Rearrangement of 2-(4-Hydroxyalkyl)-1,3-dioxolanes to 2-Hydroxyethyl Alkanoic Esters by 1,5-Hydride Shift − An Unprecedented Intramolecular Redox Reaction

Karsten Krohn,*[a] Ulrich Flörke,[a] Uwe Höfker,[a] and Marion Träubel[a]

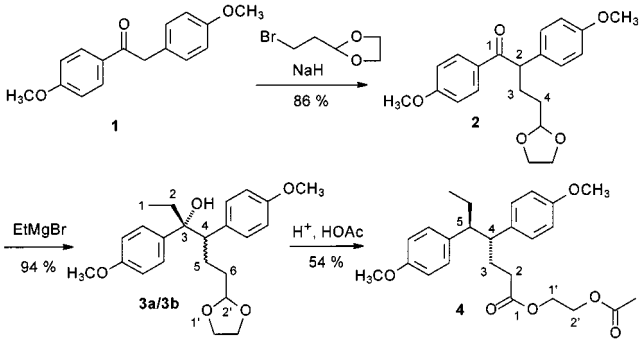
Dedicated to Professor Werner Tochtermann on the occasion of his 65th birthday

Keywords: Hydride abstraction / Carbenium ions / Rearrangement / Intramolecular redox reaction / Deuterium label

2-(4-Hydroxyalkyl)-1,3-dioxolanes (**3a/3b**, **5**–**7**) undergo an acid-catalyzed rearrangement to give 2-hydroxyethyl alkanoic esters **8**–**11**. The postulated mechanism, proceeding via the benzylic carbenium ion **B** and the 1,3-dioxolan-2-ylium cation **C**, is supported by the stereochemistry of the reaction and the results of deuterium labeling experiments.

Introduction

In connection with the synthesis of estrophilic ligands of the hexestrol series[1] with cisplatin as the toxic principle, with a view to achieving a more selective treatment of uterus and breast cancers,[2−4] we studied the perchloric acid catalyzed hydrogenolysis of a 4:1 *syn*/*anti* mixture (as racemates) of the epimeric 5-hydroxyacetals **3a/3b** (the stereochemical assignment of **3a/3b** was based on ^{1}H-NMR data[5]). The tertiary alcohols **3a/3b** were prepared in 81% overall yield by alkylation of deoxyanisoin (**1**) with the ethylene glycol acetal of 3-bromopropanal and subsequent reaction of the ketone **2** with ethylmagnesium bromide (Scheme 1). Surprisingly, instead of reductive removal of the benzylic hydroxy group to afford the expected deoxygenated acetal, the diester **4** was formed. Thus, the question arose as to how the oxidation of the acetal to an ester could have occurred under reductive conditions. Perchloric acid was only used in catalytic amounts and could be excluded as the oxidizing agent. Moreover, only a single isomer of **4** was formed stereoselectively from the diastereomeric mixture **3a/3b**. The explanation for this apparent enigma turned out to be a redox reaction proceeding via cationic intermediates, which we have observed here for the first time in an intramolecular reaction. We now report the results of our mechanistic investigations and assess the generality of this interesting new rearrangement.



Scheme 1. Preparation of 5-hydroxydioxolanes **3a/3b** and rearrangement to diester **4**

Results and Discussion

The deoxygenation of **3a/3b** to give the ester **4** was presumed not to be caused by hydrogenation and in a first series of experiments the diastereoisomers **3a/3b** were treated with perchloric acid in acetic acid in the absence of palladium/charcoal and hydrogen. Indeed, the same product **4** was obtained under these conditions, proving that the hydroxyl group was *not* removed by hydrogenation. Furthermore, it was found that acetic anhydride, which was used as a co-solvent in the initial hydrogenation experiments, was *not* required for the acylation. Therefore, the acylation reaction must be initiated by nucleophilic attack of acetic acid on an electrophilic oxygen species. Clearly, this electrophile could be a dioxolan-2-ylium cation. The existence and reactivity of such cations was postulated long ago in the work of Meerwein et al.[6][7] and was later reviewed by Pittman, Jr., et al.[8] Dioxolan-2-ylium cations are usually generated by hydride abstraction from 1,3-dioxolanes with trityl cations and form stable tetrafluoroborates.[6] In the present case, the hydride abstraction is postulated to be an *intra*molecular process. A mechanistic pathway accounting for the rearrangement is presented in Scheme 2. Thus, protonation of the hydroxyl group of the diastereomeric mixture **3a/3b** to give **A** is followed by elimination of water to afford the relatively stable tertiary benzylic cation **B**. This carbenium ion then removes an acidic proton from the dioxolane ring in a favorable six-

[a] Fachbereich Chemie und Chemietechnik, Universität Paderborn,
Warburger Straße 100, D-33098 Paderborn, Germany
Fax: (internat.) +49 (0)5251-603245
E-mail: kk@chemie.uni-paderborn.de
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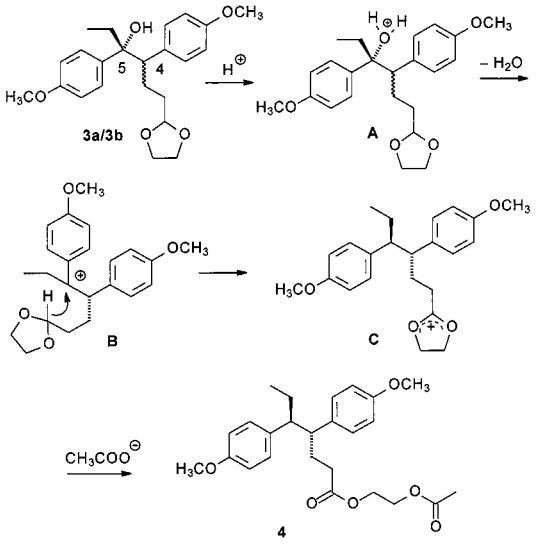
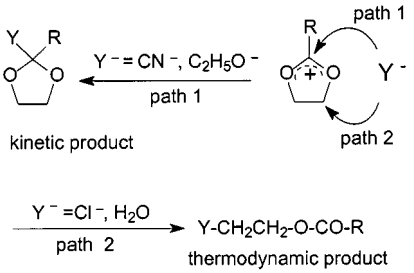
membered cyclic transition state as shown in **B** to generate the even more stable 1,3-dioxolan-2-ylium cation **C**.



Scheme 2. Acid-catalyzed rearrangement of 5-hydroxydioxolanes **3a/3b** to diester **4** via intermediates **A**−**C**

In the final step, the 1,3-dioxolan-2-ylium cation **C** is stabilized by nucleophilic attack of acetic acid to form the diester **4**. Meerwein showed that dioxolan-2-ylium cations can, in principle, react by the two pathways 1 and 2 shown in Scheme 3.[7] Highly reactive nucleophiles (e.g. cyanide or ethoxylate ions) attack at the position of lowest electron density to form the kinetic product. Less reactive nucleophiles (in the present case acetic acid or water, see below) form the ring-opened thermodynamically controlled products such as **4**.



Scheme 3. Two pathways in the reaction of dioxolan-2-ylium cations with nucleophiles

Only one stereoisomer of structure **4** is obtained from the mixture of *syn* and *anti* isomers **3a** and **3b**. Therefore, hydride abstraction from the 1,3-dioxolane by a relatively stable benzylic cation must occur stereoselectively from the bottom side, as shown in **B**, to form the *anti*-dioxolan-2-ylium cation **C**. This is then trapped by acetic acid to yield the diester **4**. Any *inter*molecular hydrogen transfer would most probably *not* show the complete stereoselectivity observed in the reaction as depicted in Scheme 2.

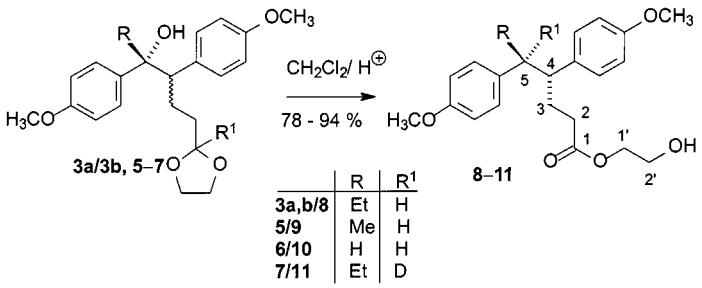
It was later found that the rearrangement also occurred in the absence of acetic acid and in even better yields. The reaction is most conveniently carried out using a solution of the acetals **3a/3b** in dichloromethane containing a few drops of perchloric acid. Under these conditions, the monoester **8** of ethylenediol is obtained in 87% yield after recrystallization.

The generality of this intramolecular redox reaction was further demonstrated by the acid-catalyzed transformation of the related hexanol **5** and the pentanol **6** to afford the corresponding esters **9** and **10** in 86% and 78% yields, respectively (Scheme 4). The alcohol **5** was prepared in an analogous manner to **3a/3b** with the sole modification that $CeCl_3$ was added to the Grignard reagent in order to avoid the facile elimination of the tertiary hydroxyl group that was observed in the reaction of ketone **2** with methylmagnesium bromide. Moreover, the stereoselectivity also increased considerably so that only one stereoisomer of **5** could be isolated from this reaction. However, as in the case of the ethyl compounds **3a/3b**,[5] an assignment of the relative stereochemistry of the tertiary alcohol was not readily achievable on the basis of NMR data. Fortunately, X-ray analysis of the crystalline compound **5** revealed the *syn*-configuration as shown in Figure 1.

Finally, convincing evidence for hydrogen transfer from C-1 to C-5 was provided by the reaction of the deuterated 1,3-dioxolane derivative **7** [prepared by alkylation of deoxyanisoin (**1**) with 1-deuterio-3′-bromomethyl-1,3-dioxolane] to form the C-5 deuterated ester **11**. The NMR spectra showed that, within experimental error, no loss of deuterium occurred during hydrogen transfer.

An interesting aspect of this work, to be verified in future experiments, is that not only cations with a 1,5-relationship, but *any* carbocation generated in a sterically favorable orientation in the vicinity of the 1,3-dioxolane ring could lead to hydride abstraction and subsequent addition of nucleophiles to the 1,3-dioxolan-2-ylium cations.

In summary, a novel rearrangement in the hexestrol and related systems resulting in an intramolecular redox reac-



	R	R^1
3a,b/8	Et	H
5/9	Me	H
6/10	H	H
7/11	Et	D

Scheme 4. Further examples of the rearrangement of 5-hydroxydioxolanes to ethyleneglycole esters

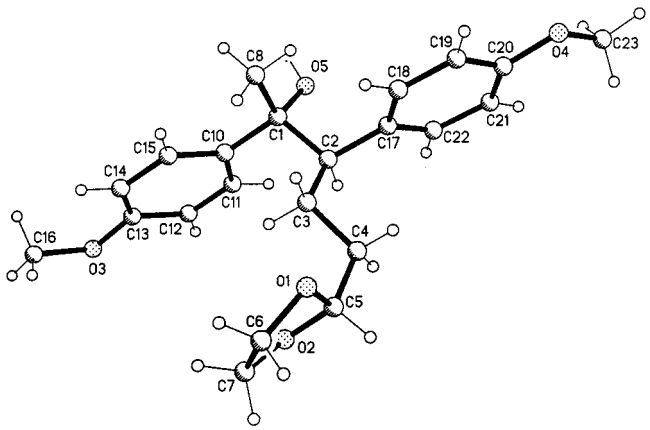


Figure 1. The molecule of alcohol **5** in the crystal

tion has been presented. Evidence for a 1,5-hydride transfer reaction proceeding via a stable benzylic cation has been provided by the stereochemistry of the process and the findings of labeling experiments. Similar reactions are postulated for any carbocations formed in a sterically favorable orientation in the vicinity of dioxolane rings

Experimental Section

General Remarks: For general information concerning the equipment, materials and methods used, see ref.[9].

***rac*-4-([1,3]Dioxolan-2-yl)-1,2-bis(4-methoxyphenyl)butan-1-one (2):** To a suspension of NaH in mineral oil (5.40 g, 0.180 mmol, 80%) in dry diethyl ether under nitrogen was added a solution of deoxy-4-anisoin (**1**) (30.00 g, 0.117 mol) and 2-(2-bromoethyl)-1,3-dioxolane (19.4 mL, 0.164 mol). The mixture was stirred for 1 h until the evolution of hydrogen had ceased (TLC monitoring) and then poured into ice/water (0.5 L). The resulting emulsion was extracted twice with CH_2Cl_2 (300 mL), the combined organic phases were washed successively with aqueous ammonium chloride solution (100 mL) and water (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure to afford a yellow oil that crystallized from diethyl ether (300 mL)/petroleum ether (40 mL); yield 35.2 g (86%); m.p. 68°C. − IR (CCl_4): $\tilde{\nu}$ = 2955−2802 cm^{-1} (CH), 1677 (CO), 1602, 1577, 1510 (Ar). − ^{1}H NMR ($CDCl_3$): δ = 1.54−2.29 (m, 4 H, 2 CH_2), 3.74 (s, 3 H, OCH_3), 3.78−3.96 (m, 4 H), 3.81 (s, 3 H, OCH_3), 4.52 (t, *J* = 7.4 Hz, 1 H, 3-H), 4.87 (t, *J* = 4.5 Hz, 1 H, 2′-H), 6.83 (dd, 4 H, ArH), 7.21 (d, *J* = 9 Hz, 2 H, ArH), 7.94 (d, *J* = 9 Hz, ArH). − ^{13}C NMR: δ = 28.27 (t), 31.96 (t), 52.24 (d), 55.52 (q), 55.73 (q), 65.18 (t), 104.80 (d), 113.97 (d), 114.62 (d), 129.57 (d), 130.19 (s), 131.27 (d), 132.16 (s), 158.88 (s), 163.51 (s), 198.76 (s). − MS; *m*/*z* (%): 356 (14) [M^+], 221 (28), 135 (100), 121 (11), 107 (9), 92 (9), 77 (17), 73 (23), 69 (6), 57 (9), 45 (15). − $C_{21}H_{24}O_5$ (356.42): calcd. C 70.77, H 6.79; found C 70.63, H 6.79.

(3*R,4*R**)- and (3*R**,4*S**)-6-([1,3]Dioxolan-2-yl)-3,4-bis(4-methoxyphenyl)hexan-3-ol (3a/3b):** A Grignard solution was prepared from Mg (6.56 g, 270 mmol) and ethyl bromide (20.7 mL, 270 mmol) in dry diethyl ether (350 mL). This solution was then added dropwise to a solution of the ketone **2** (48.00 g, 135 mmol) in dry THF (750 mL) and the mixture was stirred for 6 h at 20°C under nitrogen (TLC monitoring). The reaction was subsequently quenched by the addition of 5% aqueous ammonium chloride solution (300 mL). The organic phase was separated, the aqueous phase was extracted with diethyl ether (300 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure to afford a pale yellow oil (49.23 g, 96%); s*yn*:*anti* = 4:1 by ^{1}H NMR. − IR (CCl_4): $\tilde{\nu}$ = 3490 cm^{-1} (OH), 2954−2836 (CH), 1613, 1513 (Ar). − ^{1}H NMR ($CDCl_3$): δ = 0.71 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.26−2.14 (m, 4 H, 2 CH_2), 2.87 (dd, *J* = 3.4 Hz, *J* = 12.3 Hz, 1 H, 4-H), 3.75−3.90 (m, 4 H), 3.79 (s, 3 H, OCH_3), 4.75 (t, *J* = 4.8 Hz, 1 H, 2′-H), 6.71 (d, *J* = 8.7 Hz, 2 H, ArH), 6.81 (dd, *J* = 8.8 Hz, *J* = 14.8 Hz, 4 H, ArH), 7.08 (d, *J* = 8.8 Hz, 2 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 7.77 (q), 23.17 (t), 31.33 (t), 32.29 (t), 55.13 (q), 55.16 (q), 56.72 (d), 64.74 (t), 64.80 (t), 78.86 (s), 104.64 (d), 112.73 (d), 113.10 (d), 128.01 (d), 130.94 (d), 131.76 (s), 135.57 (s), 158.01 (s), 158.17 (s). − MS; *m*/*z* (%): 386 (1) [M^+], 369 (100), 244 (10), 165 (72), 149 (24), 124 (12), 104 (8), 73 (4), 52 (4). − $C_{23}H_{30}O_5$ (386.49): calcd. C 71.48, H 7.82; found C 70.46, H 7.40.

2-Acetyloxyethyl (4*R,5*S**)-4,5-Bis(4-methoxyphenyl)heptanoate (4):** A solution of the 4:1 *syn*/*anti* mixture of the alcohols **3a/3b** (10.00 g, 25.9 mmol) in acetic acid (400 mL) was treated with 70% perchloric acid (0.1 mL) and stirred for 14 h at 50°C. The solvent was then removed under reduced pressure, the residue was redissolved in diethyl ether (200 mL), and this solution was washed three times with saturated aqueous sodium hydrogen carbonate solution (30 mL) and then with brine (10 mL). The ethereal solution was dried ($MgSO_4$) and concentrated under reduced pressure to afford the diester (5.90 g, 54%) as colorless crystals (diethyl ether); m.p. 96°C. − IR (KBr): $\tilde{\nu}$ = 2938−2874 cm^{-1} (C−H), 1734 (C=O), 1631, 1534 (Ar). − ^{1}H NMR ($CDCl_3$): δ = 0.53 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.23−1.77 (m, 4 H, 2 CH_2), 1.93−2.00 (m, 2 H, CH_2), 2.03 (s, 3 H, CH_3COO), 2.45−2.67 (m, 2 H, 4,5-H), 3.81 (s, 6 H, 2 OCH_3), 4.05−4.20 (m, 4 H, 1′,2′-CH_2), 6.86 (d, *J* = 8.5 Hz, 4 H, ArH), 7.08 (dd, *J* = 8.5 Hz, 4 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 12.08 (q, C-7), 20.73 (q), 27.38 (t, C-6), 29.49 (t, C-3), 32.23 (t, C-2), 50.75 (d, C-4), 53.47 (d, C-5), 55.10 (q, 2 OCH_3), 61.72 (t), 62.10 (t), 113.61 (d), 113.75 (d), 129.06 (d, 4 Ar C), 135.33 (s), 135.75 (s), 157.85 (s), 158.02 (s), 170.05 (q), 173.33 (q). − MS (70 eV); *m*/*z* (%): 428 (1) [M^+], 325 (3) [$M^+ - OCH_2CH_2OOCH_3$], 279 (18), 217 (2), 150 (12), 149 (100), 87 (89), 43 (19). − HRMS: $C_{25}H_{32}O_6$: calcd. 428.2198; found 428.2121 ± 3 ppm.

(2*R,3*R**)-5-([1,3]Dioxolan-2-yl)-2,3-bis(4-methoxyphenyl)pentan-2-ol (5):** To a suspension of methylmagnesium iodide (0.94 g, 12.6 mmol) and dry $CeCl_3$ (3.15 g, 12.8 mmol) in diethyl ether (15 mL) was added a solution of ketone **2** (3.00 g, 8.4 mmol) in dry diethyl ether (15 mL). After stirring for 2 h at 20°C, the reaction was quenched by the addition of 5% aqueous ammonium chloride solution (20 mL), the organic phase was separated, and the aqueous phase was extracted with diethyl ether (30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to afford the alcohol **5** (3.04 g, 97%) as a yellow oil. − IR (KBr): $\tilde{\nu}$ = 3512−3369 cm^{-1} (OH), 2959−2827 (C−H), 1617, 1516 (Ar). − ^{1}H NMR ($CDCl_3$): δ = 1.24−1.95 (m, 4 H, 2 CH_2), 1.47 (s, 3 H, CH_3), 2.91 (dd, *J* = 3.4 Hz, *J* = 12.3 Hz, 1 H, 3-H), 3.70−3.93 (m, 4 H) + (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 6.72−7.00 (m, 6 H), 7.18−7.30 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 23.95 (t, C-2), 26.98 (q, C-6), 32.72 (t, C-3), 55.56 (q, OCH_3), 55.61 (q, OCH_3), 57.50 (s, C-4), 65.12 (t, acetal), 65.17 (t), 76.47 (s), 104.96 (d, C-2′), 113.29 (d), 113.69 (d), 127.71 (d), 131.34 (d), 132.10 (s), 139.07 (s), 158.65 (s), 158.73 (s). − MS (70 eV); *m*/*z* (%): 371 (60) [$M^+ - H$], 339 (34), 221 (92), 149 (100), 127 (57), 81 (21). − HRMS ($C_{22}H_{28}O_5$): calcd. 372.1937; found 372.1859 ± 5 ppm.

(1*R,2*R**)-4-([1,3]Dioxolan-2-yl)-2,3-bis(4-methoxyphenyl)butan-2-ol (6):** To a suspension of LAH (0.16 g, 30.0 mmol) in THF was added a solution of **2** (6.00 g, 16.8 mmol) in dry THF (20 mL). After stirring for 1 h at 20°C, the reaction was quenched by the dropwise addition of water followed by 2 N HCl. The resulting mixture was then extracted with diethyl ether (10 mL), the organic phase was washed with aqueous sodium hydrogen carbonate solution and brine, dried (Na_2SO_4), and the solvent was evaporated under reduced pressure to yield alcohol **6** (5.55 g, 92%) as colorless crystals. − IR (KBr): $\tilde{\nu}$ = 3498 cm^{-1} (OH), 2948−2839 (C−H), 1617, 1510 (Ar). − ^1H NMR ($CDCl_3$): δ = 1.35−1.70 (m, 4 H, CH_2), 2.77−2.89 (m, 1 H, 4-H), 3.64−3.94 (m, 4 H), 3.83 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.54−4.80 (m, 2 H, 1,2′-H), 6.87−6.99 (m, 4 H), 7.16−7.30 (m, 4 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 26.7 (q, C-5), 32.19 (t, C-3), 53.77 (d, C-4), 55.67 (q, 2 OCH_3), 65.11 (t), 65.18 (t), 104.83 (d, C-1), 114.08 (d), 114.51 (d), 128.52 (d), 130.15 (d), 133.17 (s), 135.25 (s), 158.96 (s), 159.53 (s). − MS (70 eV); *m/z* (%): 358 (20) [M^+], 357 (16) [M^+ − H], 325 (20), 295 (10), 221 (100), 175 (3), 79 (10), 61 (3). − HRMS ($C_{21}H_{26}O_5$): calcd. 358.1780; found 358.1702 ± 5 ppm.

2-Deuterio-2-(2-bromoethyl)-1,3-dioxolane: To a suspension of lithium aluminium deuteride (0.32 g, 7.6 mmol) in dry THF (10 mL) under argon was slowly added a solution of ethyl 3-bromopropionate (1.81 g, 10.0 mmol) in dry THF (25 mL). The mixture was stirred for 3 h at 20°C and then the reaction was carefully quenched by the dropwise addition of water. The resulting solution was acidified by the addition of 2 N HCl (2 mL) and extracted twice with diethyl ether (50 mL). The combined organic phases were washed with sodium hydrogen carbonate solution and brine, dried (Na_2SO_4), and concentrated under reduced pressure to afford oily 1,1-dideuterio-3-bromopropanol (1.18 g, 100%). To a solution of Dess−Martin periodinane[10] (2.87 g, 10.32 mmol) in CH_2Cl_2 (20 mL) was added a solution of 1,1-dideuterio-3-bromopropanol (1.18 g, 8.3 mmol) in dry CH_2Cl_2 (20 mL). Diethyl ether (50 mL) was then added and the mixture was washed with 1 N sodium hydroxide (5 mL) and brine (5 mL). The solvent was subsequently evaporated under reduced pressure to afford 1-deuterio-3-bromopropanal (1.15 g, quantitative), which was directly used in the next reaction without purification. Thus, a solution of the 1-deuterio-3-bromopropanal (1.15 g, 8.3 mmol) and ethylene glycol (0.52 g, 8.4 mmol) in CH_2Cl_2 was treated with 30 mg of *p*-toluenesulfonic acid and 5 g of freshly heated silica gel and the mixture was refluxed for 2 h. The solvent was then evaporated under reduced pressure to afford 2-deuterio-2-(2-bromoethyl)-1,3-dioxolane (1.4 g, 94%) as a colorless oil.

(3*R,4*R**)- and (3*R**,4*S**)-2-Deuterio-6-([1,3]dioxolan-2-yl)-3,4-bis(4-methoxyphenyl)hexan-3-ol (7):** 2′-Deuterio-4-[1,3]dioxolan-2-yl-1,2-bis(4-methoxyphenyl)butan-1-one was prepared as described for the nondeuterated compound **2** from NaH (0.54 g, 80%, 18 mmol), deoxy-4-anisoin (3.30 g, 11.7 mmol), and 2-deuterio-2-(2-bromoethyl)-1,3-dioxolane (2.20 g, 12.1 mmol, see below); yield 3.51 g (84%), colorless crystals; m.p. 67°C. The deuterated alcohol **7** was then prepared as described for **3a/3b** from Mg (0.30 g, 12.3 mmol), ethyl bromide (1.46 g, 13.4 mmol), and 2′-deuterio 4-[1,3]dioxolan-2-yl-1,2-bis(4-methoxyphenyl)butan-1-one (3.00 g, 7.7 mmol) to afford a 5:1 *syn/anti* mixture (^1H NMR) of **7**. − IR (KBr): $\tilde{\nu}$ = 3562−3391 cm^{-1} (OH), 2962−2862 (C−H), 1633, 1529 (Ar). − ^1H NMR ($CDCl_3$): δ = 0.73 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.18−2.12 (m, 4 H, 2,3-CH_2), 2.87 (dd, *J* = 3.4 Hz, *J* = 12.3 Hz, 1 H, 4-H), 3.75−3.90 (m, 4 H), 3.80 (s, 3 H, OCH_3), 6.71 (d, *J* = 8.7 Hz, 2 H, ArH), 6.81 (dd, *J* = 8.8 Hz, *J* = 14.8 Hz, 4 H, ArH), 7.08 (d, *J* = 8.8 Hz, 2 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 8.20 (q, C-7), 23.57 (t), 31.82 (t), 32.55 (t), 55.54 (q, OCH_3), 57.12 (q, OCH_3), 65.14 (t, acetal CH_2), 79.25 (s, C-5), 113.10 (s), 113.48 (s), 128.47 (s), 131.36 (s), 132.19 (s), 135.89 (s), 158.39 (s), 158.55 (s). − MS (70 eV); *m/z* (%): 357 (4) [M^+], 326 (6), 237 (50), 150 (100), 121 (22), 45 (5). − HRMS ($C_{23}H_{30}O_5$): calcd. 387.2156; found 387.2168 ± 3 ppm.

2-Hydroxyethyl (4*R,5*S**)-4,5-Bis(4-methoxyphenyl)heptanoate (8):** A solution of the acetals **3a/3b** (10.00 g, 25.9 mmol) in CH_2Cl_2 (100 mL) was treated with 3 drops of 70% perchloric acid. After standing for 6 h at 20°C, the solution was washed with saturated aqueous sodium hydrogen carbonate solution (10 mL) and brine (10 mL), and concentrated under reduced pressure to afford the ester **8** (7.80 g, 87%) as colorless crystals; m.p. 88°C (diethyl ether). − IR (KBr): $\tilde{\nu}$ = 3567 cm^{-1} (OH), 2956−2839 (C−H), 1712 (C=O), 1609, 1519 (Ar). − ^1H NMR ($CDCl_3$): δ = 0.56 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.23−2.09 (m, 6 H, 2,3,6-CH_2), 2.46−2.67 (m, 2 H, 4,5-H), 3.72−3.79 (m, 2 H, 2′-CH_2), 3.84 (s, 6 H, 2 OCH_3), 4.07 (t, 2 H, 1′-CH_2), 6.8 (dd, *J* = 1.6 Hz, *J* = 8.7 Hz, 4 H, ArH), 7.08 (dd, *J* = 8.5 Hz, 4 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 12.56 (q, C-7), 27.86 (t, C-6), 30.01 (t, C-3), 32.78 (t, C-2), 51.27 (d, C-4), 53.95 (d, C-5), 55.62 (q, 2 OCH_3), 61.51 (t, C-2′), 66.18 (t, C-1′), 114.14 (d), 114.28 (d), 129.56 (d, 4 ArC), 135.83 (s), 136.27 (s), 158.39 (s), 158.54 (s), 171.39 (q). − MS (70 eV); *m/z* (%): 386 (4) [M^+], 325 (10) [M^+ − OCH_2CH_2OH], 237 (92), 193 (12), 149 (100), 121 (22), 45 (5). − HRMS ($C_{23}H_{30}O_5$): calcd. 386.2093; found 386.2099 ± 3 ppm.

2-Hydroxyethyl (4*R,5*S**)-4,5-Bis(4-methoxyphenyl)hexanoate (9):** A solution of alcohol **5** in CH_2Cl_2 (100 mL) was treated with 3 drops of perchloric acid as described for **8** to afford **9** (7.11 g, 86%) as colorless crystals; m.p. 88°C. − IR (KBr): $\tilde{\nu}$ = 3563−3373 cm^{-1} (OH), 2960−2902 (C−H), 1621, 1516 (Ar). − ^1H NMR ($CDCl_3$): δ = 1.00 (d, *J* = 7.8 Hz, 3 H, CH_3), 1.61−2.09 (m, 4 H, 2,3-CH_2), 2.54−2.86 (m, 2 H, 4,5-H), 3.70−3.77 (m, 2 H, 2′-CH_2), 3.84 (s, 6 H, 2 OCH_3), 4.06−4.15 (m, 2 H, 1′-CH_2), 6.89 (dd, *J* = 1.8 Hz, *J* = 6.8 Hz, 4 H, ArH), 7.09−7.18 (m, 4 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 21.64 (q, C-6), 29.93 (t, C-3), 32.87 (t, C-2), 46.07 (d, C-5), 52.24 (d, C-4), 55.65 (q, 2 OCH_3), 61.56 (t), 66.21 (t), 114.26 (d), 128.78 (d), 129.57 (d), 135.45 (s), 138.73 (s), 158.38 (s), 158.60 (s), 174.35 (q). − MS (70 eV); *m/z* (%): 372 (5) [M^+], 311 (10) [M^+ − OCH_2CH_2OH], 237 (92), 175 (48), 135 (100), 91 (27), 18 (22). − HRMS ($C_{22}H_{28}O_5$): calcd. 372.1937; found 372.1939 ± 5 ppm.

***rac*-2-Hydroxyethyl 4,5-Bis(4-methoxyphenyl)pentanoate (10):** A solution of alcohol **6** (1.00 g, 2.79 mmol) in CH_2Cl_2 (100 mL) was treated with 3 drops of perchloric acid as described for **8** to afford the ester **10** (0.78 g, 78%) as colorless crystals; m.p. 78°C. − IR (KBr): $\tilde{\nu}$ = 3523 cm^{-1} (OH), 2933−2841 (C−H), 1711 (C=O), 1609, 1508 (Ar). − ^1H NMR ($CDCl_3$): δ = 1.84−2.24 (m, 4 H, 2 CH_2), 2.75−2.95 (m, 3 H, 4,5-H), 3.59−3.91 (m, 2 H), 3.78 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 4.12−4.27 (m, 2 H), 6.67−7.30 (m, 8 H). − ^{13}C NMR ($CDCl_3$): δ = 30.97 (t, C-3), 32.75 (t, C-2), 43.37 (t, C-5), 47.18 (d, C-4), 55.59 (q, 2 OCH_3), 61.43 (t), 66.28 (t), 114.26 (d), 128.78 (d), 129.57 (d), 135.45 (s), 138.73 (s), 158.38 (s), 158.60 (s), 174.35 (q). − MS (70 eV); *m/z* (%): 358 (16) [M^+], 297 (10), 297 (12), 237 (100), 175 (30), 147 (70), 91 (2). − HRMS ($C_{21}H_{26}O_5$): calcd. 358.1780; found 358.1773 ± 5 ppm.

2-Hydroxyethyl (4*R,5*S**)-5-Deuterio-4,5-bis(4-methoxyphenyl)heptanoate (11):** A solution of **7** (2.00 g, 5.16 mmol) in CH_2Cl_2 (100 mL) was treated with 3 drops of perchloric acid as described for **8** to afford the rearranged ester **11** (1.84 g, 92%) as colorless crystals; m.p. 90°C. − IR (KBr): $\tilde{\nu}$ = 3587 cm^{-1} (OH), 2922−2818 (C−H), 1731 (C=O), 1613, 1521 (Ar). − ^1H NMR ($CDCl_3$): δ = 0.56 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.20−2.00 (m, 6 H, 3 CH_2), 2.65

(dd, J = 3.33 Hz, J = 11.2 Hz, 1 H, 4-H), 3.70 (t, J = 4.6 Hz, 2 H, CH_2), 3.83 (s, 6 H, 2 OCH_3), 4.06 (t, J = 4.6 Hz, 2 H, CH_2), 6.89 (d, J = 8.5 Hz, 4 H, ArH), 7.11 (d, J = 8.4 Hz, 4 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 12.5 (q, C-7), 27.75 (t, C-6), 29.97 (t, C-3), 32.78 (t, C-2), 51.16 (d, C-4), 55.62 (q, 2 OCH_3), 61.46 (t), 66.18 (t), 114.14 (d), 114.28 (d), 129.56 (d, C-9,13,15,19), 135.83 (s), 136.27 (s), 158.39 (s), 158.54 (s), 171.39 (q). − MS (70 eV); *m*/*z* (%): 387 (4) [M^+], 326 (10) [$M^+ - OCH_2CH_2OH$], 237 (92), 193 (12), 149 (100), 121 (22), 45 (5).

X-ray Crystallographic Study of 5:[11] Crystal data: $C_{22}H_{28}O_5$, M_r = 372.44, monoclinic, space group $P2_1$ (no. 4), a = 5.972(2), b = 28.383(7), c = 11.674(3) Å, β = 97.59(2)°, V = 1961.4(10) Å^3, Z = 4, D_c = 1.261 Mg/m^3. Data collection: Bruker AXS P4 diffractometer; Mo-K_α radiation, λ = 0.71073 Å, graphite monochromator, crystal size 0.12 × 0.14 × 0.50 mm, T = 203(2) K, ω-scan, 2.3 ≤ Θ ≤ 26.0°, −7 ≤ h ≤ 1, −35 ≤ k ≤ 1, −14 ≤ l ≤ 14; 5306 reflections collected, 4100 independent reflections (R_{int} = 0.054), μ = 0.088 mm^{-1}. Structure solution by direct methods, full-matrix least-squares refinement based on 4100 F^2 values and 494 parameters, hydrogen atoms located from difference map and refined as a riding model; all but the hydrogen atoms were refined anisotropically; anisotropic displacement parameters of O(5) and C(8) indicate strong disorder, which could not be resolved. The asymmetric unit was found to contain two independent molecules that are mirror images of one another and thus reflect the 1:1 racemic nature of the sample. However, the space group shows neither mirror nor inversion symmetry elements (MISSYM[12]). Max (Δ.σ) < 0.001, Goof = 1.008, R1 [$I > 2\sigma(I)$] = 0.066, wR2 (all data) = 0.194, min/max. height in final ΔF map −0.26/0.35 e/Å^3. Program used: SHELXTL NT 5.10.[13]

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