Bakers' Yeast Mediated Preparation of Esters of (*R*)- and (*S*)-Ethyl 2-Formyl-3-hydroxy-2-methylpropionate

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In recent years isolated enzymes[1] and microorganisms, bakers' yeast (b.y.) in particular,[2] have been applied widely in the preparation of relatively small, highly functionalized optically active molecules used in organic synthesis as starting materials alternative or complementary to those produced by nature.[3] In this context, we report now on the preparation of compounds **6** and **7**. These are the enantiomeric forms of a chiral C_5 molecule with a C atom directly bound to four C atoms in different oxidation states. The key step in the synthetic sequence for the preparation of these C_5 building blocks is the b.y.-mediated reduction of furanone **1**. These molecules can be regarded as the 2-formyl analogues of methyl (*S*)- and (*R*)-3-hydroxy-2-methylpropionate.[4] The chemical features of **2a** and **3a** outlined in the present note and the simplicity of their preparation from **1** should render the new products here described of interest in the construction of optically active substances bearing a methyl-substituted quaternary chiral center, a topic of current interest.[5]

During recent studies on the synthesis of (*S*)-sotolon [(5*S*)-4,5-dimethyl-3-hydroxy-2(5*H*)-furanone],[6] we submitted to b.y. reduction the 5-methyl analogue of furanone **1**, unexpectedly observing that only one of the two racemic diastereoisomers present in the mixture is transformed, affording the racemic (3*RS*,4*RS*,5*SR*)-carbinol.[7] In an extension of that study we submitted to the action of several microorganisms, including b.y., a collection of substituted furanone derivatives, including furanone **1**. This latter compound, structurally related to ketopantolactone, whose mode of microbial reduction has been carefully investigated,[8] affords in b.y. nearly equal amounts of carbinols **2a** and **3a**, exhibiting 0.99 and 0.82 ee, respectively. This behavior toward b.y. reduction renders furanone **1** and its above-mentioned 5-methyl derivative dramatically different. The elevated enantiomeric purities of these reduction products and the possibility of an easy removal of the C atom at position 2 as a C_1 unit using simple chemical manipulations induced us to verify a conversion of **2a** and **3a** into **6** and **7**. We report now the results obtained.

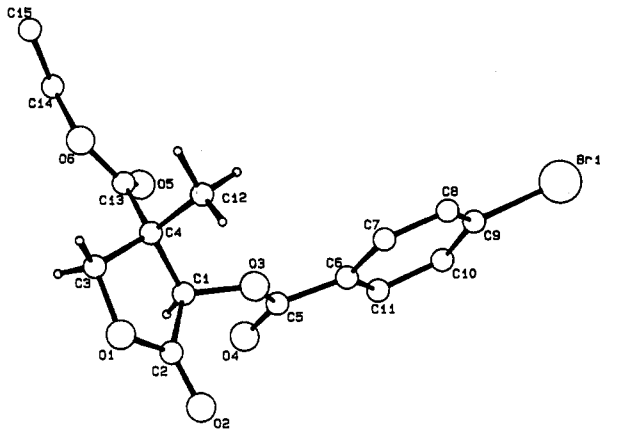

Figure 1. Perspective view of one of the two independent molecules of **2c**, showing crystallographic numbering scheme. The five-membered rings display an envelope conformation with the C(4) atom at the flap position.

Thus, b.y. reduction of **1** at 5 g/L proceeds rapidly. Column chromatography of the crude extract afforded **2a**, not separable from some unreacted **1**, and **3a**. Silylation of the mixture of **1** and **2a** gave protected **2b**. Whereas the enantiomeric composition of yeast-generated carbinols **2a** and **3a** was determined directly on the crude reduction mixture through GLC analysis on chiral capillary column[6] and comparison with racemic materials obtained from **1** by $NaBH_4$ reduction, the assignment of the absolute configuration required a direct proof. This was achieved *via* X-ray diffraction studies on a single crystal of the 4-bromobenzoate ester **2c**, mp 59–60 °C (from hexane or ethanol/water), which indicated (Figure 1) the (3*R*,4*S*) configuration. Once the absolute configuration and enantiomeric purity of yeast-generated **2a** and **3a** were firmly established, conversion into the desired C_5 units **6** and **7** was performed in several ways, differing for the step at which the aldehyde is formed. In the first instance (Scheme 1) **2b** was reduced to the protected carbohydrate **4a**, which turned out to be a mixture of anomers in 75% yields. Deprotection of **4a** afforded, in 85% yield, oily **4b**. The desired (*S*) C_5 chiral synthon was obtained directly from **4b** as formate ester **6a** on periodate cleavage.

The (*R*) enantiomer **7a** was similarly accessible from the oily carbinol **3a** of 0.82 ee. However, the ee value in this instance was enhanced through fractional crystallization of **3b** from pentane. In this series, the intermediates **5a** and **5b** showed $[\alpha]^{20}_D$ +7.9° (*c* 1, EtOH), and +8.6° (1 h) and +23.2° (5 h) (*c* 1, $CHCl_3$), respectively. The above sequences thus led to the desired C_5 synthons with formation of the aldehyde function and formate ester at the latest stage. The presence of two ester moieties in **6a** and **7a** is a drawback from the point of view of the further manipulation of the molecules.

Accordingly, we devised an alternate pathway for converting of **2a** and **3a** into **6** and **7** that allowed discrete protection of the hydroxymethyl group (Scheme 2). Reduction of **4b** afforded triol **8a**, subsequently protected as the 1,3-dioxolane derivative **8b** in 65% overall yield. The eventual hydroxymethyl group of **6** was then selectively protected. In the present instance we prepared the 4-bromobenzoate ester **8c**, mp 65 °C in 78% yield, as a possible precursor to a crystalline C_5 derivative suitable for X-ray analysis. Subsequently, careful acid hydrolysis of **8c** affords *vic*-diol **8d**, still containing the aldehyde

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(2) Servi, S. *Synthesis* **1990**, 1.
(3) Seebach, D.; Kalinowski, H.-O. *Nachr. Chem. Techn.* **1976**, *24*, 415.
(4) Goodhue, Ch. T.; Schaeffer, R. J. *Biotechnol. Bioeng.* **1971**, *13*, 203.
(5) Canet, J.-L.; Fadel, A.; Salaün, J. *J. Org. Chem.* **1992**, *57*, 3463.
(6) Fronza, G.; Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G.; Servi, S. *Tetrahedron Lett.* **1992**, *33*, 5625.
(7) In *Pichia ohmeri* reduction of the same material provides a 6:4 mixture of (3*R*,4*R*,5*S*) and (3*R*,4*S*,5*S*) carbinols, possessing 0.18 and 0.99 ee, respectively (G. Pedrocchi-Fantoni, to be published).
(8) Yamada, H.; Shimizu, S. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 622.

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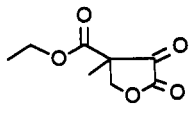
Scheme 1[a]



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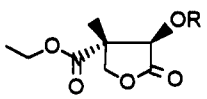
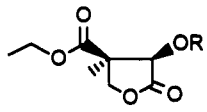
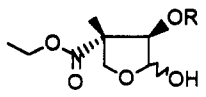


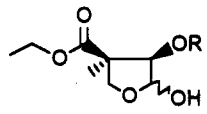
2a R = H
2b R = $Si(CH_3)_2Bu^t$
2c R = 4-BrC_6H_4CO



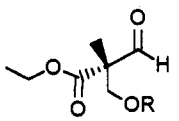
3a R = H
3b R = $Si(CH_3)_2Bu^t$



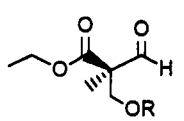
4a R = $Si(CH_3)_2Bu^t$
4b R = H



5a R = $Si(CH_3)_2Bu^t$
5b R = H



6a R = CHO
6b R = 4-BrC_6H_4CO



7a R = CHO
7b R = 4-BrC_6H_4CO

[a] Reagents and conditions: **2a** → **2b**, TBDMSiCl/imidazole, rt; **2a** → **2c**, 4-BrC_6H_4COCl/pyridine, rt; **2b** → **4a**, DIBAL-H, hexane; **4a** → **4b**, Bu_4NF/THF; **4b** → **6a**, HIO_4/THF.

moiety in masked form, in 84% yield. This was revealed by HIO_4 oxidation, which gave **6b**, unexpectedly oily. A similar sequence applied to **5b** yielded **7b**.

Finally, **2a** was submitted to a third kind of degradation, which should allow chemical manipulation of the carboxyethyl moiety eventually incorporated into **6** at early stages, prior to unmasking the other functionalities. To this end, treatment of triol **8a** with dry methanolic hydrochloric acid afforded the dihydroxy lactone **9a** quantitatively. The latter was converted into the 1,3-dioxane **9b** in 68% yield. A variety of chemical modifications can be performed on the lactone functional group of **9b**. Eventually the diol can be restored and in turn converted (*vide supra*) into a formyl, hydroxymethyl analogue of **6**, retaining the modification(s) performed at the lactone moiety.

Experimental Section

Uncorrected melting points were determined on a microstage block. ^1H (250 MHz) and ^{13}C (62.89 MHz) NMR spectra were recorded in $CDCl_3$ solutions at room temperature unless otherwise noted. The chemical shift scale is based on internal TMS. TLC analyses were performed on Merck Kieselgel 60 F_{254} plates. All the chromatographic separations were carried out on silica gel columns.

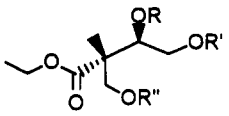
X-ray Crystallography of 2c. $C_{15}H_{15}O_6Br$, M = 371.2, monoclinic, space group $C2$, a = 20.960(7), b = 6.406(1), and c = 25.923(6)Å, β = 110.80(2)°, V = 3254(1) Å^3, λ = 1.54180 Å, Z = 8, D_c = 1.52 g cm^{-3}, $F(000)$ = 1504, μ(Cu Kα) = 36.9 cm^{-1}, room temperature; two crystallographically independent molecules; Philips PW1100 diffractometer, 5991 total reflections ($3 \le \theta \le 54$)° of which 1787 were independent. The structure was solved by the heavy-atom method using the SHELXS-86[9] program. Full matrix least-squares refinement for 250 parameters, with anisotropic O and Br and isotropic C atoms, converged at R = 0.045 and R_w = 0.047 for 4143 observed total reflections ($|F_o| \ge 3\sigma|F_o|$). The ethyl group of molecule A shows disorder about two preferred positions; each of them was refined with a site occupation factor of 0.5. The absolute configuration was determined by the Hamilton's ratio test (probability of error less than 0.5%) and by the Bijovet method on the basis of the most enentiomer-sensitive Friedel pairs. The two antipodal sets of atomic coordinates, individually refined, were used in a structure factor calculation limited to 319 Friedel pairs with $|F_o| \ge 4\sigma|F_o|$; of these 305 were in agreement with the (3*R*,4*S*) enantiomeric assignment. The discrepancy R factor was 0.034 for the (3*R*,4*S*) configuration and 0.058 for the opposite one.

Atomic coordinates and thermal parameters, bond lengths and angles, list of the observed and calculated structure factors and list of the Friedel pairs used for the determination of the absolute configuration have been deposited at the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

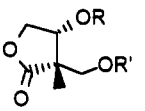
Yeast Transformation of Keto Lactone 1. In a 30-L glass jar a mixture was made up composed of 5 kg of commercial bakers' yeast and 2 kg of D-glucose in 20 L of tap water at 32 °C. As the fermentation started, 50 g of keto lactone 1[10] in 20 mL of ethanol was added under stirring. After 16 h at 23 °C, 2 kg of Celite was added, the reaction mixture was filtered on a large Buchner funnel, the solid pad was washed with 2 L of ethyl acetate, and the filtrate was extracted twice with 2-L portions of ethyl acetate. The dried organic phase was evaporated, leaving a residue of *ca.* 55 g. This material was chromatographed on 400 g of silica gel with hexane–ethyl acetate as eluent (95:5 to 70:30), giving carbinol **2a** in admixture with 20% of keto lactone 1 and carbinol **3a**, 20 g (40%), oil, $[\alpha]^{20}_D$ −2.2° (*c* 2.3, EtOH): ^1H NMR ($CDCl_3$) δ 1.29 (t, 3, J = 6.7 Hz), 1.50 (s, 3), 3.56 (br s, 1), 4.01 (d, 1, J = 9.5 Hz), 4.24 (m, 3), 4.54 (d, 1, J = 9.5 Hz). Anal. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 51.10; H, 6.38. GLC analysis on a chiral column and comparison with the racemic materials obtained from 1 by $NaBH_4$ reduction indicated that products **2a** and **3a** possess 0.99 and 0.88 ee, respectively.

***tert*-Butyldimethylsilyl Ethers 2b and 3b.** The mixture of ketone 1 and carbinol **2a** (20 g), obtained in the chromatography of the yeast extract, in 150 mL of DMF was treated with TBDMSCl (20 g, 133 mmol) and imidazole (13.6 g, 200 mmol) for 16 h at room temperature. The reaction mixture was poured into ice water and extracted with 8:2 CH_2Cl_2–hexane (3 × 120 mL). Column chromatography on silica gel of the residue obtained upon evaporation of the solvent with hexane–ethyl acetate (95:5 to 80:20) gave **2b**, oil, $[\alpha]^{20}_D$ +32.6° (*c* 1.2, EtOH), 20 g (78%): ^1H NMR ($CDCl_3$) δ 0.12 (s, 3), 0.20 (s, 3), 0.91 (s, 9), 1.30 (t, 3, J = 7.0 Hz), 1.36 (s, 3), 4.07 (d, 1, J = 9.0 Hz), 4.22 (q, 2, J = 7.0 Hz), 4.40 (d, 1, J = 9.0 Hz), 4.76 (s, 1). Anal. Calcd for $C_{14}H_{26}O_5Si$: C, 55.60; H, 8.66. Found: C, 55.52; H, 8.73. A similar procedure on **3a** gave rise to **3b**, mp 47 °C (pentane), $[\alpha]^{20}_D$ +22.1° (*c* 1, EtOH): ^1H NMR ($CDCl_3$) δ 0.13 (s, 3), 0.18 (s, 3), 0.88 (s, 9), 1.26 (t, 3, J = 7.0 Hz), 1.40 (s, 3), 3.99 (d, 1, J

Scheme 2[a]



8a R = R' = R'' = H
8b R,R' = $C(CH_3)_2$; R'' = H
8c R,R' = $C(CH_3)_2$; R'' = 4-BrC_6H_4CO
8d R = R' = H; R'' = 4-BrC_6H_4CO



9a R = R' = H
9b R,R' = $C(CH_3)_2$

[a] Reagents and conditions: **4b** → **8a**, NaBH4/EtOH; **8a** → **8b**, $Me_2C(OMe)_2$/TsOH, reflux; **8b** → **8c**, 4-BrC_6H_4COCl/pyridine, rt; **8c** → **8d**, AcOH–THF–water, 1:3:7, rt; **8d** → **6b**, HIO_4/THF; **8a** → **9a**, dry HCl/MeOH; **9a** → **9b**, $Me_2C(OMe)_2$/TsOH, reflux.

(9) Sheldrick, G. M. *Program for the solution of crystal structures*; University of Göttingen: Germany, 1986.
(10) Schinz, H.; Hinder, M. *Helv. Chim. Acta* **1947**, *39*, 1347.

= 9.0 Hz), 4.12 (s, 1), 4.03–4.44 (m, 2), 4.61 (d, 1, J = 9.0 Hz). Anal. Calcd for $C_{14}H_{26}O_5Si$: C, 55.60; H, 8.66. Found: C, 55.68; H, 8.70. Repeated crystallizations from pentane and subsequent hydrolysis gave **3a**, shown by GLC analysis to possess 0.98 ee.

4-Bromobenzoate 2c. The silyl derivative **2b** (3 g, 10 mmol) in THF (50 mL) was treated for 3 h at 23 °C with 20 mL of 1 M $Bu_4N^+F^-$(TBAF) in THF. Most of the solvent was evaporated under vacuum and the residue was partitioned between water and AcOEt (100 mL). The residue obtained upon evaporation of the washed and dried organic phase was chromatographed to give **2a**, oil, 1.5 g (80%), $[\alpha]^{20}_D$ +12.1° (*c* 1.05, $CHCl_3$): ^1H NMR ($CDCl_3$) δ 1.30 (t, 3, J = 7.0 Hz), 1.39 (s, 3), 3.94 (br s, 1), 4.13 (d, 1, J = 9.2 Hz), 4.24 (q, 2, J = 7.0 Hz), 4.42 (d, 1, J = 9.2 Hz), 4.86 (s, 1). Carbinol **2a** (0.94 g, 5 mmol) in 10 mL of dry pyridine was treated for 24 h at room temperature with 4-bromobenzoyl chloride (2.2 g, 10 mmol). The reaction mixture was concentrated under vacuum, and the residue was partitioned between AcOEt and water. The residue obtained upon evaporation of the washed (2 N HCl, 3% $NaHCO_3$, water) and dried (Na_2SO_4) organic phase was crystallized from hexane or ethanol/water to give **2c**, mp 59–60 °C; $[\alpha]^{20}_D$ +33.5° (*c* 1, EtOH): ^1H NMR ($CDCl_3$) δ 1.17 (t, 3, J = 7.0 Hz), 1.49 (s, 3), 4.23 (m, 3), 4.65 (d, 1, J = 9.5 Hz,), 6.13 (s, 1), 7.57–8.00 (m, 4). Anal. Calcd for $C_{15}H_{15}O_6Br$: C, 48.53; H, 4.07. Found: C, 48.49; H, 4.12.

Furanoses 4a, 4b, 5a, and 5b. Lactone **2b** (6 g, 20 mmol) in 50 mL of dry ether was treated under nitrogen at −30 °C with a 1 M solution of DIBAH in hexane (24 mL). After 3 h, the reaction mixture was treated with MeOH (5 mL) and diluted with water (20 mL). The organic extract was chromatographed on silica gel with increasing amounts of ethyl acetate in hexane to give the furanose derivative **4a**, 4.75 g, oil, $[\alpha]^{20}_D$ +1.2° (*c* 1.07, EtOH), in 78% yield. ^1H NMR (mixture of diastereoisomers) ($CDCl_3$+D_2O): major isomer δ 0.10 (s, 3), 0.12 (s, 3), 0.90 (s, 9), 1.26 (s, 3), 1.28 (t, 3, J = 7.1 Hz), 3.71 (d, 1, J = 9.0 Hz), 4.18 (q, 2, J = 7.1 Hz), 4.34 (d, 1, J = 1.0 Hz), 4.40 (d, 1, J = 9.0 Hz), 5.12 (d, 1, J = 1.0 Hz); minor isomer δ 0.137 (s, 3), 0.141 (s, 3), 0.94 (s, 9), 1.24 (s, 3), 1.27 (t, 3, J = 7.1 Hz), 3.73 (d, 1, J = 9.0 Hz), 4.15 (d, 1, J = 9.0 Hz), 4.17 (q, 2, J = 7.1 Hz), 4.54 (d, 1, J = 4.5 Hz), 5.32 (d, 1, J = 4.5 Hz).

Similarly, from **3b** was obtained **5a**, oil, $[\alpha]^{20}_D$ +7.9° (*c* 1, EtOH). ^1H NMR (mixture of diastereoisomers) ($CDCl_3$+D_2O): major isomer δ 0.04 (s, 3), 0.08 (s, 3), 0.83 (s, 9), 1.23 (t, 3, J = 7.0 Hz), 1.42 (s, 3), 3.86 (d, 1, J = 9.0 Hz), 3.97 (d, 1, J = 1.5 Hz), 4.0–4.3 (m, 2), 4.41 (d, 1, J = 9.0 Hz), 5.22 (d, 1, J = 1.5 Hz); minor isomer δ 0.07 (s, 3), 0.08 (s, 3), 0.86 (s, 9), 1.26 (t, 3, J = 7.0 Hz), 1.35 (s, 3), 3.59 (d, 1, J = 9.0 Hz), 3.94 (d, 1, J = 4.5 Hz), 4.0–4.3 (m, 2,), 4.38 (d, 1, J = 9.0 Hz), 5.18 (d, 1, J = 4.5 Hz). Product **4a** (3 g, 10 mmol) in 20 mL of THF was treated for 3 h at 23 °C with 1 M TBAF in THF (12 mL). The reaction mixture was concentrated under vacuum and partitioned between water and AcOEt (100 mL). The organic residue was chromatographed on silica gel with hexane–AcOEt to give **4b**, 1.5 g, oil, $[\alpha]^{20}_D$ +45.4° (1 h), +50.7° (5 h) (*c* 1, $CHCl_3$): ^1H NMR ($CDCl_3$ + D_2O) major isomer δ 1.28 (t, 3, J = 7.0 Hz), 1.36 (s, 3), 3.84 (d, 1, J = 9.0 Hz), 4.14–4.25 (m, 3), 4.51 (d, 1, J = 4.5 Hz), 5.46 (d, 1, J = 4.5 Hz); minor isomer δ 1.29 (t, 3, J = 7.0 Hz), 1.36 (s, 3), 3.76 (d, 1, J = 9.0 Hz), 4.17 (q, 2, J = 7.0 Hz), 4.40 (d, 1, J = 2.0 Hz), 4.45 (d, 1, J = 9.0 Hz), 5.26 (d, 1, J = 2.0 Hz). Anal. Calcd for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.48; H, 7.52. In an analogous way, from **5a** was obtained **5b**, oil, $[\alpha]^{20}_D$ +8.6° (1 h) and +23.2° (5 h) (*c* 1, $CHCl_3$): ^1H NMR ($CDCl_3$ + D_2O) major isomer δ 1.30 (t, 3, J = 7.0 Hz), 1.30 (s, 3), 3.64 (d, 1, J = 9.0 Hz), 3.99 (d, 1, J = 4.0 Hz), 4.23 (q, 2, J = 7.0 Hz), 4.33 (d, 1, J = 9.0 Hz), 5.38 (d, 1, J = 4.0 Hz). Anal. Calcd for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.57; H, 7.48.

Formate Ester of (*S*)- and (*R*)-Ethyl 2-Formyl-3-hydroxy-2-methylpropionate (6a and 7a). Furanose **4b** (1.9 g, 10 mmol) in 10 mL of THF was treated under stirring, at once, with H_5IO_6 (2.28 g, 10 mmol) in 15 mL of THF. After 10 min, a few drops of 1,2-ethanediol were added, and the reaction mixture was filtered, concentrated under vacuum, and partioned between water and AcOEt (100 mL). Silica gel column chromatography of the organic residue afforded **6a**, 1.3 g, oil, $[\alpha]^{20}_D$ −14.7° (*c* 1, $CHCl_3$), in 70% yield. ^1H NMR ($CDCl_3$): δ 1.29 (t, 3, J = 7.1 Hz), 1.40 (s, 3), 4.26 (q, 2, J = 7.1 Hz), 4.45 (dd, 1, J = 11.2 and 1.0 Hz), 4.57 (dd, 1, J = 11.2 and 1.0 Hz), 8.01 (t, 1, J = 1.0 Hz), 9.75 (s, 1). ^{13}C NMR ($CDCl_3$): δ 14.03 (CH_3), 15.62 (CH_3CH_2O), 57.19 (CH_3C), 62.11 (*C*HH'O), 64.14 (CH_3CH_2O), 159.99 (*H*COO), 169.76 (*C*OOCH$_2$), 196.75 (*H*CO). Anal. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 51.13; H, 6.39. In similar way, from **5b** was obtained **7a**, identical in every respect to **6a**, but showing $[\alpha]^{20}_D$ +13.95° (*c* 1.07, $CHCl_3$).

4-Bromobenzoate of (2*S*,3*R*)-Ethyl 2-Methyl-2-(hydroxymethyl)-3,4-(isopropylidenedioxy)butyrate (8d). To 50 mL of an ethanolic solution of **4b** (5.7 g, 30 mmol) was added portionwise under stirring at 0 °C 2 g of $NaBH_4$. After 2 h the reaction mixture was concentrated under vacuum and partitioned between water and AcOEt. The crude organic residue, *ca.* 5.2 g, was treated at reflux with 2,2-dimethoxypropane (30 mL) and toluene-4-sulfonic acid monohydrate (1 g) for 5 h. The reaction mixture was diluted with ethyl acetate, washed with $NaHCO_3$ solution, evaporated, and chromatographed to give dioxolane **8b**, 4.5 g (65% overall), oil, $[\alpha]^{20}_D$ −4.3° (*c* 1, EtOH): ^1H NMR ($CDCl_3$) δ 1.24 (s, 3), 1.28 (t, 3, J = 7.1 Hz), 1.35 (s, 3), 1.43 (s, 3), 2.55 (t, 1, J = 7.0 Hz), 3.66 (dd, 1, J = 11.5 and 7.0 Hz), 3.69 (dd, 1, $J_{H\text{-}H'}$ = 11.5 and 7.0 Hz), 4.05 (d, 2 J = 6.5 Hz), 4.20 (q, 2, J = 7.1 Hz), 4.31 (t, 1, J = 6.5 Hz). Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.77; H, 8.60. Product **8b** (4.65 g, 20 mmol) in 20 mL of dry pyridine was reacted overnight at room temperature with 4-bromobenzoyl chloride (5.25 g, 24 mmol). The reaction mixture was poured into ice water, extracted with AcOEt (3 × 100 mL), and washed with water, dilute HCl, and $NaHCO_3$. The residue obtained upon evaporation of the solvent separated, from hot hexane, **8c**, mp 65 °C, 6.5 g (78%), $[\alpha]^{20}_D$ −11.2° (*c* 1.3, EtOH): ^1H NMR ($CDCl_3$) δ 1.23 (t, 3, J = 7.0 Hz), 1.33 (s, 3), 1.35 (s, 3), 1.40 (s, 3), 4.05 (dd, 1, J = 9.0 and 6.5 Hz), 4.09 (dd, 1, J = 9.0 and 6.5 Hz), 4.19 (q, 2, J = 7.0 Hz), 4.37 (t, 1, J = 6.5 Hz), 4.39 (d, 1, J = 11.5 Hz), 4.59 (d, 1, J = 11.5 Hz), 7.51–7.65 (m, 4). Anal. Calcd for $C_{18}H_{23}O_6Br$: C, 52.05; H, 5.58. Found: C, 52.10; H, 5.53. The 1,3-dioxolane **8c** (4.15 g, 10 mmol) was stirred overnight in AcOH–THF–water 1:3:7 (100 mL) to give, after extractive workup, diol **8d**, mp 56–58 °C (from hexane–AcOEt), 3.15 g (84%), $[\alpha]^{20}_D$ −12.6° (*c* 1.1, EtOH): ^1H NMR ($CDCl_3$) δ 1.26 (t, 3, J = 7.1 Hz), 1.32 (s, 3), 2.46 (br s, 1), 3.46 (br d, 1, J = 5.5 Hz), 3.68 (dd, 1, J = 7.0 and 11.0 Hz), 3.79 (dd, 1, J = 3.5 and 11.0 Hz), 3.96 (m, 1), 4.21 (q, 2, J = 7.1 Hz), 4.54 (s, 2), 7.52–7.63 (m, 4). Anal. Calcd for $C_{15}H_{19}O_6Br$: C, 48.01; H, 5.10. Found: C, 48.07; H, 5.14.

Aldehydes 6b and 7b. Diol **8d** (2.25 g, 6 mmol) in THF (15 mL) was treated for 10 min with H_5IO_6 (1.5 g, 6.6 mmol) in THF (10 mL) under stirring. After addition of one drop of 1,2-ethanediol, the filtered solution was concentrated and partitioned between water and AcOEt (100 mL). The residue obtained upon evaporation of the organic phase was chromatographed on SiO_2 with hexane–AcOEt to give aldehyde **6b**, 1.7 g (83%), oil, $[\alpha]^{20}_D$ −7.45° (*c* 1.2, EtOH): ^1H NMR ($CDCl_3$) δ 1.26 (t, 3, J = 7.1 Hz), 1.45 (s, 3), 4.26 (q, 2, J = 7.0 Hz), 4.59 (d, 1, J = 11.0 Hz) 4.70 (d, 1, J = 11.0 Hz), 7.52–7.88 (m, 4), 9.83 (s, 1). Anal. Calcd for $C_{14}H_{15}O_5Br$: C, 48.99; H, 4.40. Found: C, 48.94; H, 4.37. In a similar way, from **5b** was obtained **7b**, $[\alpha]^{20}_D$ +7.34 (*c* 1, EtOH).

1,3-Dioxane 9b. Triol **8a** (5.76 g, 30 mmol) was treated overnight with *ca.* 3% methanolic dry HCl (50 mL). The reaction mixture was concentrated to a small volume and partitioned between AcOEt and $NaHCO_3$ solution to give **9a**, 4.35 g (99%), oil, $[\alpha]^{20}_D$ +45.5° (*c* 1, EtOH): ^1H NMR ($CDCl_3$ + D_2O) δ 1.17 (s, 3), 3.61 (d, 1, J = 10.0 Hz), 3.82 (d, 1, J = 10.0 Hz), 4.06 (dd, 1, J = 9.5 and 7.5 Hz), 4.50 (dd, 1, J = 9.5 and 7.5 Hz), 4.70 (t, 1, J = 7.5 Hz). Anal. Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.37; H, 6.85. Dihydroxy lactone **9a** (2.92 g, 20 mmol) was refluxed for 12 h in 2,2-dimethoxypropane (30 mL) in the presence of toluene-4-sulfonic acid (1 g). The concentrated solution was diluted with AcOEt (100 mL) and washed with $NaHCO_3$. The organic residue was chromatographed on SiO_2 with hexane–AcOEt to give **9b**, 2.53 g (68%), oil, $[\alpha]^{20}_D$ +64° (*c* 1, EtOH): ^1H NMR ($CDCl_3$ + D_2O) δ 1.12 (s, 3), 1.30 (s, 3), 1.42 (s, 3), 3.32 (d, 1, J = 9.5 Hz), 3.63 (d, 1, J = 9.5 Hz), 3.91(t, 1, J = 9.5 Hz), 4.40 (dd, 1, J = 9.5 and 8.9 Hz), 4.96 (dd, 1, J = 9.5 and 8.9 Hz). Anal. Calcd for $C_9H_{14}O_4$; C, 58.05; H, 7.58. Found: C, 58.09; H, 7.62.

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