JOC*Note*

pubs.acs.org/joc

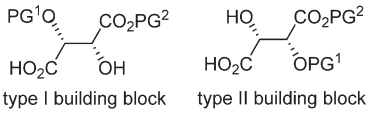
Total Regioselective Control of Tartaric Acid

Jan Spengler,*[,†,‡] Ana I. Fernández-Llamazares,[†,‡] Javier Ruiz-Rodríguez,[†,‡] Klaus Burger,[§] and Fernando Albericio*[,†,‡,⊥]

[†]*Institute for Research in Biomedicine, Barcelona Science Park, Baldiri Reixac 10, 08028-Barcelona, Spain,* [‡]*CIBER-BBN, Networking Centre on Bioengineering, Biomaterials and Nanomedicine, Barcelona Science Park, Baldiri Reixac 10, 08028-Barcelona, Spain,* [§]*Institut für Organische Chemie, Universität Leipzig, Johannisallee 29, D-04103 Leipzig, Germany, and* [⊥]*Department of Organic Chemistry, University of Barcelona, Martí i Franqués 1-11, 08028-Barcelona, Spain*

jan.spengler@irbbarcelona.org; fernando.albericio@irbbarcelona.org

Received May 27, 2010



PG[1]: Bzl, *p*-nitrobenzyl, *p*-methoxybenzyl
PG[2]: Me, allyl, *tert*-butyl

An efficient strategy to synthesize tartaric acid building blocks for totally regioselective transformations or derivatizations was disclosed. Starting from L-tartaric acid or L-dimethyl tartrate, respectively, we obtained type I and II building blocks with orthogonal sets of protecing groups (4−8 steps, 38−56% overall yield).

Although tartaric acid is a structurally simple molecule, it is a key chiral pool compound in organic chemistry. It is a very useful starting material for the total synthesis of natural and non-natural products, and it also serves as a core for chirality-inducing ligands.[1] The use of tartaric acid as a chiral building block often requires the appropriate differentiation between the functional groups present in its structure. The distinction between the two pairs of hydroxy and carboxy groups is easy to accomplish. These functionalities can be efficiently monoderivatized by several methods.[2]

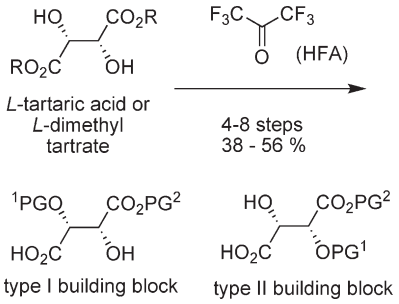


FIGURE 1. Totally regioselective controlled tartaric acid building blocks I and II.

However, what still remains a challenge is the independent modification of the carboxy and the hydroxy group in a regioselective manner, which is crucial for the synthesis of certain products. The strategies reported to date require extensive preparative work, considerable study of reaction conditions, structural assignments, and sometimes cumbersome or impossible separations between regioisomers. For example, the totally regioselective synthesis of tartaric acid derivatives bearing four distinct substituents on the hydroxy and carboxy function requires 12 steps starting from 2-hydroxy-2-(4-[1,3]dioxolanyl)acetate, a building block that is accessible from ascorbic acid in three steps.[3] Apparently, more straightforward is the monosaponification of monoethers of dialkyl tartrates with potassium carbonate or,[4a] alternatively, with pig liver esterase, which has the advantage of providing higher regioselectivity.[4b,c] However, in both cases, the separation of the desired product from the undesired regioisomers and the totally saponified compounds may be difficult to achieve. A few examples of total differentiation have been achieved during the course of multistep syntheses.[5]

While working on the synthesis of anticancer depsipeptides containing tartaric acid as the core unit, we found it highly desirable to develop a general and flexible synthetic route to tartaric acid building blocks of type I and II, in which all four functionalities are differentiated by orthogonal protecting groups. Here we disclose an efficient strategy to synthesize such tartaric acid derivatives on a multigram scale (4−8 steps starting from L-tartaric acid or L-dimethyl tartrate, respectively, with overall yields between 38 and 56%; Figure 1).

Hexafluoroacetone (HFA) is a bidentate protecting/activating reagent with several applications in the chemistry

(1) Comprehensive reviews of applications in organic synthesis: (a) Coppola, G. M.; Schuster, H. F. *Chiral α-Hydroxy Acids in Enantioselective Synthesis*; Wiley-VCH: Weinheim, Germany, 1997. (b) Gawronski, J.; Gawronska, K. *Tartaric and Malic Acids in Synthesis: A Source Book of Building Blocks, Ligands, Auxiliaries, and Resolving Agents*; John Wiley: New York, 1999. Source for chiral auxiliaries: (c) Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem.* **2001**, *113*, 96; *Angew. Chem., Int. Ed.* **2001**, *40*, 92. (d) Dieguez, M.; Pamies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189.

(2) Some representative routes not discussed in ref 1: (a) Gonzalez, S. V.; Carlsen, P. *Eur. J. Org. Chem.* **2007**, *21*, 3495. (b) McNulty, J.; Mao, J. *Tetrahedron Lett.* **2002**, *43*, 3857.

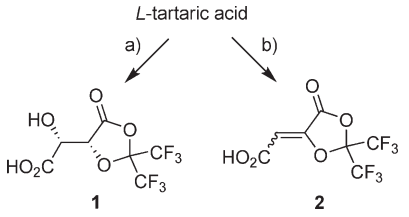
(3) (a) Usui, H.; Kagechika, K.; Nagashima, H. European Patent Application EP0949238, 1999. (b) Wei, C. C.; De Bernardo, S.; Tengi, J. P.; Borgese, J.; Weigele, M. *J. Org. Chem.* **1985**, *50*, 3462.

(4) (a) Barton, D. H. R.; Cleophax, J.; Gateau-Olesker, A.; Gero, S. D.; Tachdjian, C. *Tetrahedron* **1993**, *49*, 8381. (b) Gateau-Olesker, A.; Cleophax, J.; Gero, S. D. *Tetrahedron Lett.* **1986**, *27*, 41. (c) Siddiqui, M. A.; Mansoor, U. F.; Reddy, P. A.; Madison, V. S. US Patent Application 2007/0167426, 2007.

(5) (a) Tartaric acid monohydroxamates can be regioselectively O-monosilylated to give the α- or β-hydroxyhydroxamates, depending on the reaction conditions: Kolasa, T.; Miller, M. J. *Tetrahedron* **1989**, *45*, 3071. (b) O-Monobenzylated *tert*-butyl tartrate can be regioselectively reduced with $LiBH_4$ to a 1,3-diol: Nakamura, S.; Hirata, Y.; Kurosaki, T.; Anada, M.; Kataoka, O.; Kitagaki, S.; Hashimoto, S. *Angew. Chem.* **2003**, *115*, 5509; *Angew. Chem., Int. Ed.* **2003**, *42*, 5351.

Published on Web 07/26/2010 DOI: 10.1021/jo101001s

SCHEME 1. Reaction of Tartaric Acid with Hexafluoroacetone (HFA)[a]



[a]Conditions: (a) ≤3 equiv of HFA, DMSO, 4 days, 64%; (b) ≥4 equiv of HFA, DMSO, 15 h, 64%.

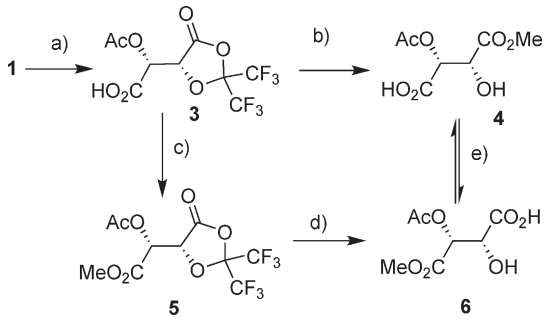
of α-hydroxy acids.[6] HFA reacts with α-hydroxy acids to give five-membered lactones (2,2-bistrifluoromethyl-1,3-dioxolan-4-ones). This reaction also proceeds regioselectively when more carboxy groups are present in the molecule (e.g., in malic acid). In a previous report, structure **1** was proposed as the reaction product of tartaric acid and HFA.[7] To the best of our knowledge, this is the only chemical reaction in which a total differentiation of all four functional groups of tartaric acid can be achieved in one step. Therefore, we considered the dioxolane **1** an ideal key intermediate for the concise preparation of type I and II building blocks (Scheme 1).

First, we had to make a considerable effort to obtain **1** in a reproducible way. We found that the product is contaminated with the inseparable *β*-elimination product **2** in variable amounts. A more detailed examination of the reaction conditions revealed that both the amount of HFA and the reaction time are crucial factors. The best results were obtained when no more than 3 equiv of gaseous HFA was absorbed by a stirred solution of tartaric acid in DMSO. In the reaction mixture, **1**, unreacted tartaric acid and one major intermediate were detected by ^{1}H and ^{19}F NMR spectroscopy (see Experimental Section). When the reaction mixture was allowed to react in a sealed flask for 4 days, the intermediate disappeared to give **1**, which was isolated by extraction in up to 64% yield (depending on the amount HFA added). However, when more than 4 equiv of HFA was added, only **2** was formed.[8]

Next, we envisaged the introduction of conventional protecting groups into **1** in order to obtain building blocks of type I and II. Nucleophilic ring opening of the dioxolane proceeds with concomitant deprotection of the adjacent hydroxy group.[6] Therefore, to maintain the differentiation of the two hydroxy groups, the free hydroxy group in **1** requires protection before nucleophilic ring opening of the dioxolane. Initially, acetyl was chosen as the OH protecting group because the acetylation of **1** was found to proceed smoothly. The resulting lactone **3** was reacted with methanol to give the methyl ester **4** in excellent yield. The structure of **4**, a type I building block, was confirmed by X-ray spectroscopy (see Supporting Information).[9]

The type II building block **6** was prepared by esterification of the free carboxy group of **3** and subsequent hydrolysis of the lactone **5**. However, **4** and **6** were found to slowly interconvert in aq $NaHCO_3$ solution (^{1}H NMR spectroscopy). Such base-promoted acyl migration[10] is well-known in carbohydrate chemistry and limits the utility of **4** and **6** as totally differentiated tartaric acid building blocks (Scheme 2).

SCHEME 2. Synthesis of *O*-Acetyl/Methyl-Ester-Protected Building Blocks 4 and 6[a]



[a]Conditions: (a) AcCl, 15 h, 84%; (b) MeOH/DCM, 15 h, 90%; (c) CH_2N_2 in Et_2O, 15 min, 88%; (d) H_2O/2-PrOH, 15 h, 79%; (e) in aq $NaHCO_3$ at rt, the equilibrium of 2:1 (**4**/**6**) is reached after 3 days.

Consequently, the choice of an OH protecting group that does not migrate is mandatory. Silyl ether migration has been reported for tartaric acid derivatives.[5a] Benzyl ethers are not prone to migration and can be cleaved with a broad range of conditions orthogonally to those for the deprotection of methyl esters.[11] Given that the dioxolane **1** decomposes in the presence of bases, the benzylation of **1** was found not to be feasible, and consequently, we changed the strategy. Thus, the monobenzyl (Bzl), *p*-nitrobenzyl (Pnb), and *p*-methoxybenzyl (Mob) ethers of dimethyltartrate (**7a**−**c**) were prepared via a stannylene acetal following efficient protocols cited in the literature.[12] After saponification of **7a**−**c** to the free acids (**8a**−**c**), the differentiation between the carboxylic groups was achieved by reaction with HFA (**8a**−**c** to **9a**−**c**). These reactions required less time than that required for the synthesis of **1** (typically overnight), and no *β*-elimination was observed.[13] Methanolysis of **9a**−**c** (same conditions as for **3** to **4**) enabled us to obtain the first set of type I building blocks **10a**−**c** with variable O-protection. The set of type II building blocks **12a**−**c** was prepared via the methyl esters **11a**−**c** (Scheme 3).

To introduce further dimensions of orthogonality, building blocks with allyl and *tert*-butyl-ester-protected carboxyl groups were prepared by modified protocols. The allyl ester **13** was obtained by nucleophilic ring opening of the dioxolane **9c** with allyl alcohol. In contrast to the methanolysis, this reaction required heating. To synthesize the regioisomer **15**, the carboxy group of **9c** was activated as acid chloride,

(6) Spengler, J.; Boettcher, C.; Albericio, F.; Burger, K. *Chem. Rev.* **2006**, *106*, 4728.

(7) Weygand, F.; Burger, K. *Chem. Ber.* **1966**, *99*, 2880.

(8) Compound **2** is under current investigation as building block for α-oxo acids.

(9) A sample of *rac*-**4**, prepared from racemic tartaric acid, could be crystallyzed from $CHCl_3$. Crystal data: see Supporting Information.

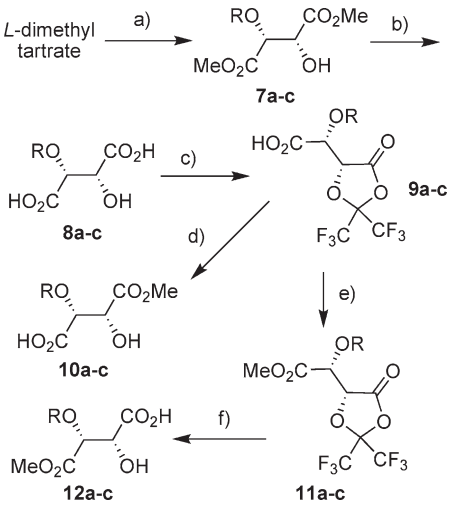
(10) Roslund, M. U.; Aitio, O.; Warna, J.; Maaheimo, H.; Murzin, D. Y.; Leino, R. *J. Am. Chem. Soc.* **2008**, *130*, 8769. Encouraged by the reported observation that pivaloyl migration takes places considerably more slowly than acetyl migration, we also prepared the pivaloyl analogues. However, migration in aqueous $NaHCO_3$ was also observed in this case.

(11) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley: New York, 1999.

(12) (a) Nagashima, N.; Ohno, M. *Chem. Lett.* **1987**, 141. (b) Nagashima, N.; Ohno, M. *Chem. Pharm. Bull.* **1991**, *39*, 1972. (c) The protocol used here was adapted from ref 5b.

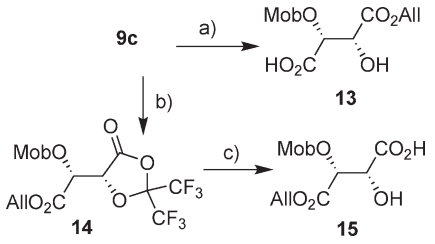
(13) The formation of six-membered rings, which could give undesired regioisomers, was not observed, and it is known that their formation requires special conditions: Spengler, J.; Ruiz-Rodriguez, J.; Yraola, F.; Royo, M.; Winter, M.; Burger, K.; Albericio, F. *J. Org. Chem.* **2008**, *73*, 2311.

SCHEME 3. Synthesis of *O*-Benzyl/Methyl-Ester-Protected Building Blocks 10a−c and 12a−c (7−12a, R = Bzl; 7−12b, R = Pnb; 7−12c, R = Mob)[a]



[a]Conditions: (a) $SnOBu_2$, toluene, reflux, 2 h, then CsF, benzylbromide, DMF, 10 h, 80−96%; (b) LiOH, H_2O/dioxane, 1 h, 77−89%; (c) HFA, DMSO, 15 h, 83−98%; (d) MeOH/DCM, 15 h, 81−98%; (e) CH_2N_2 in Et_2O, 15 min, 81−95%; (f) H_2O/2-PrOH, 15 h, 83−100%.

SCHEME 4. Synthesis of *O*-Benzyl/Allyl-Ester-Protected Building Blocks 13 and 15[a]

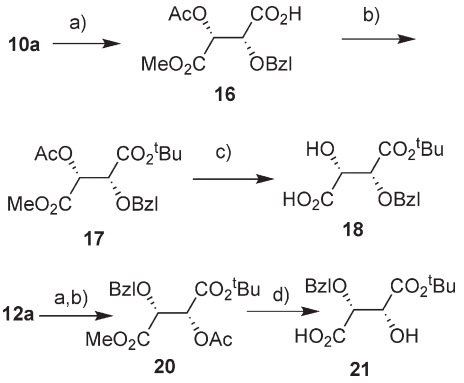


[a]Conditions: (a) allyl−OH/DCM, rt → reflux, 15 h, 93%; (b) $(COCl)_2$, 15 min, then allyl−OH/Et_2O, 4 h, 95%; (c) H_2O/2-PrOH, 15 h, 97%.

which quickly reacted with allyl alcohol at room temperature, affording the ester **14**. Finally, **15** was obtained by hydrolysis of **14** (Scheme 4).

The *tert*-butyl esters **18** and **21** were more difficult to obtain. All of our initial attempts at esterification and nucleophilic ring opening of the dioxolanes **9a−c** with *tert*-butyl alcohol failed. Thus, the methyl esters **10a** and **12a** were, respectively, chosen as an alternative starting point. After acetylating the hydroxy group in both **10a** and **12a**, treatment of the resulting **16** and **19** with *tert*-butyl bromide under phase transfer conditions allowed us to form the *tert*-butyl esters **17** and **20**. The methyl ester and the acetate were then hydrolyzed in one step to give **18** and **21**, respectively. We found that lithium hydroxide in aqueous dioxane promotes the hydrolysis of **17**, yielding **18** exclusively; however, in the case of **20**, considerable amounts of the β-elimination product were formed under the same conditions. We assume that the neighboring CH proton in **17** is protected toward base-mediated abstraction as a result of the steric demand of the adjacent *tert*-butyl group, which hinders elimination. In contrast, acetate hydrolysis becomes more difficult in **20** and, for the same reason, elimination takes place. Elimination was completely

SCHEME 5. Synthesis of *O*-Benzyl/*tert*-Butyl-Ester-Protected Building Blocks 18 and 21[a]



[a]Conditions: (a) AcCl, cat. DMAP, 2 h, 94−96%; (b) ^{t}BuBr, TBACl/DMA, K_2CO_3, 55 °C, 24 h, 80−87%; (c) LiOH, H_2O/dioxane, 2 h, 94%; (d) LiOOH, H_2O/dioxane, 0 °C → rt, 17 h, 97%.

suppressed by using the less basic lithium hydroperoxide instead (Scheme 5).[14]

All of these transformations were robust and proceeded with good overall yields, thus making type I and II building blocks valuable as starting materials for synthesis. These tartaric acid derivatives may contribute to significantly speed up the syntheses of products in which all four functional groups of tartaric acid have to be differentiated. Moreover, the use of these building blocks in some established synthetic routes should now make it possible to obtain products with additional points for structural modification.

Experimental Section

General Procedure A: Reaction of Tartaric Acid and Derivatives with Hexafluoroacetone. ***Caution:*** *Hexafluoroacetone is a toxic gas. All operations must be performed in a well-ventilated fume hood with proper protection of skin and eyes.* A solution of L-tartaric acid or derivative (15−70 mmol, as indicated) in DMSO was stirred in a 250 mL flask equipped with a dry ice condenser and bubbler. The atmosphere in the apparatus was replaced with typically 3 equiv (if not otherwise specified) of hexafluoroacetone gas and stirred for 15 h (if not otherwise indicated). Then, a cold saturated solution of NaCl in water (50−120 mL, prepared by mixing of crushed ice and NaCl) was added to the solution, and it was stirred for 5 min. It was extracted with diethyl ether (3 × 50 mL), and the pooled organic layer was washed with brine and dried over $MgSO_4$. After filtration and evaporation of most of the solvent, it was heated under vacuum (membrane pump) to 50 °C for approximately 30 min in order to remove remaining volatiles from the product.

(2*R*)-(Hydroxy)-{(4*R*)-5-oxo-2,2-bistrifluoromethyl-[1,3]dioxolan-4-yl}acetic acid (1). Compound **1** was prepared following the general procedure A from L-tartaric acid (10.7 g, 71.3 mmol) in DMSO (40 mL) and hexafluoroacetone (3 equiv, 35 g, 210 mmol; added in 5 h). The formation of an intermediate product, which slowly converts into the product, was observed in the reaction mixture. NMR spectra of the reaction mixture after 48 h: ^{1}H NMR (acetone-d_6) δ = 2.59 (s, DMSO, major signal), 4.48 (s, 4.8H, tartaric acid), 4.59 (d, J = 3.0 Hz, 1H, intermediate), 4.71 (d, J = 1.7 Hz, 1.5H, **1**), 4.98 (d, J = 3.0 Hz, 1H, intermediate), 5.53 (m, 1.5H, **1**) ppm; ^{19}F NMR (acetone-d_6) δ = −83.0 (s, 16F, signal HFA*H_2O), −82.31 (q, J = 8.3 Hz,

(14) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

1.6F, **1**), −80.92 (q, J = 8.77 Hz, 1F, intermediate), −80.48 (m, 2.6F, intermediate and **1**) ppm. It was stirred until the intermediate product has converted into product (~4 days). After addition of the NaCl solution, the product was extracted with diethyl ether (4 × 100 mL) and washed with brine (4 × 50 mL) to give 13.6 g (64%) of **1** as white crystalline mass: mp 162−163 °C (recrystallized from $CHCl_3$); ^{1}H NMR (acetone-d_6) δ = 4.82 (d, J = 1.7 Hz, 1H), 5.58 (m, 1H) ppm; ^{13}C NMR (acetone-d_6) δ = 70.7, 79.3, 99.2 (m), 120.8 (q, J = 286 Hz), 121.9 (q, J = 288 Hz), 167.1, 171.7 ppm; ^{19}F NMR (acetone-d_6) δ = −82.31 (q, J = 8.3 Hz, 3F), −80.56 (q, J = 8.3 Hz, 3F) ppm; IR (KBr) ν = 1866, 1841, 1760, 1752, 981 cm^{-1}; $[\alpha]^{20}_D$ +51.5 (c 2.0, acetone); HRMS (ES^-) calcd for $[C_7H_4F_6O_6 - H]^-$ 296.9834, found 296.9830.

(5-Oxo-2,2-bistrifluoromethyl[1,3]dioxolan-4-ylidene)acetic acid (2). Compound **2** was prepared following the general procedure A from L-tartaric acid (4.9 g, 32.6 mmol) in DMSO (20 mL) and hexafluoroacetone (4.3 equiv, 23 g, 140 mmol; added in 1 h). A slight exothermic reaction was observed. It was stirred for 15 h. After addition of the NaCl solution, precipitated product was filtered off and dried in air to give 5.89 g (64%) of crystalline **2**: mp 125 °C; ^{1}H NMR (acetone-d_6) δ = 6.34 (s) ppm; ^{13}C NMR (acetone-d_6) δ = 99.4 (m), 107.0, 120.5 (q, J = 288 Hz), 142.2, 159.1, 163.7 ppm; ^{19}F NMR (acetone-d_6) δ = −81.92 (s) ppm; IR (KBr) ν = 1847, 1726, 1688, 1443, 990 cm^{-1}; HRMS (ES^-) calcd for $[C_7H_2F_6O_5 - H]^-$ 278.9728, found 278.9731.

(2*R*)-Benzyloxy-{(4*R*)-5-oxo-2,2-bistrifluoromethyl[1,3]dioxolan-4-yl}acetic acid (9a). Following the general procedure A with **8a** (1.61 g, 6.72 mmol) in DMSO (20 mL) and hexafluoroacetone (added in 1.5 h), **9a** (2.19 g, 83%) was obtained as viscous oil: ^{1}H NMR ($CDCl_3$) δ = 4.44 (d, J = 2.1 Hz, 1H), 4.61 (d, J = 11.2 Hz, 1H), 4.87 (d, J = 11.2 Hz, 1H), 5.13 (d, J = 1.9 Hz, 1H), 7.35 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) δ = 74.4, 74.5, 76.4, 97.9 (m), 118.4 (q, J = 287 Hz), 119.7 (q, J = 289 Hz), 128.3, 128.5, 128.5, 135.3, 164.9, 171.9 ppm; ^{19}F NMR ($CDCl_3$) δ = −81.4 (q, J = 8.1 Hz), −79.8 (q, J = 8.0 Hz) ppm; IR (film) ν = 1849, 1737, 1319, 1241, 1132, 983 cm^{-1}; $[\alpha]^{20}_D$ +68.6 (c 2.5, $CHCl_3$); HRMS (ES^-) calcd for $[C_{14}H_{10}F_6O_6 - H]^-$ 387.0303, found 387.0296.

(2*R*)-(4-Nitrobenzyloxy)-{(4*R*)-5-oxo-2,2-bistrifluoromethyl-[1,3]dioxolan-4-yl}acetic acid (9b). Following the general procedure A with **8b** (4.07 g, 14.26 mmol) in DMSO (25 mL) and hexafluoroacetone (added in 1.5 h), **9b** (6.0 g, 98%) was obtained as dense oil: ^{1}H NMR ($CDCl_3$) δ = 4.52 (d, J = 2.0 Hz, 1H), 4.67 (d, J = 11.9 Hz, 1H), 5.01 (d, J = 11.9 Hz, 1H), 5.21 (d, J = 1.7 Hz, 1H), 7.48 (d, J = 8.6 Hz, 2H), 8.22 (d, J = 8.7 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ = 73.1, 75.4, 76.3, 97.9 (m), 116.1 (m), 121.9 (m), 123.7, 128.2, 143.0, 147.8, 164.8, 171.5 ppm; ^{19}F NMR ($CDCl_3$) δ = −81.3 (q, J = 7.9 Hz), −79.8 (q, J = 8.0 Hz) ppm; IR (film) ν = 1842, 1738, 1524, 1239, 1131, 983 cm^{-1}; $[\alpha]^{20}_D$ +52.3 (c 2.0, $CHCl_3$); HRMS (ES^-) calcd for $[C_{14}H_9F_6NO_8 - H]^-$ 432.0154, found 432.0166.

(2*R*)-(4-Methoxybenzyloxy)-{(4*R*)-5-oxo-2,2-bistrifluoromethyl-[1,3]dioxolan-4-yl}acetic acid (9c). The general procedure A was followed with **8c** (6.93 g, 25.65 mmol) in DMSO (60 mL) and hexafluoroacetone (added in 2 h). After addition of the NaCl solution, the product was extracted with DCM (3 × 100 mL) and then the pooled organic layer was washed with brine (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. After evaporation of most of the solvent, the residue was purified by flash chromatography with hexanes/AcOEt/AcOH 2:1:0.1 (R_f = 0.40, UV) to give 10.7 g (98%) **9c** as dense oil: ^{1}H NMR ($CDCl_3$) δ = 3.81 (s, 3H), 4.40 (d, J = 2.1 Hz, 1H), 4.54 (d, J = 11.1 Hz, 1H), 4.80 (d, J = 11.1 Hz, 1H), 5.12 (d, J = 1.9 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H), 9.61 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ = 55.2, 73.9, 74.0, 76.5, 97.9 (m), 113.9, 118.4 (q, J = 287.0 Hz), 119.7 (q, J = 288.9 Hz), 127.5, 130.1, 159.8, 165.0, 172.7 ppm; ^{19}F NMR ($CDCl_3$) δ = −81.4 (q, J = 8.1 Hz, 3F), −79.8 (q, J = 8.0 Hz, 3F) ppm; IR (film) ν = 2942. 1857, 1740, 1516, 1320, 1242, 1132, 983, 721 cm^{-1}; $[\alpha]^{20}_D$ +22.9 (c 2.0, $CHCl_3$); HRMS (ES^-) calcd for $[C_{15}H_{12}F_6O_7 - H]^-$ 417.0409, found 417.0403.

Acknowledgment. This work was partially supported by CICYT (CTQ2009-07758 and CTQ2008-02856/BQU), the Generalitat de Catalunya (2009SGR 1024, 2009SGR-1472) and the IRB. We thank the Barcelona Science Park (Mass Spectrometry Core Facility, Nuclear Magnetic Resonance Laboratory) and the Universitat de Barcelona (Xavier Alcobé, Mercè Font, Unitat de Difracció de Raigs X Serveis Cientificotècnics) for the facilities.

Supporting Information Available: Full experimental details for the preparation of all other compounds, together with copies of ^{1}H and ^{13}C NMR spectra of compounds **1**−**6**, and crystal X-ray data for compound **4** are provided in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.