^{13}C-NMR data of the methyl esters **7d** and **8d** (see Experimental). The diastereomeric mixtures **7d/8d**, obtained by addition of (*R*)-HYTRA **1** to the aldehyde **4d**, was transformed into the γ-lactones **23/24** in a two-step procedure: Cleavage of the MEM protecting group (to give the diols **21/22**) and subsequent cyclization. The presumed configu-



ration **23** of the main diastereomer was confirmed by comparison of the ^{1}H- and ^{13}C-NMR data with those described in the literature[20]. A high-field shift of the doublet of the methyl group is characteristic of the *anti* isomer **23**.

As the methyl esters **7e** and **8e** have been well-characterized by their ^{1}H- and ^{13}C-NMR data[10], the assignment of the structures of the adducts **11i,k** and **12i,k**, of the acids **5e** and **6e** as well as of the esters **7e** and **8e** is possible in a simple way by comparison of the NMR data of the latter pair (see Experimental).

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Experimental

General: Melting points (uncorrected) were determined with a Büchi/Tottoli melting point apparatus. – IR spectra: Perkin-Elmer 221 and 297, Beckman Acculab 8. – NMR spectra: Bruker WH 90 and WH 250, Varian VXR 300; all spectra were recorded with $CDCl_3$ as solvent and tetramethylsilane as internal standard. The chemical shift values of the hydroxy groups are omitted, because of their strong dependence on the concentration. – Mass spectra: Varian MAT CH-5. – Specific rotations were determined with a Perkin-Elmer 141 polarimeter at room temperature without thermostat. – TLC: Polygram-Sil-G/UV_{254}-Fertigfolien (Macherey-Nagel). – Preparative thin-layer chromatography: Kieselgel-Fertigplatten Sil G-200/UV_{254} (Merck). – Column chromatography: Kieselgel 60, mesh size 0.2–0.5 mm (Merck).

The solvents THF, 2-methylbutane, and diethyl ether were distilled first from sodium and then under nitrogen from $LiAlH_4$; they can be taken from the receiving flasks, which are closed by septums, with syringes or cannulas. Dimethyl ether was passed successively through aqueous KOH solution, through a cylinder, filled with granulated KOH, through a freezing trap, cooled to –20°C, and finally again through a cylinder with solid, granulated KOH.

General remarks concerning the handling of organolithium and organomagnesium reagents are given in ref.[5b]. Reactions, which are performed at low temperatures, are monitored by introducing a thermocouple, connected with a resistance thermometer (Ebro), through a septum into the reaction mixture.

(R)- and (S)-2-Hydroxy-1,2,2-triphenylethyl Acetate (**1**) are prepared according to the previously described[5b,21] procedure.

Ethyl (R)-(3-Benzyloxybutyrate) [(*R*)-**10a**]: In a three-necked flask, equipped with an overhead stirrer, a reflux condenser, and a stopper, a solution of 26.44 g (200 mmol) of **9** and 85.52 g (375 mmol) of benzyl bromide in 200 ml of dry diethyl ether is heated at reflux under nitrogen. The heating bath is removed, and silver oxide [freshly prepared from 74.5 g (440 mmol) $AgNO_3$ and 34 g NaOH][22] is added in 10–12 portions, so that the reaction mixture continues to boil without external heating. Thereafter, the mixture is refluxed for 3 h. The solid material is filtered off, the filtrate is washed with water, dried with $MgSO_4$, and concentrated in vacuo. Careful vacuum distillation with a 20-cm Vigreux column affords 31.5 g (71%) of **10a**; b.p. 78–82°C/0.001 Torr. – ^{1}H NMR (90 MHz): δ = 1.15 (t, *J* = 7 Hz, 3H, OCH_2CH_3), ABX signal (δ_{AB} = 2.50, δ_X = 3.91, 2H and 1H, 2-H and 3-H), 4.04 (q, *J* = 7 Hz, 2H, OCH_2CH_3), 4.44 (s, 2H, $OCH_2C_6H_5$), 7.22 (m_c, 5H, aromatic H). According to the ^{1}H-NMR spectrum, the distilled product is contaminated with about 5% dibenzyl ether. Nevertheless, the material is used without further purification in the next step.

Ethyl (R)-[3-(2-Methoxyethoxy)methoxy]butyrate [(*R*)-**10b**]: To a solution of 31.0 g (240 mmol) of diisopropylethylamine in 150 ml of dry dichloromethane, which is stirred in an ice bath under nitrogen, is added 23.8 g (180 mmol) **9** in one portion. The mixture is allowed to warm to room temperature. Within 90 min, 29.9 g (240 mmol) (2-methoxyethoxy)methyl chloride (MEM chloride) is added drop by drop. Thereafter, the mixture is stirred for 4 h at room temperature. The yellowish brown solution is washed three times with a total amount of 120 ml of 10% hydrochloric acid and with water and finally dried with Na_2SO_4. The solvent is removed in a rotary evaporator. Distillation of the residue delivers 32.5 g (82%) of **10b**; b.p. 76°C/5 Torr. – $[\alpha]_D$ = –11.77 (*c* = 1.73 in 95% aqueous ethanol; $[\alpha]_D$ = –8.67 (in chloroform). – IR (neat): 2980 cm^{-1}, 2940, 2890, 2820, 1740, 1480, 1460, 1455, 1425, 1415, 1380, 1360, 1305, 1255, 1195, 1170, 1135, 1115, 1095, 1040, 990, 900, 855, 815, 790, 725. – ^{1}H NMR (250 MHz): δ = 1.24 (d, *J* = 5.4 Hz, 3H, 4-H), 1.26 (t, *J* = 7 Hz, 3H, OCH_2CH_3), ABX signal (δ_{AB} = 2.50, δ_X = 4.20, 2H and 1H, 2-H and 3-H), 3.39 (s, 3H, OCH_3), 3.56–3.72 (m, 4H, OCH_2CH_2O), 4.14 (q, *J* = 7 Hz, 2H, OCH_2CH_3), 4.76 (s, 2H, OCH_2O). – MS (70 eV): *m/z* (%) = 175 (4) [M – $C_2H_5O^+$], 161 (2) [M – $C_2H_3O_2$], 145 (41) [M – $C_3H_2O_2^+$], 131 (14) [M – $C_4H_9O_2$], 115 (45) [M – $C_4H_9O_3^+$], 105 (10) [$C_4H_9O_3^+$], 89 (69) [$C_4H_9O_2^+$], 73 (45) [$C_3H_5O_2^+$], 59 (100) [$C_3H_7O^+$], 45 (35) [$C_2H_5O^+$], 43 (27) [$C_2H_3O^+$].

$C_{10}H_{20}O_5$ (220.2) Calcd. C 54.55 H 9.15
Found C 54.66 H 9.20

Reduction of the Esters **10a** *and* **10b** *to the Aldehydes* **4a** *and* **4b**: A solution of 100 mmol of **10a** or **10b** in 120 ml of dry dichloromethane is cooled to –78°C under nitrogen in a three-necked flask, equipped with a dropping funnel and a mechanical stirrer. Within 10–15 min, 110 ml (110 mmol) of a 1 M solution of DIBAL in *n*-hexane is added. Stirring is continued for 4 h at –78°C. After addition of 50 ml of a satd. aqueous NH_4Cl solution and 50 ml of 50% hydrochloric acid, the mixture is allowed to warm to room temperature. The organic layer is separated, and the aqueous phase is extracted five times with a total amount of 700 ml of dichloromethane. The combined organic layers are dried with Na_2SO_4, and the solvent is removed in a rotary evaporator. The crude product is purified by distillation with a 20-cm Vigreux column to give:

(R)-3-Benzyloxybutanal [(*R*)-**4a**]: 15.1 g (85%); b.p. 64–65°C/0.02 Torr; $[\alpha]_D$ = –29.8 (*c* = 1.36 in dichloromethane). – ^{1}H NMR (250 MHz): δ = 1.28 (d, *J* = 7 Hz, 3H, 4-H), 2.38–2.71 (m, 2H, 2-H), 3.73 (m, 1H, 3-H), 4.36–4.66 (AB signal, 2H, $OCH_2C_6H_5$), 7.33 (m_c, 5H, aromatic H), 9.77 (t, *J* = 2 Hz, 1H, 1-H).

(R)-3-[(2-Methoxyethoxy)methoxy]butanal [(*R*)-**4b**]: 13.13 g (81%); b.p. 40°C/0.5 Torr; $[\alpha]_D$ = –19.3 (*c* = 1.1 in ethanol); $[\alpha]_D$ = –32.6 (*c* = 1.1 in chloroform). – IR (neat): 2980 cm^{-1}, 2930, 2890, 2820, 2730, 1725, 1475, 1460, 1450, 1425, 1415, 1400, 1380, 1365, 1340, 1275, 1245, 1200, 1175, 1135, 1115, 1095, 1040, 985, 935, 925, 850. – ^{1}H NMR (250 MHz): δ = 1.26 (d, *J* = 6.5 Hz, 3H, 4-H), 2.40–2.75 (m, 2H, 2-H), 3.38 (s, 3H, OCH_3), 3.56–3.70 (m, 4H, OCH_2CH_2O), 4.28 (m_c, 1H, 3-H), 4.76 (m_c, 2H, OCH_2O), 9.76 (t, *J* = 2.5 Hz, 1H, 1-H). – MS (70 eV): *m/z* (%) = 105 (13) [$C_4H_9O_3^+$], 101 (8) [M – $C_3H_7O_2$], 89 (48) [$C_4H_9O_2^+$], 71 (11) [$C_4H_7O^+$], 59 (100) [$C_3H_7O^+$], 45 (29) [$C_2H_5O^+$], 31 (29) [CH_3O^+].

$C_8H_{16}O_4$ (176.2) Calcd. C 54.55 H 9.16
Found C 54.28 H 9.10

General Procedure 1 (G. P. 1) for the Addition of Doubly Deprotonated (R)- or (S)-1 to Aldehydes **4a–e** *after Addition of $MgBr_2$:* A 100-ml two-necked flask is equipped with a magnetic stirrer, a septum, and a three-way stop-cock, which allows to maintain a nitrogen atmosphere (about 7 Torr excess pressure) in the flask[5b]. Dry THF (40 ml) and 3.1 ml (22 mmol) diisopropylamine are injected by syringes through the septum. The mixture is cooled to −78°C and treated under stirring with 13.75 ml (22 mmol) of a 1.6 M solution of *n*-butyllithium in *n*-hexane. Thereafter, stirring is continued for 30 min at 0°C. – In a 250-ml two-necked flask, equipped with a three-way stop-cock, a septum, and a magnetic stirrer, a suspension of 3.32 g (10 mmol) (*R*)- or (*S*)-**1** in 40 ml of THF is cooled to −78°C. The precooled (−78°C) solution of lithium diisopropylamide, prepared as described above, is added by a cannula with 1–2 mm inside diameter, whereby the 250-ml flask is slightly evacuated. The reaction mixture is stirred at 0°C for 30 min in order to complete the double deprotonation. Thereby, a clear yellow solution of the lithium enolate **2** forms, which is cooled again to −78°C. Magnesium powder (0.5 g; 20.5 mmol) is weighted in a 500-ml three-necked flask, equipped with an overhead stirrer, a three-way stop-cock, and a septum. The flask is filled with nitrogen, then 20 ml of THF is added, and the suspension is slightly refluxed. The heating is interrupted, and 1.72 ml (20 mmol) of 1,2-dibromoethane is injected in a way that the mixture continues to boil without external heating. A white precipitate of $MgBr_2$ appears. Another amount of 20 ml of THF is added, and the suspension is stirred for another 30 min at room temperature. A thermocouple is introduced through the septum. When the temperature of the suspension has reached −90°C, a precooled solution of the lithium enolate **2** is added under vigrous stirring by a cannula. During that operation, the temperature should not exceed −65°C. Thereafter, 240 ml of precooled 2-methylbutane is added. The reaction flask is plunged into a bath of liquid nitrogen (depth of immersion: 3–4 cm). When a temperature of −130°C is reached, a −78°C cold solution of 10.0 mmol of aldehyde **4** is added by a cannula under vigrous stirring. Finally, the reaction mixture is stirred for 1 h at −130 to −110°C. A satd. aqueous solution of NH_4Cl is added, and the mixture is allowed to reach room temperature. The organic layer is separated, and the aqueous phase is extracted five times with about 750 ml of chloroform. The combined organic layers are washed with water and dried with Na_2SO_4. The solvent is removed in a rotary evaporator. The solid crude adducts **11/12** are either purified by recrystallization or – as stated below – hydrolyzed according to G. P. 3 to give the carboxylic acids **5/6**.

General Procedure (G. P. 2) for the Addition of Doubly Deprotonated (R)- or (S)-1 to Aldehydes **4a–e** *after Addition of MgI_2:* Magnesium powder (0.3 g; 12.3 mmol) and iodine (2.6 g; 10.5 mmol) are weighted in a 500-ml four-necked flask, which is equipped with an overhead stirrer, a septum, a three-way stop-cock (connection to a vacuum pump and to the nitrogen line), and a two-way stop-cock for the introduction of dimethyl ether. When a nitrogen atmosphere has established in the flask (two-way stop-cock-closed), 40 ml of dry diethyl ether is injected through the septum. Soon, an exothermic reaction starts. The mixture is stirred until the red colour has completely disappeared (1–2 h). Thereby, the flask is protected against the action of light with an aluminum foil. The solvent is evaporated (oil pump), and the colourless solid residue is heated in vacuo with a Bunsen burner for a few min. After cooling down to toom temperature, the nitrogen atmosphere in the flask is restored, and the thermocouple is introduced through the septum. The flask is cooled with a liquid nitrogen-acetone bath to −90°C, and 40 ml of THF is injected. Now, a precooled (−78°C) solution of 10.0 mmol of dilithiated (*R*)- or (*S*)-**1**, prepared according to G. P. 1, is added by a cannula, whose inside diameter is 2 mm. During the addition, the temperature in the flask should not exceed −65°C. The two-way stop-cock is opened, and 200–240 ml of dimethyl ether is condensed into the reaction vessel. Thereafter, the mixture is cooled to −135 to −140°C with liquid nitrogen (see above), and a precooled (−78°C) solution of 10.0 mmol aldehyde **4** in 10 ml of THF is added by a cannula under vigrous stirring. The temperature is allowed to rise to −110°C within 1 h. A satd. aqueous solution of NH_4Cl (about 100 ml) is added, and the cooling bath is removed. When the mixture has reached room temperature , it is transferred into a separatory funnel, containing 500 ml of water. The crude products are isolated by extraction with chloroform, as described in G. P. 1.

According to these general procedures are obtained:

(1'R,3S,5R)-5-Benzyloxy-3-hydroxyhexanoic Acid 2'-Hydroxy-1',2',2'-triphenylethyl Ester (**11a**) *and (1'R,3R,5R)-5-Benzyloxy-3-hydroxyhexanoic Acid 2'-Hydroxy-1',2',2'-triphenylethyl Ester* (**12a**) *by Addition of (R)-1 to* **4a**: 4.14 g (81%) of crude product; **11a**:**12a** = 90:10.

11a (main diastereomer): ^{1}H NMR (250 MHz): δ = 1.18 (d, *J* = 6.5 Hz, 3H, 6-H), 1.51 (m_c, 2H, 4-H), 2.38 (m_c, 2H, 2-H), 3.66 (m_c, 1H, 5-H), 4.06 (m_c, 1H, 3-H), 4.39 and 4.58 (2 pseudo d, 2H, $OCH_2C_6H_5$), 6.70 (s, 1H, 1'H), 7.10 (m_c, 10H, aromatic H), 7.30 (m_c, 8H, aromatic H), 7.58 (m_c, 2H, aromatic H).

12a (minor diastereomer): ^{1}H NMR (250 MHz) differs from that of **11a** in: δ = 1.16 (d, *J* = 6.5 Hz, 3H, 6-H), 4.36 and 4.63 (2 pseudo d, 2H, $OCH_2C_6H_5$).

(1'S,3S,5R)-5-Benzyloxy-3-hydroxyhexanoic Acid 2'-Hydroxy-1',2',2'-triphenylethyl Ester (**11b**) *and (1'S,3R,5R)-5-Benzyloxy-3-hydroxyhexanoic Acid 2'-Hydroxy-1',2',2'-triphenylethyl Ester* (**12b**) *by Addition of (S)-1 to* **4a**: 4.19 g (82%) of crude product; **11b**:**12b** = 5:95.

12b (main diastereomer): ^{1}H NMR (250 MHz): δ = 1.14 (d, *J* = 6.5 Hz, 3H, 6-H), 1.48 (m_c, 2H, 4-H), 2.37 (m_c, 2H, 2-H), 3.66 (m_c, 1H, 5-H), 4.06 (m_c, 1H, 3-H), 4.36 and 4.63 (2 pseudo d, 2H, $OCH_2C_6H_5$), 6.70 (s, 1H, 1'-H), 7.10 (m_c, 10H, aromatic H), 7.30 (m_c, 8H, aromatic H), 7.58 (m_c, 2H, aromatic H).

11b (minor diastereomer): ^{1}H NMR (250 MHz) differs from that of **12b** in: δ = 1.11 (d, *J* = 6.5 Hz, 3H, 6-H), 4.39 and 4.58 (2 pseudo d, 2H, $OCH_2C_6H_5$).

A mixture of **11b**/**12b** is purified by preparative thin-layer chromatography; m.p. 94–96°C.

$C_{33}H_{34}O_5$ (510.6) Calcd. C 77.62 H 6.71
Found C 77.69 H 6.95

(1'R,3S,5R)-3-Hydroxy-5-[(2-methoxyethoxy)methoxy]hexanoic Acid 2'-Hydroxy-1',2',2'-triphenylethyl Ester (**11c**) *and (1'R-,3R,5R)-3-Hydroxy-5-[(2-methoxyethoxy)methoxy]hexanoic Acid 2'-Hydroxy-1',2',2'-triphenylethyl Ester* (**12c**) *by Addition of (R)-1 to* **4b**: 4.98 g (98%) of crude product; **11c**:**12c** = 91:9.

11c (main diastereomer): ^{1}H NMR (250 MHz): δ = 1.14 (d, *J* = 6.3 Hz, 3H, 6-H), 1.45 (m_c, 2H, 4-H), 2.28–2.55 (m, 2H, 2-H), 3.23 (s, 3H, OCH_3), 3.40–3.70 (m, 4H, OCH_2CH_2O), 3.96 (m_c, 1H, 5-H), 4.16 (m_c, 1H, 3-H), 4.62 and 4.76 (2 pseudo d, 2H, OCH_2O), 6.68 (s, 1H, 1'-H), 7.00–7.73 (m, 15H, aromatic H).

12c (minor diastereomer): ^{1}H NMR (250 MHz) differs from that of **11c** in: δ = 1.09 (d, *J* = 7.5 Hz, 3H, 6-H), 4.63 and 4.77 (2 pseudo d, 2H, OCH_2O).

The pure diastereomer **11c** can be obtained by twofold recrystallization of the crude adduct from aqueous ethanol; 3.71 g (73%); m.p. 123°C; $[\alpha]_D$ = 120.6 (*c* = 1.1 in chloroform). – IR ($CHCl_3$): 3680 cm^{-1}, 3590, 3480, 3010, 2960, 2930, 2890, 2400, 1950, 1880, 1735, 1600, 1580, 1490, 1445, 1410, 1370, 1335, 1255, 1220, 1160,

1095, 1060, 1025, 920, 890, 750, 690. – ^{13}C NMR (75 MHz): δ = 19.94 (C-6), 42.34 (C-4), 43.83 (C-2), 58.94 (OCH_3), 63.97 (C-3), 66.96 and 71.73 (OCH_2CH_2O), 69.22 (C-5), 78.76 (C-1'), 80.20 (C-2'), 93.01 (OCH_2O), 126.22, 126.41, 126.95, 127.34, 127.38, 127.71, 127.84, 128.34, 128.49 (aromatic C), 135.73, 142.62, 144.92 (aromatic ipso H), 170.69 (C-1). – MS (70 eV): *m/z* (%) = 289 (6) [$C_{20}H_{17}O_2^+$], 183 (100) [$C_{13}H_{11}O^+$], 165 (6) [$C_{13}H_9^+$], 144 (15) [$C_7H_{12}O_3^+$], 105 (82) [$C_4H_9O_3^+$], 77 (40) [$C_6H_5^+$], 64 (10) [$C_5H_4^+$], 51 (6) [$C_4H_3^+$], 43 (40) [$C_2H_3O^+$], 31 (52) [CH_3O^+].

$C_{30}H_{36}O_7$ (508.6) Calcd. C 70.84 H 7.13
Found C 70.86 H 6.90

(1'S,3S,5R)-3-Hydroxy-5-[(2-methoxyethoxy)methoxy]hexanoic Acid 2'-Hydroxy-1',2',2'-triphenylethyl Ester (**11d**) *and (1'S,3R,5R)-3-Hydroxy-5-[(2-methoxyethoxy)methoxy]hexanoic Acid 2-Hydroxy-1',2',2'-triphenylethyl Ester* (**12d**) *by Addition of (S)-***1** *to* **4b**: 4.83 g (95%) crude product; **11d**:**12d** = 11:89.

12d (main diastereomer): ^{1}H NMR (250 MHz): δ = 1.11 (d, *J* = 6.2 Hz, 3H, 6-H), 1.50 (m_c, 2H, 4-H), 2.33 (m_c, 2H, 2-H), 3.35 (s, 3H, OCH_3), 3.47–3.73 (m, 4H, OCH_2CH_2O), 3.86 (m_c, 1H, 5-H), 4.03 (m_c, 1H, 3-H), 4.63 and 4.78 (2 pseudo d, 2H, OCH_2O), 6.71 (s, 1H, 1'-H), 7.00–7.73 (m, 15H, aromatic H).

11d (minor diastereomer): ^{1}H NMR (250 MHz) differs from that of **12d** in: δ = 1.02 (d, *J* = 5.4 Hz, 3H, 6-H, 6.69 (s, 1H, 1'H).

(1'R,3S,5S)-3,5,6-Trihydroxy-5,6-O-isopropylidenehexanoic Acid 2'-Hydroxy-1',2',2'-triphenylethyl Ester (**11e**) *and (1'R,3R,5S)-3,5,6-Trihydroxy-5,6-O-isopropylidenehexanoic Acid 2'-Hydroxy-1',2',2'-triphenylethyl Ester* (**12e**) *by Addition of (R)-***1** *to* **4c**: 4.67 g (98%) crude product; **11e**:**12e** = 87:13.

11e (main diastereomer): ^{1}H NMR (300 MHz): δ = 1.34 and 1.38 (2 s, 3H each, CH_3), 1.59 (m_c, 2H, 4-H), 2.44 (m_c, 2H, 2-H), 3.46 and 4.00 (2 m_c, 1H each, 6-H), 4.09 (m_c, 1H, 3-H), 4.20 (m_c, 1H, 5-H), 6.70 (s, 1H, 1'-H), 7.00–7.72 (m, 15H, aromatic H).

12e (minor diastereomer): ^{1}H NMR (300 MHz) differs from that of **11e** by: δ = 1.36 and 1.42 (2 s, 3H each, CH_3).

Recrystallization of the crude adduct from aqueous ethanol affords 3.24 g (68%) of **11e** with d.e. = 96%; m.p. 99–100°C; $[\alpha]_D$ = 145.1 (*c* = 0.9 in chloroform). – IR ($CHCl_3$): 3560 cm^{-1}, 3020, 2980, 2930, 2880, 1725, 1590, 1490, 1445, 1435, 1415, 1370, 1335, 1210, 1165, 1065, 1030, 990, 955, 925, 895, 860, 825, 790, 690, 665. – MS (70 eV): *m/z* (%) = 273 (4) [$C_{20}H_{17}O^+$], 183 (95) [$C_{13}H_{11}O^+$], 165 (8) [$C_{13}H_9^+$], 105 (100) [$C_7H_5O^+$], 85 (43) [$C_5H_9O^+$], 77 (37) [$C_6H_5^+$], 71 (45) [$C_4H_7O^+$], 57 (86) [$C_3H_5O^+$], 43 (55) [$C_3H_7^+$], 31 (55) [CH_3O^+].

$C_{29}H_{32}O_6$ (476.6) Calcd. C 73.08 H 6.76
Found C 72.83 H 6.70

(1'S,3S,5S)-3,5,6-Trihydroxy-5,6-O-isopropylidenehexanoic Acid 2'-Hydroxy-1',2',2'-triphenylethyl Ester (**11f**) *and (1'S,3R,5S)-3,5,6-Trihydroxy-5,6-O-isopropylidenehexanoic Acid 2'-Hydroxy-1',2',2'-triphenylethyl Ester* (**12f**) *by Addition of (S)-***1** *to* **4c**: 4.52 g (95%) of crude product; **11f**:**12f** = 8:92. – ^{1}H NMR (250 MHz): δ = 1.30 and 1.35 (2 s, 3H each, CH_3), 1.59 (m_c, 2H, 4-H), 2.31–2.56 (m, 2H, 2-H), 3.45 and 3.98 (2 m_c, 1H each, 6-H), 4.08 (m_c, 1H, 3-H), 4.18 (m_c, 1H, 5-H), 6.70 (s, 1H, 1'-H), 7.00–7.72 (m, 15H, aromatic H). No significant differences in the ^{1}H NMR spectra of the diastereomers **11f** and **12f** can be detected.

(1'R,3R,4S)-3-Hydroxy-4-[(2-methoxyethoxy)methoxy]pentanoic Acid 2'-Hydroxy-1',2',2'-triphenylethyl Ester (**11g**) *and (1'R,3S,4S)-3-Hydroxy-4-[(2-methoxyethoxy)methoxy]pentanoic Acid 2'-Hydroxy-1',2',2'-triphenylethyl Ester* (**12g**) *by Addition of (R)-***1** *to* **4d**: 4.65 g (94%) of crude product; **11g**:**12g** = 92:8.

11g (main diastereomer): ^{1}H NMR (300 MHz): δ = 1.06 (d, *J* = 6 Hz, 3H, 5-H), 2.45 (m_c, 2H, 2-H), 3.36 (s, 3H, OCH_3), 3.52 (m_c, 2H, $OCH_2CH_2OCH_3$), 3.64 (m_c, 3H, $OCH_2CH_2OCH_3$ and 4-H), 3.90 (m_c, 1H, 3-H), 4.67 (pseudo q, 2H, OCH_2O), 6.70 (s, 1H, 1'-H), 7.10–7.60 (m, 15H, aromatic H).

12g (minor diastereomer): ^{1}H NMR (300 MHz) differs from that of **11g** by: δ = 1.08 (d, *J* = 6 Hz, 3H, 5-H), 4.66 (pseudo q, 2H, OCH_2O).

Recrystallization of the crude mixture **11g**/**12g** from aqueous ethanol affords 3.86 g (78%) of the diastereomer **11g** with at least 96% d.e.; m.p. 122–123°C; $[\alpha]_D$ = 155.2 (*c* = 2 in chloroform). – IR (KBr): 3400 cm^{-1}, 3060, 2950, 2890, 1725, 1600, 1450, 1375, 1345, 1280, 1245, 1155, 1050, 990, 890, 750, 695, 640. – MS (70 eV): *m/z* (%) = 273 (10) [$C_{20}H_{17}O^+$], 183 (100) [$C_{13}H_{11}O^+$], 165 (15) [$C_{13}H_9^+$], 105 (99) [$C_7H_5O^+$], 89 (69) [$C_4H_9O_2^+$], 77 (58) [$C_6H_5^+$], 43 (30) [$C_2H_3O^+$].

$C_{29}H_{34}O_7$ (494.6) Calcd. C 70.42 H 6.92
Found C 70.40 H 6.85

(1'S,3R,4S)-3-Hydroxy-4-[(2-methoxyethoxy)methoxy]pentanoic Acid 2'-Hydroxy-1',2',2'-triphenylethyl Ester (**11h**) *and (1'S,3S,4S)-3-Hydroxy-4-[(2-methoxyethoxy)methoxy]pentanoic Acid 2'-Hydroxy-1',2',2'-triphenylethyl Ester* (**12h**) *by Addition of (S)-***1** *to* **4d**: 4.25 g (86%) of crude product; **11h**:**12h** = 13:87.

12h (main diastereomer): ^{1}H NMR (250 MHz): δ = 1.08 (d, *J* = 6 Hz, 3H, 5-H), 2.45 (m_c, 2H, 2-H), 3.37 (s, 3H, OCH_3), 3.45–3.68 (m, 5H, OCH_2CH_2O and 4-H), 3.76 (m_c, 1H, 3-H), 4.65 (pseudo q, 2H, OCH_2O), 6.72 (s, 1H, 1'-H), 7.10–7.60 (m, 15H, aromatic H).

11h (minor diastereomer): ^{1}H NMR (250 MHz) differs from that of **12h** by: δ = 1.05 (d, *J* = 6 Hz, 3H, 5-H).

(1'R,3S,4R)-3,4,5-Trihydroxy-4,5-O-isopropylidenepentanoic Acid 2'-Hydroxy-1',2',2'-triphenylethyl Ester (**11i**) *and (1'R,3R,4R)-3,4,5-Trihydroxy-4,5-O-isopropylidenepentanoic Acid 2'-Hydroxy-1',2',2'-triphenylethyl Ester* (**12i**) *by Addition of (R)-***1** *to* **4e**: 3.47 g (75%) of crude product; **11i**:**12i** = 30:70.

12i (main diastereomer): ^{1}H NMR (250 MHz): δ = 1.28 and 1.36 (2 s, 3H each, CH_3), 2.42 (m_c, 2H, 2-H), 3.66–3.93 (m, 4H, 3-H, 4-H, and 5-H), 6.71 (s, 1H, 1'-H), 7.01–7.59 (m, 15H, aromatic H).

11i (minor diastereomer): ^{1}H NMR (250 MHz) differs from that of **12i** by: δ = 1.25 and 1.33 (2 s, 3H each, CH_3), 6.73 (s, 1H, 1'-H).

(1'S,3S,4R)-3,4,5-Trihydroxy-4,5-O-isopropylidenepentanoic Acid 2'-Hydroxy-1',2',2'-triphenylethyl Ester (**11k**) *and (1'S,3R,4R)-3,4,5-Trihydroxy-4,5-O-isopropylidene-3,4,5-trihydroxypentanoic Acid 2'-Hydroxy-1',2',2'-triphenylethyl Ester* (**12k**) *by Addition of (S)-***1** *to* **4e**: 3.78 g (82%) of crude product; **11k**:**12k** > 97:3; m.p. 135–138°C. – IR ($CHCl_3$): 3570 cm^{-1}, 3530, 2990, 2970, 2930, 2890, 2870, 1725, 1670, 1615, 1490, 1440, 1370, 1330, 1250, 1215, 1155, 1060, 1030, 990, 940, 915, 890, 845, 770, 690, 660, 645, 605. – MS (70 eV): *m/z* (%) = 279 (50) [M – $C_{13}H_{11}O^+$], 243 (3) [$C_{19}H_{15}^+$], 183 (10) [$C_{13}H_{11}O^+$], 105 (10) [$C_7H_6O^+$], 101 (75) [$C_5H_9O_2^+$], 85 (25) [$C_5H_9O^+$], 72 (15) [$C_4H_8O^+$], 59 (40) [$C_3H_7O^+$], 57 (30) [$C_4H_7^+$], 43 (100) [$C_3H_7^+$].

11k (main diastereomer): ^{1}H NMR (250 MHz): δ = 1.28 and 1.35 (2 s, 3H each, CH_3), 2.39–2.60 (m, 2H, 2-H), 3.70–3.97 (m, 4H, 3-H, 4-H, and 5-H), 6.73 (s, 1H, 1'-H), 7.01–7.59 (m, 15H, aromatic H).

When the dilithiated ester (*S*)-**1** is added to **4e** without addition of magnesium salts, the adducts **11k** and **12k** are obtained in a 84:16 ratio.

12k (minor diastereomer): ^{1}H NMR (250 MHz) differs from that of **11k** in: δ = 1.33 and 1.39 (2 s, 3H each, CH_3), 6.71 (s, 1H, 1'-H).

General Procedure (G. P. 3) for the Hydrolysis of the Adducts **11**/**12** *to Carboxylic Acids* **5**/**6**: A solution of 1.5 mmol of the esters **11**/**12** and of 0.8–1.0 g of KOH in 30 ml of water and 60 ml of

methanol is refluxed under nitrogen for 2 h. Methanol is removed in a rotary evaporator, whereby a triphenylethylene glycol precipitates. The suspension is transferred into a separatory funnel and extracted four times with chloroform. From the combined chloroform layers, the chiral auxiliary reagent (*R*)- or (*S*)-triphenylethylene glycol might be recovered and used again for the preparation of HYTRA **1**. The aqueous layer is treated with about 100 g of ice and acidified to pH = 3 with 1 M hydrochloric acid in a beaker. Thereby, the mixture is stirred vigrously, and the pH is controlled carefully, in order to avoid over-acidification. The clear solution is poured again into a separatory funnel, saturated with NaCl, and extracted five times with dimethyl ether, three times with ethyl acetate, and once with chloroform. The combined organic layers (total amount: about 500 ml) are dried with $MgSO_4$. The solvent is removed in vacuo. The crude carboxylic acids **5/6**, prepared in this way in 85 to >95% yield, are characterized by their spectra and/or methylated according to G. P. 4 (see below) without purification.

(3S,5R)-5-Benzyloxy-3-hydroxyhexanoic Acid (**5a**). – *Main Product from* **7a/8a**: ^{1}H NMR (250 MHz): δ = 1.24 (d, *J* = 6.5 Hz, 3H, 6-H), 1.54–1.85 (m, 2H, 4-H), 2.47 (m_c, 2H, 2-H), 3.84 (m_c, 1H, 5-H), 4.20 (m_c, 1H, 3-H), 4.41 and 4.59 (2 pseudo d, 2H, $OCH_2C_6H_5$), 7.33 (m_c, 5H, aromatic H).

(3R,5R)-5-Benzyloxy-3-hydroxyhexanoic Acid (**6a**). – *Main Product from* **11b/12b**: ^{1}H NMR (250 MHz) differs from that of **5a** in: δ = 4.38 and 4.64 (2 pseudo d, 2H, $OCH_2C_6H_5$).

(3S,5R)-3-Hydroxy-5-[(2-methoxyethoxy)methoxy]hexanoic Acid (**5b**). – *Main Product from* **11c/12c**: ^{1}H NMR (250 MHz): δ = 1.14 (d, *J* = 7.5 Hz, 3H, 6-H), 1.62 (m_c, 2H, 4-H), 2.52 (m_c, 2H, 2-H), 3.35 (s, 3H, OCH_3), 3.60 (m_c, 2H, $OCH_2CH_2OCH_3$), 3.84 (m_c, 2H, $OCH_2CH_2OCH_3$), 4.04 (m_c, 1H, 5-H), 4.32 (m_c, 2H, 3-H), 4.66 and 4.80 (2 pseudo d, 2H, OCH_2O).

(3R,5R)-3-Hydroxy-5-[(2-methoxyethoxy)methoxy]hexanoic Acid (**6b**). – *Main Product from* **11d/12d**: ^{1}H NMR (250 MHz) differs from that of **5b** in: δ = 1.16 (d, *J* = 7.5 Hz, 3H, 6-H), 3.38 (s, 3H, OCH_3), 4.72 and 4.82 (2 pseudo d, 2H, OCH_2O).

(3R,4S)-3-Hydroxy-4-[(2-methoxyethoxy)methoxy]pentanoic Acid (**5d**). – *Main Product from* **11g/12g**: ^{1}H NMR (250 MHz): δ = 1.15 (d, *J* = 6.5 Hz, 3H, 5-H), 2.53 (m_c, 2H, 2-H), 3.35 (s, 3H, OCH_3), 3.52 (m_c, 2H, $OCH_2CH_2OCH_3$), 3.63–3.83 (m, 3H, $OCH_2CH_2OCH_3$ and 3-H), 4.05 (m_c, 1H, 4-H), 4.75 (pseudo q, 2H, OCH_2O).

(3S,4S)-3-Hydroxy-4-[(2-methoxyethoxy)methoxy]pentanoic Acid (**6d**). – *Main Product from* **11h/12h**: ^{1}H NMR (250 MHz) differs from that of **5d** in: δ = 1.18 (d, *J* = 6.5 Hz), 4.76 (pseudo q, 2H, OCH_2O).

General Procedure (G. P. 4) for the Preparation of the Methyl Esters **7/8** *from Carboxylic Acids* **5/6**: To an ice-cold solution of 0.1 g of the carboxylic acids **5/6** in 10–20 ml of 95% aqueous methanol or moist diethyl ether is added under stirring as much of a freshly prepared etheral diazomethane solution, that the yellow colour of the reaction mixture just persists. After 15 min, the same amount of an etheral diazomethane solution is added, and stirring is continued overnight at room temperature. The mixture is washed with brine, containing a few milligrams of K_2CO_3. Drying with $MgSO_4$ and evaporation of the solvent afford the crude methyl esters **7/8** in >95% yield. All attempts to distill these products led to their decomposition; purification is possible, however, by preparative thin-layer chromatography with silica gel.

According to G. P. 3/G. P. 4 are obtained:

Methyl (3S,5R)-5-Benzyloxy-3-hydroxyhexanoate (**7a**). – *Main Product from* **11a/12a**: ^{1}H NMR (250 MHz): δ = 1.26 (d, *J* = 7.5 Hz, 3H, 6-H), 1.58–1.86 (m, 2H, 4-H), 2.36–2.57 (m, 2H, 2-H), 3.69 (s, 3H, OCH_3), 3.85 (m_c, 1H, 5-H), 4.26 (m_c, 1H, 3-H), 4.45 and 4.63 (2 pseudo d, 2H, $OCH_2C_6H_5$), 7.33 (m_c, 5H, aromatic H). – ^{13}C NMR (60 MHz): δ = 18.57 (C-6), 40.77 and 42.04 (C-2, C-4), 50.57 (OCH_3), 64.19 (C-3), 69.77 ($OCH_2C_6H_5$), 71.23 (C-5), 126.60, 126.74, 127.39 (aromatic C), 137.59 (aromatic ipso C), 171.89 (C-1).

Methyl (3R,5R)-5-Benzyloxy-3-hydroxyhexanoate (**8a**). – *Main Product from* **11b/12b**: ^{1}H NMR (250 MHz) differs from that of **7a** in: δ = 4.43 and 4.65 (2 pseudo d, 2H, $OCH_2C_6H_5$). – ^{13}C NMR (60 MHz): δ = 18.57 (C-6), 40.64 and 42.29 (C-2, C-4), 50.57 (OCH_3), 60.66 (C-3), 69.36 ($OCH_2C_6H_5$), 73.85 (C-5), 126.73, 127.47 (aromatic C), 137.15 (aromatic ipso C), 171.45 (C-1).

Methyl (3S,5R)-3-Hydroxy-5-[(2-methoxyethoxy)methoxy]hexanoate (**7b**). – *Main Product from* **11c/12c**: IR ($CHCl_3$): 3680 cm^{-1}, 3500, 3020, 2970, 2940, 2900, 2410, 1735, 1445, 1420, 1385, 1370, 1340, 1265, 1220, 1180, 1100, 1040, 935, 855, 760, 665. – ^{1}H NMR (250 MHz): δ = 1.13 (d, *J* = 7.5 Hz, 3H, 6-H), 1.45–1.62 (m, 2H, 4-H), 2.33–2.51 (m, 2H, 2-H), 3.33 (s, 3H, OCH_3), 3.50–3.86 (m, 4H, OCH_2CH_2), 3.64 (s, 3H, $COOCH_3$), 4.02 (m_c, 1H, 5-H), 4.25 (m_c, 2H, 3-H), 4.63 and 4.76 (2 pseudo d, 2H, OCH_2O). – ^{13}C NMR (60 MHz): δ = 20.23 (C-6), 41.92 and 43.92 (C-2, C-4), 51.58 (CO_2CH_3), 58.99 (OCH_3), 64.50 (C-3), 67.12 and 71.90 (OCH_2CH_2O), 70.00 (C-5), 93.49 (OCH_2O), 172.75 (C=O). – MS (70 eV): *m/z* (%) = 175 (5) [M – $C_3H_7O_2$], 127 (20) [$C_7H_{11}O_2^+$], 89 (14) [$C_4H_9O_2^+$], 85 (32) [$C_5H_9O^+$], 59 (100) [$C_2H_5O_2^+$], 45 (55) [$C_2H_5O^+$], 43 (77) [$C_2H_3O^+$], 31 (32) [CH_3O].

$C_{11}H_{22}O_6$ (250.2) Calcd. C 52.80 H 8.85
Found C 52.12 H 8.53

Methyl (3R,5R)-3-Hydroxy-[(2-methoxyethoxy)methoxy]hexanoate (**8b**). – *Main Product from* **11d/12d**: ^{1}H NMR (250 MHz) differs from that of **7b** in: δ = 1.17 (d, *J* = 7.5 Hz, 3H, 6-H), 4.66 and 4.72 (2 pseudo d, 2H, OCH_2O). – ^{13}C NMR (60 MHz): δ = 20.23 (C-6), 41.72 and 43.60 (C-2, C-4), 51.58 (CO_2CH_3), 58.99 (OCH_3), 67.35 (C-3), 67.12 and 71.90 (OCH_2CH_2O), 72.38 (C-5), 93.69 (OCH_2O), 172.79 (C-1).

Methyl (3S,5S)-3,5,6-Trihydroxy-5,6-O-isopropylidenehexanoate (**7c**). – *Main Product from* **11e/12e**: IR ($CHCl_3$): 3580 cm^{-1}, 3500, 2990, 2940, 2880, 1725, 1435, 1400, 1370, 1300, 1250, 1210, 1165, 1130, 1080, 1050, 1015, 990, 970, 895, 870, 840, 825, 770. – ^{1}H NMR (250 MHz): δ = 1.33 and 1.38 (2 s, 3H each, CH_3), 1.73 (m_c, 2H, 4-H), 2.51 (m_c, 2H, 2-H), 3.55 and 4.07 (2 m_c, 1H each, 6-H), 3.69 (s, 3H, OCH_3), 4.24 (m_c, 1H, 3-H), 4.30 (m_c, 1H, 5-H). – ^{13}C NMR (75 MHz): δ = 25.67 and 26.91 (CH_3), 39.90 (C-4), 41.45 (C-2), 51.68 (OCH_3), 65.47 (C-3), 69.52 (C-6), 73.20 (C-5), 108.68 (CH_3C-CH_3), 172.68 (C-1). – MS (70 eV): *m/z* (%) = 218 (3) [M^+], 187 (6) [M – CH_3O], 144 (13) [M – $C_3H_6O_2$], 85 (3) [$C_5H_9O^+$], 72 (11) [$C_4H_8O^+$], 69 (17) [$C_4H_5O^+$], 59 (46) [$C_2H_3O^+$], 43 (100) [$C_3H_7^+$], 31 (28) [CH_3O^+].

$C_{10}H_{18}O_5$ (218.2) Calcd. C 55.04 H 8.31
Found C 54.69 H 8.19

Methyl (3R,5S)-3,5,6-Trihydroxy-5,6-O-isopropylidenehexanoate (**8c**). – *Main Product from* **11f/12f**: ^{1}H NMR (250 MHz) differs from that of **7c** in: δ = 1.38 and 1.40 (2 s, 3H each, CH_3). – ^{13}C NMR (75 MHz): δ = 25.67 and 26.86 (CH_3), 39.69 (C-4), 41.31 (C-2), 51.68 (OCH_3), 66.82 (C-3), 69.43 (C-6), 74.44 (C-5), 109.15 (CH_3C-CH_3), 172.30 (C-1).

Methyl (3R,4S)-3-Hydroxy-4-[(2-methoxyethoxy)methoxy]pentanoate (**7d**). – *Main Product from* **11g/12g**: IR ($CHCl_3$): 3585 cm^{-1}, 3415, 2990, 2915, 2895, 2810, 1725, 1450, 1435, 1375, 1335, 1285, 1270, 1240, 1200, 1165, 1130, 1100, 1040, 990, 850. – ^{1}H NMR (300 MHz): δ = 1.19 (d, *J* = 6.5 Hz, 3H, 5-H), 2.50 (m_c,

2H, 2-H), 3.38 (s, 3H, OCH_3), 3.55 (m_c, 2H, OCH_2CH_2O), 3.67–3.80 (m, 3H, OCH_2CH_2O and 4-H), 3.71 (s, 3H, CO_2CH_3), 4.04 (m_c, 1H, 3-H), 4.79 (pseudo q, 2H, OCH_2O). – ^{13}C NMR (75 MHz): δ = 15.58 (C-5), 36.71 (C-2), 51.63 (CO_2CH_3), 58.82 (OCH_3), 67.08 (OCH_2CH_2O), 70.63 (C-3), 71.54 (OCH_2CH_2O), 76.53 (C-4), 94.43 (OCH_2O), 172.70 (C-1). – MS (70 eV): *m/z* (%) = 205 (3) [M – CH_3O], 165 (6) [$C_{13}H_9^+$], 164 (36) [M – C_4H_8O], 147 (2) [M – $C_4H_9O_2$], 131 (7) [M – $C_4H_9O_3$], 103 (19) [$C_5H_{11}O_2^+$], 89 (54) [$C_4H_9O_2^+$], 71 (10) [$C_4H_7O^+$], 59 (100) [$C_2H_3O_2^+$], 57 (25) [$C_3H_5O^+$], 45 (22) [$C_2H_5O^+$], 43 (17) [$C_2H_3O^+$], 31 (20) [CH_3O^+].

$C_{10}H_{20}O_6$ (236.2) Calcd. C 54.50 H 9.10
Found C 53.80 H 8.60

Methyl (3S,4S)-3-Hydroxy-4-[(2-methoxyethoxy)methoxy]pentanoate (**8d**). – *Main Product from* **11h/12h**: ^1H NMR (300 MHz) differs from that of **7d** in: δ = 1.21 (d, *J* = 6.5 Hz, 3H, 5-H). – ^{13}C NMR (75 MHz): δ = 15.91 (C-5), 37.69 (C-2), 51.63 (CO_2CH_3), 58.85 (OCH_3), 67.12 (OCH_2CH_2O), 71.01 (C-3), 71.54 (OCH_2CH_2), 75.78 (C-4), 94.27 (OCH_2O), 172.50 (C-1).

Methyl (3S,4R)-3,4,5-Trihydroxy-4,5-O-isopropylidenepentanoate (**7e**). – *Main Product from* **11k/12k**: ^1H NMR (250 MHz): δ = 1.30 and 1.37 (2 s, 3H each, CH_3), 2.41–2.64 (m, 2H, 2-H), 3.71 (s, 3H, OCH_3), 3.90–4.10 (m, 4H, 3-H, 4-H, 5-H) [ref.[10]: 1.30 (s), 1.40 (s), 2.50 (s), 3.10, 3.95 (m_c)]. – ^{13}C NMR (75 MHz): δ = 25.17 and 26.69 (CH_3), 37.25 (C-2), 51.88 (OCH_3), 66.59 (C-5), 69.16 (C-3), 77.48 (C-4), 109.42 (CH_3CCH_3), 172.92 (C-1) [ref.[10]: 25.0, 26.5, 37.6, 51.1, 66.2, 77.7, 109.5].

Methyl (3R,4R)-3,4,5-Trihydroxy-4,5-O-isopropylidenepentanoate (**8e**). – *Main Product from* **11i/12i**: ^1H NMR (250 MHz): δ = 1.34 and 1.42 (2 s, 3H each, CH_3), 2.55 (m_c, 2H, 2-H), 3.71 (s, 3H, OCH_3), 3.80–4.20 (m, 4H, 3-H, 4-H, 5-H). – ^{13}C NMR (75 MHz): δ = 26.39 and 26.69 (CH_3), 38.08 (C-2), 51.88 (OCH_3), 65.55 (C-5), 68.26 (C-3), 77.84 (C-4), 109.42 (CH_3CCH_3), 172.92 (C-1) [ref.[10]: 26.3, 26.5, 38.1, 51.1, 65.5, 77.7, 109.5].

(3S,5R)-5-Benzyloxy-3-hydroxy-1-phenyl-1-hexanone (**13**) *and (3R,5R)-5-Benzyloxy-3-hydroxy-1-phenyl-1-hexanone* (**14**): A mixture of 0.25 g (1.05 mmol) of crude **5a/6a** in diethyl ether is stirred under nitrogen at 0°C and treated with 2.3 ml of a 2.3 M solution of phenyllithium in diethyl ether. Stirring is continued for 10 h at 0°C, and 20 ml of water is added. The mixture is extracted several times with a total amount of 200 ml of chloroform. The combined organic layers are washed with water and dried with Na_2SO_4. Evaporation of the solvent delivers 0.27 g (86%) of crude product **13/14**, which is purified by column chromatography on silica gel with chloroform/ethyl acetate to give:

13. – *Main Product from* **11a/12a**: ^1H NMR (90 MHz): δ = 1.31 (d, *J* = 7 Hz, 3H, 6-H), 1.55–1.75 (m, 2H, 4-H), 2.93–3.08 (m, 2H, 2-H), 3.77 (m_c, 2H, 3-H, 5-H), 4.46 (pseudo q, 2H, $OCH_2C_6H_5$), 7.48 (m_c, 8H, aromatic H), 7.86 (m_c, 2H, aromatic H). – ^{13}C NMR (60 MHz): δ = 65.28 (C-3), 72.39 (C-5), 70.85 ($CH_2C_6H_5$), 200.42 (C-1) [ref.[16b,c]: 65.0, 72.1].

14. – *Main Product from* **11b/12b**: ^{13}C NMR (60 MHz): δ = 67.18 (C-3), 74.46 (C-5), 70.36 ($CH_2C_6H_5$), 199.85 (C-1) [ref.[16b,c]: 66.9, 74.2].

Methyl (3S,5R)-3,5-Dihydroxyhexanoate (**15**) *and Methyl (3R,5R)-3,5-Dihydroxyhexanoate* (**16**) *from* **7b/8b**[23]: In a two-necked flask, equipped with a reflux condenser, a magnetic stirrer, and a septum, a solution of 1.0 g (4 mmol) of **7b** (main)/**8b** (minor diastereomer) in 20 ml of dry acetonitrile is stirred under nitrogen at –20°C. The septum is removed for a short time, and 2.3 g of dry NaI is added. Thereafter, 2.30 ml (1.76 g, 16 mmol) of chlorotrimethylsilane is injected. The mixture is stirred for 30 min at –20 to –15°C; then another 1.19 g (8 mmol) of NaI and 1.01 ml (8 mmol) of chlorotrimethylsilane is added. Stirring is continued for 1 h at the same temperature. The mixture is transferred into a separatory funnel, filled with ice, and extracted several times with total amounts of 200 ml of diethyl ether and 200 ml of ethyl acetate. The combined organic layers are washed with saturated aqueous sodium thiosulfate and with brine and are dried with Na_2SO_4. Evaporation of the solvent delivers 0.45 g (69%) of crude mixture **15/16** as a colourless oil.

15 (main product): ^1H NMR (250 MHz): δ = 1.33 (d, *J* = 6.5 Hz, 3H, 6-H), 1.62–1,83 (m, 2H, 4-H), 2.38–2.73 (m, 2H, 2-H), 3.72 (s, 3H, OCH_3), 4.08–4.43 (m, 2H, 3-H, 5-H). – ^{13}C NMR (60 MHz): δ = 18.95 (C-6), 35.45 and 38.30 (C-2, C-4), 51.67 (OCH_3), 67.43 and 68.08 (C-3, C-5), 171.05 (C-1).

16 (minor product): ^1H NMR (250 MHz) differs from that of **15** in: δ = 1.23 (d, *J* = 6.5 Hz, 3H, 6-H). – ^{13}C NMR (60 MHz): δ = 21.42 (C-6), 38.77 and 40.69 (C-2, C-4), 51.67 (OCH_3), 72.33 and 72.75 (C-3, C-5), 171.05 (C-1).

(3R,4S)-3-Hydroxy-4-methyl-γ-butyrolactone (**23**) *and (3S,4S)-3-Hydroxy-4-methyl-γ-butyrolactone* (**24**): As described for the preparation of **15** and **16**, a mixture of the methyl esters **7d/8d** is transformed into the dihydroxycarboxylic esters **21/22**; **21**: ^1H NMR (250 MHz): δ = 1.33 (d, *J* = 6.5 Hz, 5-H), 2.54 (m_c, 2H, 2-H), 3.72 (s, 3H, OCH_3), 4.21 (m_c, 1H, 4-H), 4.44 (m_c, 1H, 3-H); **22**: ^1H NMR (250 MHz) differs from that of **21** in: δ = 1.19 (d, *J* = 6.5 Hz, 3H, 5-H). The crude mixture **21/22** (0.1 g; 0.675 mmol) is dissolved in 50 ml of methanol and treated with 50 ml of 1 N hydrochloric acid. The solution is stirred at room temperature overnight and concentrated in a rotary evaporator. Water is added and the pH is adjusted to 5.5 by addition of K_2CO_3. The solution is saturated with NaCl and extracted several times with diethyl ether and with ethyl acetate. The combined organic layers are washed with an ice-cold saturated aqueous solution of K_2CO_3 and dried with Na_2SO_4. The evaporation of the solvent delivers 0.06 g (76%) of **23/24** as a colourless oil. – IR ($CHCl_3$): 1785 cm^{-1} [ref.[24] 1780]. – **23** (main product): ^1H NMR (250 MHz): δ = 1.35 (d, *J* = 6.3 Hz, 3H, CH_3), 2.44–2.84 (m, 2H, 2-H), 4.20 (m_c, 1H, 3-H), 4.45 (m_c, 1H, 4-H). – ^{13}C NMR (75 MHz): δ = 18.47 (CH_3), 72.63 (C-3), 84.44 (C-4) [ref.[20]: 18.6, 73.1, 84.0]. – **24** (minor product): ^1H NMR (250 MHz) differs from that of **23** in: δ = 1.43 (d, *J* = 6.3 Hz, 3H, CH_3). – ^{13}C NMR (75 MHz): δ = 13.71 (CH_3), 69.28 (C-3), 81.49 (C-4) [ref.[20]: 13.7, 69.6, 80.9].

CAS Registry Numbers

1 (*R* isomer): 95061-47-5 / **1** (*S* isomer): 95061-51-1 / **4a** (*R* isomer): 86040-07-5 / **4b** (*R* isomer): 115407-82-4 / **4c**: 32233-44-6 / **4d**: 86163-01-1 / **4e**: 15186-48-8 / **5a**: 115407-97-1 / **5b**: 115407-99-3 / **5d**: 115408-01-0 / **6a**: 115407-98-2 / **6b**: 115408-00-9 / **6d**: 115408-02-1 / **7a**: 115408-03-2 / **7b**: 115408-05-4 / **7c**: 115408-07-6 / **7d**: 115408-09-8 / **7e**: 83159-90-4 / **8a**: 115408-04-3 / **8b**: 115408-06-5 / **8c**: 115408-08-7 / **8d**: 115408-10-1 / **8e**: 84064-19-7 / **9**: 24915-95-5 / **10a** (*R* isomer): 115460-90-7 / **10b** (*R* isomer): 115407-83-5 / **11a**: 115407-84-6 / **11b**: 115460-92-9 / **11c**: 115407-85-7 / **11d**: 115460-95-2 / **11e**: 115419-77-7 / **11f**: 115407-87-9 / **11g**: 115407-89-1 / **11h**: 115407-91-5 / **11i**: 115407-93-7 / **11k**: 115407-95-9 / **12a**: 115460-91-8 / **12b**: 115460-93-0 / **12c**: 115460-94-1 / **12d**: 115460-96-3 / **12e**: 115407-86-8 / **12f**: 115407-88-0 / **12g**: 115407-90-4 / **12h**: 115407-92-6 / **12i**: 115407-94-8 / **12k**: 115407-96-0 / **13**: 115460-97-4 / **14**: 115460-98-5 / **15**: 115460-99-6 / **16**: 115461-00-2 / **21**: 115408-11-2 / **22**: 115408-12-3 / **23**: 98512-76-6 / **24**: 105881-47-8 / methyl lithioacetate: 57570-85-1 / benzyl bromide: 100-39-0 / MEM chloride: 3970-21-6

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