Reaction of 6-(CF_3)- and 6-(CH_3)-2-(*tert*-Butyl)-1,3-dioxan-4-one Li Enolate with Two Equivalents of an Aldehyde – Unusual Reorganizations of Aldolates

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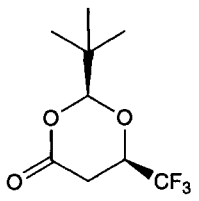
The Li enolate of (2*S*,6*R*)-2-(*tert*-butyl)-6-trifluoromethyl-1,3-dioxan-4-one (**1**) reacts with isobutyraldehyde, pivalaldehyde and cyclohexanecarboxaldehyde to give unexpected aldols [**3a–5a**, (1′*R*,2*R*,5*R*,6*R*)-2,6-dialkyl-5-(2′,2′,2′-trifluoro-1′-hydroxyethyl)-1,3-dioxan-4-ones]. The Li enolate of (2*R*,6*R*)-2-(*tert*-butyl)-6-methyl-1,3-dioxan-4-one (**2**) reacts with pivalaldehyde to give (1′*R*,2*S*,5*S*,6*R*)-2,6-di-(*tert*-butyl)-5-(1′-hydroxyethyl)-1,3-dioxan-4-one (**7**), another "strange" aldol-type product resulting from one enolate and two aldehyde molecules. There is an unusual reorganization involving a transacetalization process under basic conditions. The structures of two products (**4a** and **7**) were determined by X-ray crystallography, and a mechanism of formation is proposed.

The chemistry of the dioxanones **1** and **2** has been extensively explored in our laboratory for many years[1–4]. We have demonstrated that the substitution of a hydrogen at C(5) via the enolate of the dioxanone **2** takes place with a high stereoselectivity[2] while the enolate of **1** with a CF_3 instead of a CH_3 group in the 6-position reacts somewhat less selectively[3]. The aldol addition of dioxanone **2** Li enolate also shows good diastereoselectivity[2b,4] and was employed in the syntheses of 5-alkylidene-dioxanones[2b] and of chiral triols[4].



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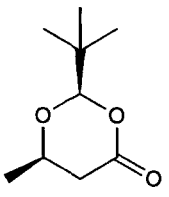

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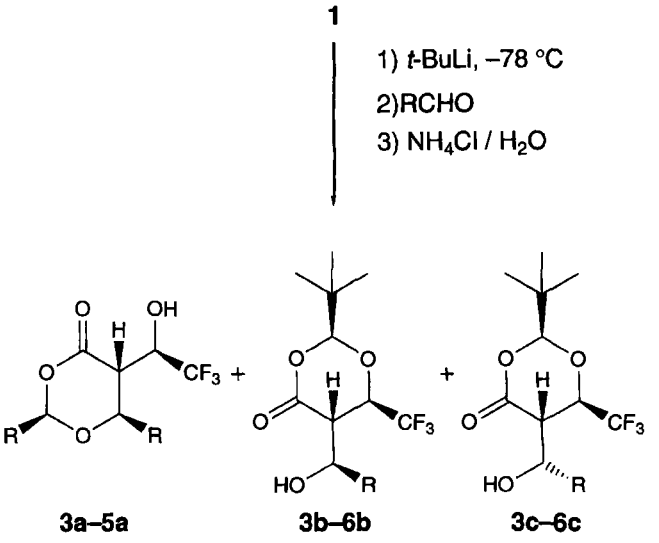
In this paper we wish to report on a surprising 1:2 reaction of the Li enolates generated from dioxanones **1** and **2** with aldehydes involving a transacetalization during the aldol addition reaction. To our knowledge, this is the first mention of such a process under basic conditions.

Results and Discussion

The dioxanone **1** was deprotonated with *tert*-BuLi at −78°C[3b] and then treated with different aldehydes (Scheme 1). We observed the formation of not only the two expected C(1′) epimers **3b–6b** and **3c–6c**, but also of a second type of aldol compound, **3a–5a**, which was actually the major product of the reaction. Only with acrolein, the formation of this new compound was not detected and a mixture of C(1′) epimers in a ratio of 5:1 (**6b/6c**) was obtained. In fact, it was very astonishing that the major product obtained by the aldol addition reaction of **1** with isobutyraldehyde and cyclohexanecarboxaldehyde, **3a** and **5a**, lacked the typical *tert*-butyl signal in the NMR spectra!

Scheme 1



3 R = *iso*-Pr
4 R = *tert*-Bu
5 R = cyclohexyl
6 R = vinyl

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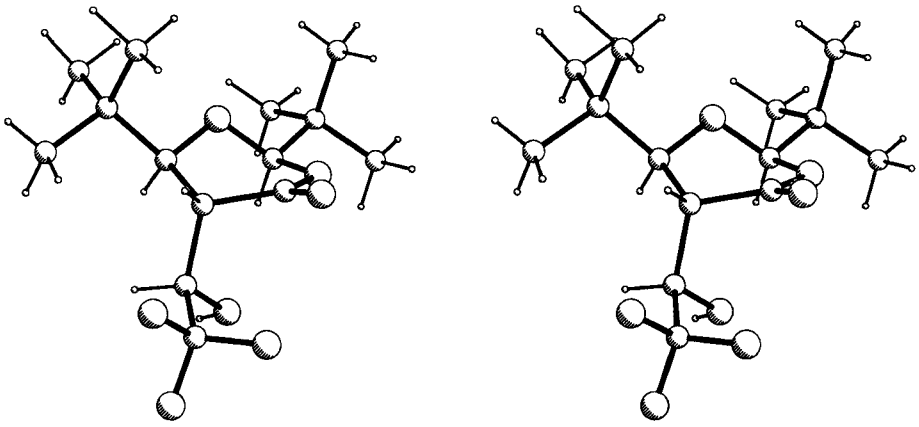


Figure 1. PLUTO stereoview[11] of the reorganized aldol **4a**

Table 1. Stoichiometric effect on the ratio of the isomers **a**, **b**, and **c** formed during the reaction of the Li enolate of dioxanone **1** with isobutyraldehyde, pivalaldehyde, cyclohexanecarboxaldehyde and acrolein (Scheme 1). The yields given are based on the dioxanone **1** amounts

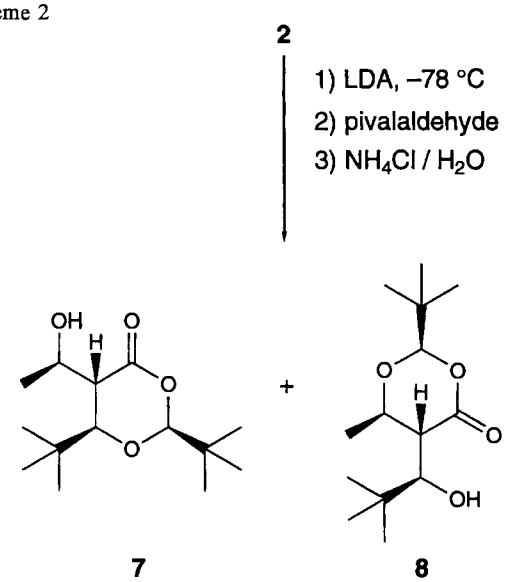
Products	Equiv. of RCHO	Reaction time (h)	Ratio a:b:c	Selectivity at C(1')	Yields (%)
3	3	20	8.9 : 3.2 : 1	12:1	95
3	1	0.5	7.7 : 2.6 : 1	10:1	95
4	3	20	10.5 : 3 : 1	13:1	95
4	1	18	1.5 : 1.5 : 1	3:1	28
5	3	20	8.5 : 2.5 : 1	11:1	95
5	1	0.5	2.9 : 4.6 : 1	7:1	65
6	1.5	3.0	-- : 5.0 : 1	5:1	81

With the enolate generated from **1** and pivalaldehyde, the aldol addition gave again three isomers – now with the expected pattern and number of signals – and, we first thought that the bond formation at C(5) was not totally stereoselective which it usually is. Of the major isomer **4a** isolated, we were able to obtain crystals suitable for X-ray structure determination (Figure 1), to find out that, again, the structure was not as expected. Considering the subtle differences between the observed and the expected NMR spectra, it is not surprising that we published a wrong structure[3b] for the main product prepared from **1** and isobutyraldehyde!

As can be seen from Figure 1, no doubt exists that the isolated aldol adduct **4a**, from **1** and pivalaldehyde, arises from a rearrangement of the acetal function of the original dioxanone ring. The X-ray structure shows the dioxanone ring in a twist boat[5] conformation with the two *tert*-butyl groups in a pseudo-equatorial position. From all our experience with the chemistry of the dioxanone **1**, so far, we assume that the configuration of the carbon bearing the trifluoromethyl substituent is *R* as in the starting material, the dioxanone **1**. For aldols **3a** and **5a**, the evidence for a structure analogous to that of **4a** comes from the fact that their ^{1}H-NMR and ^{13}C-NMR spectra do not contain *tert*-butyl signals.

Table 1 shows the ratio of the three isomers formed (**a**, **b** and **c**) during the aldol and transacetalization processes depicted in Scheme 1. In the case of isobutyraldehyde, the use of 3 equivalents of aldehyde gave a ratio (**a**, **b** and **c**) of 8.9:3.2:1 favoring the rearranged aldol adduct while a stoichiometric amount of aldehyde and a shorter reaction time did not change this ratio dramatically. On the other hand, with pivalaldehyde and cyclohexanecarboxaldehyde, the variation in the number of equivalents of aldehyde employed affected the ratio of **a**, **b** and **c** substantially; in both these cases, with only one equivalent of RCHO, the major product was the expected aldol **4b** and **5b**. Except in one experiment, the yields were generally high (65–95%).

Scheme 2



It also turned out that the non-fluorinated dioxanone **2** behaves similarly in the aldol addition to pivalaldehyde (Scheme 2) – but not to other aldehydes. Deprotonation of **2** with LDA at –78°C followed by treatment of the enolate formed with an excess of pivalaldehyde (1.45 equiv.) gave a product which showed the expected NMR pattern, and to which we assigned, in a previous report[4], a wrong structure. We were quite sure at that

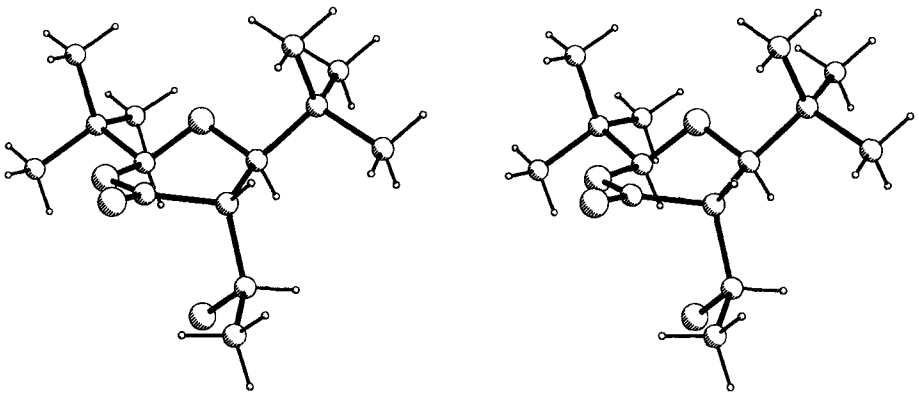


Figure 2. PLUTO stereoview[11] of the reorganized aldol **7**

time that we had obtained aldol adduct **8** since all the NMR data were similar to those of other compounds in the series. Just to have another example of definite structure proof for aldols of this type, we crystallized the single product isolated from this reaction and obtained an X-ray structure which is presented in Figure 2.

As for **4a**, the structure determination of **7** revealed that we actually had isolated the rearranged aldol adduct. The dioxanone ring conformation of **7**[5] is similar to that of **4a**, and the two *tert*-butyl substituents are pseudo-equatorial.

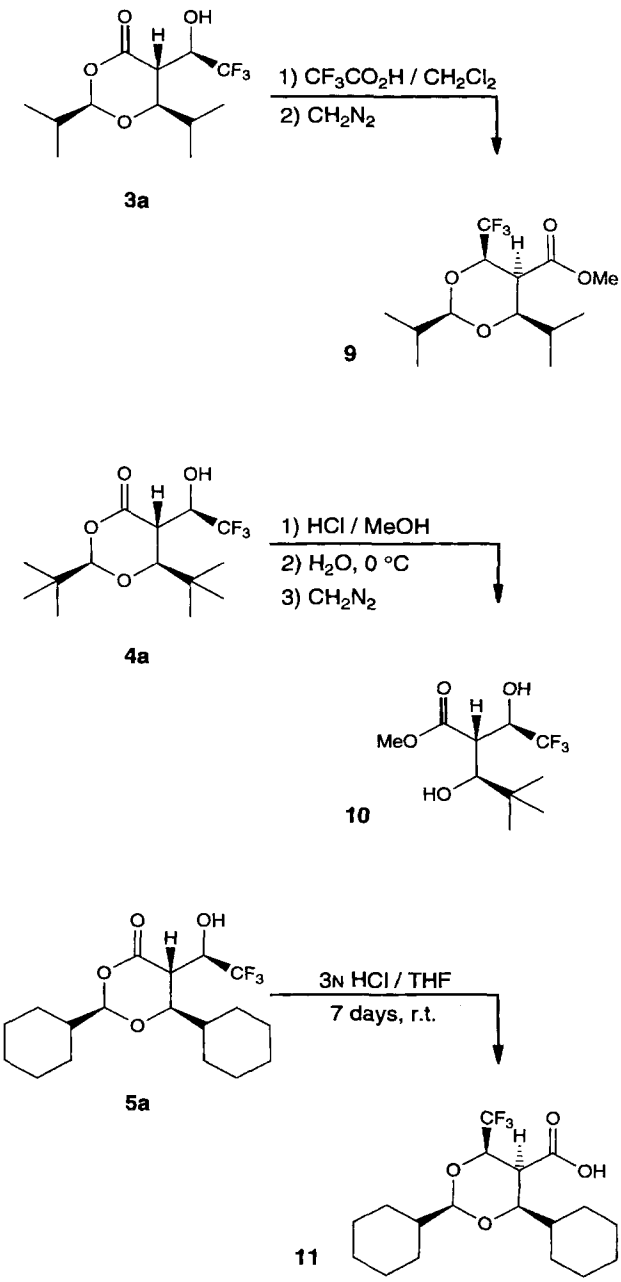
We made three experiments to verify again the effect of the stoichiometry of the aldehyde relative to the dioxanone **2** enolate (Table 2). With an excess of pivalaldehyde (3 equiv.) and a long reaction time, the sole product isolated is **7** besides some of the starting dioxanone **2**. Using 1.05 equivalents of pivalaldehyde and a reaction time of only 15 min, we found a ratio of **7**/**8** of 2.7:1. When be employed the enolate in excess (0.80 equiv. of RCHO), the major product was the normal aldol **8** in a ratio of **7**/**8** of 1:1.2. The aldol adduct **8** can also be converted to its isomer **7** by using the same reaction conditions as in the aldol addition (treatment of **8** with LDA and 0.5 equiv. of RCHO → 80% of **7**).

Table 2. Stoichiometric effect on the ratio of the isomers **7** and **8** formed during the reaction of the Li enolate of dioxanone **2** with pivalaldehyde (Scheme 2). The yields given are based on the dioxanone **2** amounts

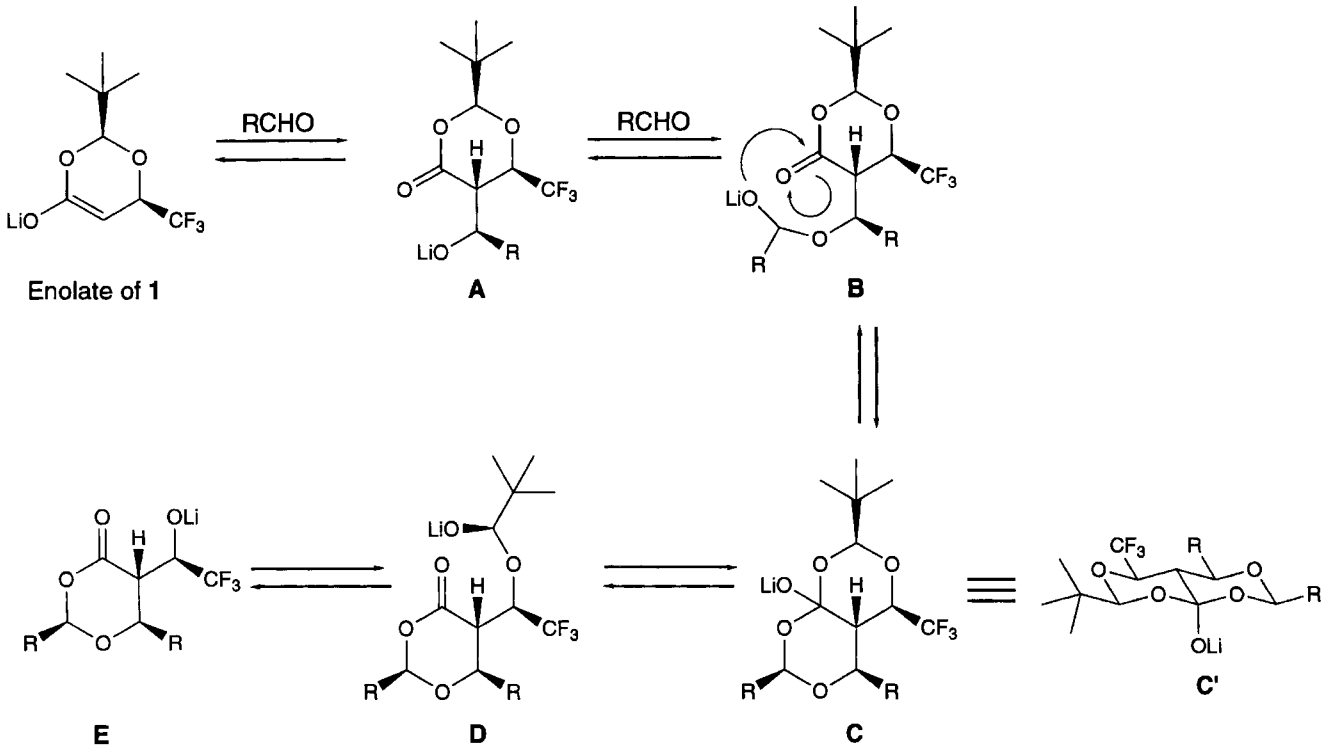
Equiv. of aldehyde	Reaction time (h)	Ratio **7**:**8**	Yields (%)
1.45	3.0	>99:1	68
1.05	0.25	2.7:1	85
0.80	0.25	1:1.2	74

The first idea that came to our mind to explain these results was that the transacetalization process happened during the work-up which consists of quenching the reaction at −78°C with a sat. aq. NH_4Cl and then to warm the reaction mixture to room temp. prior to extraction. But the fact that the ratio is affected by the

Scheme 3



Scheme 4



stoichiometry of the reaction is not consistent with this proposal since no aldehyde molecule is necessary to achieve the transacetalization under acidic conditions (in fact, a different product forms with acid, *vide infra*). The other point that came out from the experiment was the isomerization of the aldol **8** to **7**. If the transacetalization would occur during the work-up, we should be able, at least, to detect some non-rearranged aldol. However, we isolated only the isomerized product **7**.

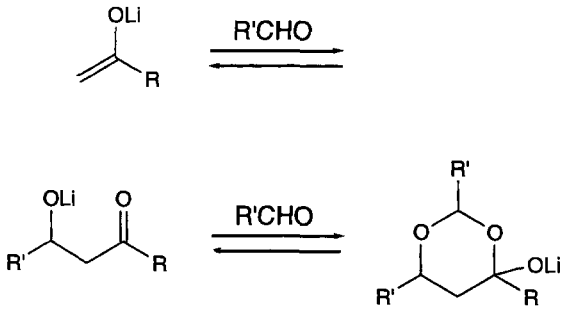
In previous work[2a], aldols obtained from dioxanone **2** were subjected to trifluoroacetic acid treatment, yielding the corresponding dioxanecarboxylic acids. In order to verify the possibility of an acid-catalyzed transacetalization in the present case, we also treated the aldols **3a–5a** under various acidic conditions (Scheme 3).

Treatment of compound **3a** with trifluoroacetic acid in CH_2Cl_2 followed by esterification with diazomethane gave the methyl dioxanecarboxylate **9** in 77% yield. The aldol **4a** was treated with HCl/MeOH, then with water; after treatment with diazomethane, the diol methyl ester **10** was isolated in low yield (31%). A prolonged reaction of **5a** with 3 M HCl in THF led to the transacetalized dioxanecarboxylic acid **11** (55%). In all these experiments, we were not able to detect the formation of aldols of the type **3b–5b**. Thus, acid treatment of the rearranged aldols **3a–5a** always leads to the dioxanecarboxylic acid derivatives as it has been demonstrated earlier for the nonfluorinated series[2a]. Therefore, we can be quite confident that the transacetalization occurring during the aldol reaction is not promoted by an acid and is not happening during work-up.

The mechanism proposed for the formation of the reorganized aldols **3a–5a** and **7** is depicted in Scheme 4. The Li aldolate **A**, primarily formed from the Li enolate of **1** and aldehyde, adds to another aldehyde molecule to give the intermediate **B** (adducts of LiOR and $LiNR_2$ to aldehydes are well known[6]). This second addition to an aldehyde molecule must be of comparable rate to the first one, the aldolate formation, since the use of excess enolate (see Table 2) led to nearly 40% of the reorganized aldol **7**. The adduct **B** could then undergo a cyclization to the intermediate **C**[7]. Subsequently, a ring opening can occur: back to the intermediate **B** or, with breakage of the original dioxanone ring bonds, to the unexpected aldolate **E** (via **D** and expulsion of a pivalaldehyde molecule). The tendency of this latter ring opening[8] could be well explained in the fluorinated series. The presence of three electronegative atoms such as fluorine stabilizes the intermediate **E**. For comparison, the pK_a values for CH_3CH_2OH and CF_3CH_2OH are 15.5 and 12.4, respectively[9]. This mechanism is in accord with all the observations mentioned above concerning the stoichiometric effect and the transformation of **8** to **7**.

The overall transformation discussed in this paper can, thus, be regarded as a 1:2 reaction of enolates with aldehydes, leading to a cyclic intermediate (see the general equation in Scheme 5). When no other pathway of fragmentation of this 1:2 intermediate is possible, the aldolate formed is the one expected. In our case, this was not true. Therefore, synthetic chemists should be aware that such a transformation is possible and may lead to other compounds than the ones, at first desired.

Scheme 5



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Experimental

^1H and ^{13}C NMR: Bruker AMX 400, Bruker WM 300, Varian XL-300 or Varian Gemini 200; ^{19}F NMR: Varian XL-300 or Varian Gemini 300 (282.2 MHz); multiplicities determined with DEPT pulse sequence; solvent $CDCl_3$ unless noted otherwise; chemical shifts in values relative to TMS (δ = 0) for protons, $CDCl_3$ (δ = 77) for carbons or $CFCl_3$ (δ = 0) for fluorine atoms. – Melting points: Büchi 510 (uncorrected values). – IR: Perkin-Elmer 983. – MS: Hitachi-Perkin-Elmer RMU-6M or VG Tribrid. – Optical rotations: Perkin-Elmer 241 (in 1-dm cells). – Microanalyses were performed by Mikroanalytisches Laboratorium der ETH-Zürich. – TLC: Glass plated Kieselgel 60 F_{254} (Merck). – Flash chromatography (FC): Kieselgel 60 (Merck) 40–60 µm, eluant in parentheses. Dioxanone **1**[3a] and dioxanone **2**[10] were prepared as described in the literature.

(1'R,2R,5R,6R)-2,6-Diisopropyl-5-(2',2',2'-trifluoro-1'-hydroxyethyl)-1,3-dioxan-4-one (**3a**), *(1'R,2S,5R,6R)- and (1'S,2S,5R,6R)-2-(tert-Butyl)-5-(1'-hydroxy-2'-methylpropyl)-6-trifluoromethyl-1,3-dioxan-4-one* (**3b**) *and* (**3c**), *resp.:* To a solution of dioxanone **1** (4.52 g, 20 mmol) in 80 ml of THF cooled at −78°C was added *tert*-BuLi (14.5 ml, 1.54 M, 22 mmol) at such a rate that the temperature never exceeded −70°C. The mixture was kept at −78°C for 20 min then isobutyraldehyde (5.5 ml, 60 mmol) was added slowly; the reaction mixture was maintained at −78°C for 20 h and the reaction quenched by the addition of 80 ml of sat. aq. NH_4Cl at −78°C. The mixture was extracted three times with Et_2O (100 ml), the combined organic extracts were dried ($MgSO_4$) and the volatile components evaporated in vacuo; yield 5.68 g of a mixture of **3a**, **b**, **c**. ^1H and ^{19}F NMR of the crude product showed a ratio (**3a/3b/3c**) of 8.9:3.2:1. The crude product was stirred overnight with pentane and the remaining solid was crystallized from pentane/Et_2O to give 3.05 g (51%) of pure **3a**. We were not able to obtain compounds **3b** and **3c** in a pure form. Data for **3a**: m.p. 122.5–123.0°C. – $[\alpha]_D^{rt}$ = −19.6 (*c* = 1.0, C_2H_5OH). – IR (KBr): $\tilde{\nu}$ = 3330 cm^{-1} (s), 2970 (m), 1715 (s), 1475 (m), 1400 (m), 1390 (s), 1350 (m), 1295 (s), 1270 (s), 1235 (s), 1160 (s), 1140 (s), 1130 (s), 1020 (s), 975 (s), 955 (s). – ^1H NMR (400 MHz): δ = 0.95 (d, *J* = 6.8, 3H, CH_3), 0.99 (d, *J* = 6.8, 3H, CH_3), 1.00 (d, *J* = 6.9, 3H, CH_3), 1.08 (d, *J* = 6.9, 3H, CH_3), 1.94–2.07 [m, 2H, $CH(CH_3)_2$], 3.05 (dd, J_1 = 10.1, J_2 = 2.4, 5-H), 3.52 (s, OH), 3.84 (dd, J_1 = 10.1, J_2 = 1.5, 6-H), 4.43 (m, 1'-H), 5.13 (d, *J* = 4.5, 2-H). – ^{13}C NMR (100 MHz): δ = 14.29 (CH_3), 15.71 (CH_3), 16.10 (CH_3), 19.54 (CH_3), 30.25 (CH), 32.65 (CH), 45.06 (CH), 69.50 (q, J_{CF} = 32.0), 80.44 (CH), 106.65 (CH), 124.34 (q, J_{CF} = 283.5), 168.27 (C). – ^{19}F NMR: δ = −76.21 (d, J_{HF} = 7.5). – MS: *m/z* (%) = 285 (6) [M^+ + 1], 241 (27), 195 (65), 150 (66), 123 (49), 99 (30), 97 (24), 81 (28), 73 (78), 71 (71), 69 (92), 55 (65), 43 (100), 41 (60), 39 (30), 29 (48). – $C_{12}H_{19}F_3O_4$ (284.27): calcd. C 50.70, H 6.74, F 20.05; found C 50.48, H 6.89, F 19.80.

(1'R,2R,5R,6S)-Isomer **4a**, *(1'S,2S,5S,6R)-isomer* **4b** *and (1'R,2S,5S,6R)-isomer* **4c**: As described for **3a**, **3b** and **3c**, dioxanone **1** (4.52 g, 20 mmol) was allowed to react with *tert*-BuLi (14.5 ml, 1.54 M, 22 mmol) and pivalaldehyde (6.6 ml, 60 mmol). The crude product was stirred overnight with pentane and the remaining solid consisted of only **4a** (46%). The filtrate was concentrated in vacuo and the residue was crystallized from hexanes/ethyl acetate, giving **4b** (14%). The minor isomer **4c** was not isolated in pure form. Data for **4a**: m.p. 201.5–202.5°C. – $[\alpha]_D^{rt}$ = −35.9 (*c* = 0.27, C_2H_5OH). – IR (KBr): $\tilde{\nu}$ = 3345 cm^{-1} (br.), 2985 (m), 1710 (s), 1385 (m), 1295 (m), 1225 (m), 1165 (m), 1140 (s), 1125 (m), 1020 (w), 960 (m). – ^1H NMR (300 MHz, [D_6]acetone): δ = 0.97 (s, 9H, *tert*-butyl), 0.98 (s, 9H, *tert*-butyl), 3.09 (dd, J_1 = 5.5, J_2 = 2.4, 5-H), 3.88 (d, *J* = 5.5, 6-H), 4.34 (dq, J_1 = 2.2, J_2 = 7.3, 1'-H), 5.29 (s, 2-H), 6.30 (s, OH). – ^{13}C NMR (75 MHz, [D_6]acetone): δ = 24.09 (CH_3), 25.15 (CH_3), 35.58 (C), 36.24 (C), 72.80 (q, J_{CF} = 31.0), 85.43 (CH), 106.04 (CH), 125.56 (q, J_{CF} = 283.0), 166.90 (C). – ^{19}F NMR (282.2 MHz): δ = −75.52 (d, J_{HF} = 7.3). – MS: *m/z* (%) = 313 (5) [M^+ + 1], 255 (26), 209 (95), 181 (96), 164 (72), 122 (50), 113 (29), 87 (100), 83 (32), 71 (24), 69 (22), 57 (58), 43 (19), 41 (28). – $C_{14}H_{23}F_3O_4$ (312.32): calcd. C 53.84, H 7.42; found C 54.12, H 7.15.

Data for **4b**: m.p. 144.0–145.0°C. – $[\alpha]_D^{rt}$ = −22.0 (*c* = 1.07, C_2H_5OH). – IR ($CHCl_3$): $\tilde{\nu}$ = 3410 cm^{-1} (br.), 2965 (s), 2875 (m), 1745 (s), 1485 (m), 1400 (m), 1370 (m), 1340 (m), 1285 (s), 1145 (s), 1070 (m), 1015 (m). – ^1H NMR (300 MHz): δ = 0.98 (s, 9H, *tert*-butyl), 1.00 (s, 9H, *tert*-butyl), 2.33 (d, *J* = 4.5, OH), 3.11 (dd, J_1 = 2.8, J_2 = 2.4, 5-H), 3.81 (dd, J_1 = 4.5, J_2 = 2.8, 1'-H), 4.91 (dq, J_1 = 2.4, J_2 = 6.2, 6-H), 5.43 (s, 2-H). – ^{13}C NMR (75 MHz): δ = 23.63 (CH_3), 25.44 (CH_3), 34.80 (C), 36.77 (C), 70.58 (q, J_{CF} = 31.5), 79.31 (CH), 103.94 (CH), 124.16 (q, J_{CF} = 281.0), 170.11 (C). – ^{19}F NMR (282.2 MHz): δ = −78.64 (d, J_{HF} = 6.2). – MS: *m/z* (%) = 313 (2) [M^+ + 1], 227 (10), 209 (39), 193 (17), 122 (44), 87 (98), 71 (17), 69 (31), 57 (100), 43 (20), 41 (35), 29 (21). – $C_{14}H_{23}F_3O_4$ (312.32): calcd. C 53.84, H 7.42; found C 53.76, H 7.43.

(1'R,2R,5S,6R)-Isomer **5a**, *(1'R,2S,5S,6R)-isomer* **5b** *and (1'S,2S,5S,6R)-isomer* **5c**: As described for **3a**, **3b** and **3c**, dioxanone **1** (2.26 g, 10 mmol) was allowed to react with *tert*-BuLi (7.5 ml, 1.46 M, 11 mmol) and cyclohexanecarboxaldehyde (3.6 ml, 30 mmol). The crude product was stirred overnight with pentane and the remaining solid was crystallized from hexanes/ethyl acetate to give **5a** (52%). The filtrate was concentrated in vacuo and the residue chromatographed twice (pentane/acetone, 20:1) to give pure **5b** and **5c**. Data for **5a**: m.p. 143.0–144.0°C. – $[\alpha]_D^{rt}$ = −5.3 (*c* = 1.04, C_2H_5OH). – IR ($CHCl_3$): $\tilde{\nu}$ = 3345 cm^{-1} (br.), 2935 (s), 2855 (s), 1730 (s), 1450 (m), 1410 (m), 1360 (m), 1260 (s), 1170 (s), 1145 (s), 1010 (m), 970 (m). – ^1H NMR (300 MHz): δ = 1.06–1.48 (m, 10H, cyclohex.), 1.57–1.84 (m, 12H, cyclohex.), 3.11 (dd, J_1 = 10.0, J_2 = 2.3, 5-H), 3.59 (d, *J* = 8.0, OH), 3.77 (d, *J* = 10.0, 6-H), 4.35–4.41 (m, 1'-H), 5.10 (d, *J* = 4.7, 2-H). – ^{13}C NMR (75 MHz): δ = 24.86 (CH_2), 25.48 (CH_2), 25.98 (CH_2), 26.19 (CH_2), 26.35 (CH_2), 26.51 (CH_2), 30.08 (CH_2), 39.97 (CH), 42.05 (CH), 44.25 (CH), 69.48 (q, J_{CF} = 32.0), 80.57 (CH), 106.24 (CH), 124.30 (q, J_{CF} = 283.5), 168.14 (C). – ^{19}F NMR (282.2 MHz): δ = −76.09 (d, J_{HF} = 7.6). – MS: *m/z* (%) = 364 (0.5) [M^+], 281 (65), 235 (100), 190 (25), 95 (72), 83 (31), 81 (20), 69 (6), 67 (21), 55 (35), 41 (26). – $C_{18}H_{27}F_3O_4$ (364.40): calcd. C 59.33, H 7.47; found C 59.29, H 7.26.

Data for **5b**: m.p. 123.0°C. – $[\alpha]_D^{rt.} = -30.7$ ($c = 1.13$, C_2H_5OH). – R_f(pentane/acetone, 10:1) = 0.18. – IR ($CHCl_3$): $\tilde{\nu}$ = 2930 cm^{-1} (s), 2855 (m), 1740 (s), 1485 (m), 1450 (m), 1370 (m), 1350 (m), 1285 (s), 1150 (s), 1095 (m), 995 (m). – ^1H NMR (300 MHz): δ = 0.78–0.96 (m, 2H, cyclohex.), 0.99 (s, 9H, *tert*-butyl), 1.06–1.43 (m, 3H, cyclohex.), 1.68–1.81 (m, 3H, cyclohex.), 1.90–2.03 (m, 3H, cyclohex.), 2.07 (dd, $J_1 = 5.7$, $J_2 = 1.0$, OH), 3.17 (d, $J = 7.8$, 5-H), 3.39 (dd, $J_1 = 8.3$, $J_2 = 6.1$, 1'-H), 4.47 (dq, $J_1 = 7.7$, $J_2 = 6.0$, 6-H), 5.11 (s, 2-H). – ^{13}C NMR (75 MHz): δ = 23.60 (CH_3), 25.40 (CH_2), 26.03 (CH_2), 28.88 (CH_2), 29.49 (CH_2), 35.01 (C), 40.40 (CH), 42.38 (CH), 75.43 (q, $J_{CF} = 31.5$), 78.11 (CH), 106.27 (CH), 123.48 (q, $J_{CF} = 281.0$), 166.00 (C). – ^{19}F NMR (282.2 MHz): δ = –78.89 (d, $J_{HF} = 6.5$). – MS: *m/z* (%) = 281 (11), 255 (54), 123 (43), 112 (31), 95 (75), 87 (49), 83 (38), 71 (29), 69 (66), 57 (100), 55 (62), 43 (27), 41 (61). – $C_{16}H_{25}F_3O_4$ (338.36): calcd. C 56.80, H 7.45; found C 57.02, H 7.63.

Data for **5c**: m.p. 143.0–144.0°C. – $[\alpha]_D^{rt.} = -10.7$ ($c = 0.94$, C_2H_5OH). – R_f(pentane/acetone, 10:1) = 0.21. – IR ($CHCl_3$): $\tilde{\nu}$ = 3425 cm^{-1} (br.), 2935 (s), 2855 (m), 1735 (s), 1485 (m), 1450 (m), 1400 (m), 1368 (m), 1275 (m), 1145 (s), 1095 (m), 1070 (m), 1050 (m), 1005 (m). – ^1H NMR (300 MHz): δ = 0.87–1.38 (m, 6H, cyclohex.), 0.99 (s, 9H, *tert*-butyl), 1.63–1.96 (m, 5H, cyclohex.), 2.31 (br., OH), 3.13 (dd, $J_1 = 5.4$, $J_2 = 2.7$, 5-H), 3.90 (dd, $J_1 = 9.4$, $J_2 = 2.6$, 1'-H), 4.67 (dq, $J_1 = 5.4$, $J_2 = 6.2$, 6-H), 5.23 (s, 2-H). – ^{13}C NMR (75 MHz): δ = 23.63 (CH_3), 25.51 (CH_2), 25.60 (CH_2), 26.05 (CH_2), 28.17 (CH_2), 29.40 (CH_2), 34.90 (C), 40.60 (CH), 42.83 (CH), 71.18 (q, $J_{CF} = 33.0$), 104.88 (CH), 121.80 (q, $J_{CF} = 281.0$), 169.66 (C). – ^{19}F NMR (282.2 MHz): δ = –79.05 (d, $J_{HF} = 6.2$). – MS: *m/z* (%) = 281 (4), 255 (21), 123 (51), 113 (36), 95 (100), 87 (62), 83 (68), 71 (23), 69 (36), 57 (94), 55 (71), 41 (68), 29 (27).

(1'R,2S,5S,6R)-Isomer **6b** *and (1'S,2S,5S,6R)-isomer* **6c**: As described for **3a**, **3b** and **3c**, dioxanone **1** (4.52 g, 20 mmol) was allowed to react with *tert*-BuLi (14.8 ml, 1.49 M, 22 mmol) and acrolein (2.0 ml, 60 mmol). Two flash chromatographies (pentane/ether, 5:1) gave pure **6b** and **6c**. Data for **6b**: m.p. 110.0–111.5°C. – $[\alpha]_D^{rt.} = -3.9$ ($c = 1.02$, C_2H_5OH). – R_f(pentane/Et_2O, 5:1) = 0.11. – IR (KBr): $\tilde{\nu}$ = 3490 cm^{-1} (s), 2980 (m), 1715 (s), 1485 (m), 1375 (m), 1360 (s), 1340 (m), 1280 (s), 1260 (s), 1245 (s), 1175 (s), 1145 (s), 1125 (s), 1120 (s), 1100 (s), 1025 (s), 980 (s), 940 (s). – ^1H NMR (300 MHz): δ = 1.00 (s, 9H, *tert*-butyl), 3.02 (d, $J = 4.7$, OH), 3.02–3.05 (m, 5-H), 4.43 (dq, $J_1 = 5.9$, $J_2 = 5.9$, 6-H), 4.78–4.86 (m, 1'-H), 5.14 (s, 2-H), 5.37 (ddd, $J_1 = 10.5$, $J_2 = 1.4$, $J_3 = 1.4$, 3'-H), 5.46 (ddd, $J_1 = 17.1$, $J_2 = 1.6$, $J_3 = 1.2$, 3'-H), 5.85 (dddd, $J_1 = 17.1$, $J_2 = 10.5$, $J_3 = 4.9$, $J_4 = 1.0$, 2'-H). – ^{13}C NMR (75 MHz): δ = 23.60 (CH_3), 34.96 (C), 44.93 (CH), 71.20 (q, $J_{CF} = 32.0$), 72.45 (CH), 105.63 (CH), 117.73 (CH_2), 123.22 (q, $J_{CF} = 280.5$), 136.40 (CH), 168.79 (C). – ^{19}F NMR (282.2 MHz): δ = –78.70 (d, $J_{HF} = 5.6$). – MS: *m/z* (%) = 282 (0.2) [M^+], 179 (31), 123 (45), 87 (16), 71 (11), 69 (9), 57 (100), 43 (14), 41 (15). – $C_{12}H_{17}F_3O_4$ (282.25): calcd. C 51.06, H 6.07; found C 51.21, H 6.18.

Data for **6c**: m.p. 82.5–84.0°C. – $[\alpha]_D^{rt.} = -15.8$ ($c = 1.13$, C_2H_5OH). – R_f(pentane/Et_2O, 5:1) = 0.08. – IR ($CHCl_3$): $\tilde{\nu}$ = 3385 cm^{-1} (br.), 2965 (m), 1740 (s), 1485 (m), 1370 (m), 1360 (m), 1280 (s), 1150 (s), 1095 (m), 1030 (m), 1000 (m), 940 (m). – ^1H NMR (300 MHz): δ = 1.00 (s, 9H, *tert*-butyl), 2.25 (dd, $J_1 = 3.8$, $J_2 = 1.0$, OH), 3.03 (ddd, $J_1 = 7.3$, $J_2 = 0.9$, 5-H), 4.41–4.43 (m, 1'-H), 4.55 (dq, $J_1 = 7.3$, $J_2 = 6.0$, 6-H), 5.09 (s, 2-H), 5.32 (ddd, $J_1 = 10.3$, $J_2 = 1.0$, $J_3 = 1.0$, 3'-H), 5.35 (ddd, $J_1 = 17.1$, $J_2 = 1.1$, $J_3 = 1.1$, 3'-H), 6.22 (ddd, $J_1 = 17.1$, $J_2 = 10.3$, $J_3 = 6.8$, 2'-H). – ^{13}C NMR (75 MHz): δ = 23.54 (CH_3), 35.00 (C), 46.34 (CH), 73.49 (CH), 74.28 (q, $J_{CF} = 31.5$), 106.17 (CH), 117.80 (CH_2), 123.28 (q, $J_{CF} = 279.5$), 137.07 (CH), 165.74 (C). – ^{19}F NMR (282.2 MHz): δ = –79.17 (d, $J_{HF} = 5.9$). – MS: *m/z* (%) = 282 (0.3) [M^+], 179 (14), 123 (54), 86 (17), 71 (11), 69 (15), 57 (100), 43 (18), 41 (35), 29 (34). – $C_{12}H_{17}F_3O_4$ (282.25): calcd. C 51.06, H 6.07; found C 50.96, H 5.90.

(1'R,2S,5S,6R)-Isomer **7** *and (1'R,2R,5R,6R)-isomer* **8**: An ice-cold solution of (*iso*-Pr)NH_2 (0.93 ml, 6.6 mmol) in THF (13 ml) was treated with BuLi (4.2 ml, 1.6 M, 6.6 mmol), kept at 0°C for 15 min, then cooled to –78°C. To this solution of LDA was added the dioxanone **2** (1.0 g, 5.8 mmol) in THF (7 ml) at such a rate that the temperature never exceeded –70°C, then the mixture was maintained at –78°C for 45 min. To the resulting enolate solution was added pivalaldehyde (0.66 ml, 6.1 mmol) in THF (7 ml). The mixture was kept at –78°C for 15 min, then the reaction was quenched by the addition of sat. aq. NH_4Cl (15 ml). The mixture was extracted with Et_2O (3 × 20 ml), the combined extracts were dried ($MgSO_4$) and the volatile components evaporated in vacuo. – ^1H NMR of the crude products showed a ratio of 2.7:1 (**7**/**8**). FC (hexanes/Et_2O, 2:1) gave 0.93 g (62%) of pure **7** and 0.35 g (23%) of pure **8**. Data for **7**: m.p. 153–154°C. – $[\alpha]_D^{rt.} = +10.5$ ($c = 2.12$, $CHCl_3$). – IR ($CHCl_3$): $\tilde{\nu}$ = 3620 cm^{-1} (br.), 3450 (w), 3005 (m), 2980 (s), 2960 (s), 2910 (s), 2870 (s), 1725 (s), 1480 (s), 1460 (m), 1450 (w), 1410 (m), 1400 (m), 1370 (s), 1330 (m), 1280 (m), 1260 (s), 1240 (s), 1130 (m), 1115 (m), 1040 (m), 1030 (m), 1010 (m), 990 (s), 955 (w), 940 (w), 880 (m), 850 (m). – ^1H NMR (300 MHz): δ = 0.92 (s, 9H, *tert*-butyl), 0.97 (s, 9H, *tert*-butyl), 1.48 (d, $J = 6.5$, CH_3), 1.84 (br. s, OH), 2.63 (dd, $J_1 = 6.4$, $J_2 = 2.5$, 5-H), 3.71 (d, $J = 6.4$, 1'-H), 3.75 (m, 6-H), 5.11 (s, 2-H). – ^{13}C NMR (75 MHz): δ = 22.60 (CH_3), 23.86 (CH_3), 25.15 (CH_3), 35.09 (C), 35.32 (C), 49.66 (CH), 70.48 (CH), 84.52 (CH), 106.01 (CH), 169.72 (C). – MS: *m/z* (%) = 259 (14) [M^+ + 1], 241 (7), 201 (81), 185 (2), 173 (30), 155 (55), 144 (3), 137 (10), 129 (75), 111 (100), 95 (4), 87 (28), 71 (36), 57 (16), 41 (12). – $C_{14}H_{26}O_4$ (258.35): calcd. C 65.09, H 10.14; found C 64.99, H 10.14.

Data for **8**: m.p. 116–117°C. – $[\alpha]_D^{rt.} = +0.6$ ($c = 2.40$, $CHCl_3$). – IR ($CHCl_3$): $\tilde{\nu}$ = 3550 cm^{-1} (br.), 2965 (s), 2905 (w), 2875 (w), 1725 (s), 1485 (m), 1410 (m), 1370 (m), 1340 (m), 1285 (m), 1255 (m), 1150 (m), 1105 (w), 1030 (m), 1005 (s), 980 (m), 935 (w), 820 (w). – ^1H NMR (300 MHz): δ = 0.97 (s, 9H, *tert*-butyl), 1.00 (s, 9H, *tert*-butyl), 1.35 (d, $J = 6.2$, CH_3), 2.60 (dd, $J_1 = 10.1$, $J_2 = 0.9$, 5-H), 2.65 (d, $J = 11.8$, OH), 3.24 (dd, $J_1 = 11.8$, $J_2 = 0.9$, 1'-H), 3.96 (dq, $J_1 = 10.1$, $J_2 = 6.1$, 6-H), 4.98 (s, 2-H). – ^{13}C NMR (75 MHz): δ = 20.17 (CH_3), 23.90 (CH_3), 26.67 (CH_3), 35.09 (C), 36.13 (C), 50.24 (CH), 75.26 (CH), 78.38 (CH), 107.96 (CH), 169.31 (C). – MS: *m/z* (%) = 259 (0.3) [M^+ + 1], 257 (0.6), 241 (0.2), 201 (26), 155 (16), 129 (11), 111 (31), 97 (4), 87 (100), 69 (53), 57 (36), 41 (29). – $C_{14}H_{26}O_4$ (258.35): calcd. C 65.09, H 10.14; found C 65.18, H 10.43.

Conversion of **8** *to* **7**: An ice-cold solution of (*iso*-Pr)NH_2 (0.30 ml, 2.07 mmol) in THF (5 ml) was treated with BuLi (1.6 ml, 1.6 M, 2.07 mmol), kept at 0°C for 15 min then cooled to –78°C. To this solution of LDA was added **8** (0.47 g, 1.82 mmol) and pivalaldehyde (0.1 ml, 0.91 mmol) in THF (8 ml) at such a rate that the temperature never exceeded –70°C, then the mixture was maintained at –78°C for 3 h and the reaction subsequently quenched by the addition of sat. aq. NH_4Cl (5 ml). The mixture was extracted with Et_2O (3 × 30 ml), the combined extracts were dried ($MgSO_4$) and the volatile components evaporated in vacuo. The crude product showed no starting material **8** (NMR) and was crystallized from Et_2O/pentane to give 0.37 g (80%) of pure **7**.

(2R,4R,5S,6R)-Isomer **9**: To aldol **3a** (0.6 g, 2.1 mmol) in 30 ml of CH_2Cl_2 was added 15 drops of trifluoroacetic acid then the mix-

ture was heated to reflux until no starting compound **3a** remained (tlc control). The reaction mixture was diluted with Et_2O (50 ml) and then extracted with sat. aq. Na_2CO_3. The combined aq. phases were acidified with 6 N HCl to pH 2 and reextracted with Et_2O. Drying ($MgSO_4$) of the extract and evaporation of the volatile components gave a yellow oil which was dissolved in methanol (10 ml). The obtained solution was treated with an ethereal solution of diazomethane until the yellow color remained. The solvent was removed in vacuo then the residue was distilled (kugelrohr, 30°C/0.02 Torr) to give 0.482 g (77%) of pure **9** as colorless solid; m.p. 39.0–41.0°C. – $[\alpha]_D^{rt}$ = +4.8 (*c* = 1.05, C_2H_5OH). – IR (KBr): $\tilde{\nu}$ = 2970 cm^{-1} (m), 1750 (s), 1725 (m), 1475 (m), 1440 (m), 1395 (m), 1370 (m), 1305 (m), 1280 (m), 1265 (m), 1240 (m), 1165 (s), 1155 (s), 1075 (m), 1040 (m). – ^1H NMR (400 MHz): δ = 0.92 (d, *J* = 6.8, 3H, CH_3), 1.00 (d, *J* = 6.9, 3H, CH_3), 1.01 (d, *J* = 6.8, 3H, CH_3), 1.02 (d, *J* = 6.5, 3H, CH_3), 1.69–1.82 [m, 1H, C*H*(CH_3)$_2$], 1.95–2.06 [m, 1H, C*H*(CH_3)$_2$], 2.82 (dd, J_1 = 2.8, J_2 = 2.8, 5-H), 3.19 (dd, J_1 = 9.9, J_2 = 2.7, 4-H), 3.71 (s, OCH_3), 4.09 (qd, J_1 = 6.8, J_2 = 3.0, 6-H), 4.32 (d, *J* = 5.1, 2-H). – ^{13}C NMR (100 MHz): δ = 16.65 (CH_3), 16.99 (CH_3), 17.90 (CH_3), 19.26 (CH_3), 30.78 (CH), 32.51 (CH), 40.74 (CH), 51.84 (CH_3), 76.07 (q, J_{CF} = 33.0), 82.81 (CH), 106.39 (CH), 122.75 (q, J_{CF} = 280.0), 168.6 (C). – MS: *m/z* (%) = 297 (5) [M^+ – 1], 255 (64), 227 (22), 209 (43), 195 (51), 155 (58), 149 (47), 135 (29), 123 (55), 73 (45), 71 (44), 69 (29), 59 (47), 55 (59), 43 (100), 41 (57), 29 (45), 27 (43). – $C_{13}H_{21}F_3O_4$ (298.30): calcd. C 52.34, H 7.10; found C 52.56, H 7.33.

(1'R,2S,3S)-Isomer **10**: A solution of compound **4a** (1.0 g, 3.2 mmol) in methanolic HCl (30 ml) was stirred at room temp. for 2 h then poured onto ice-water (30 ml) and the aq. phase extracted with Et_2O (3 × 50 ml). The combined org. extracts were dried ($MgSO_4$) and the volatile components evaporated in vacuo. The residue was diluted with Et_2O (20 ml) and treated with ethereal diazomethane until the yellow color remained. FC (hexanes/ethyl acetate, 5:1) and short-path distillation (100°C/0.02 Torr) gave 0.255 g (31%) of pure **10** as a colorless solid; m.p. 54.0–55.0°C. – $[\alpha]_{365}^{rt}$ = –7.4 (*c* = 1.0, C_2H_5OH). – R_f(hexanes/ethyl acetate, 5:1) = 0.13. – IR ($CHCl_3$): $\tilde{\nu}$ = 3420 cm^{-1} (br.), 2960 (m), 1715 (s), 1440 (m), 1370 (m), 1275 (s), 1175 (s), 1135 (s), 1010 (m). – ^1H NMR (300 MHz): δ = 0.95 (s, 9H, *tert*-butyl), 3.10 (dd, J_1 = 4.1, J_2 = 2.8, 2-H), 3.44 (br., 1H, 3-H), 3.62 (br., 1H, OH), 3.76 (s, 3H, OCH_3), 4.23–4.31 (m, 1H, 1'-H), 4.56 (br., 1H, OH). – ^{13}C NMR (75 MHz): δ = 25.81 (CH_3), 36.16 (C), 43.81 (CH), 52.44 (CH_3), 72.72 (q, J_{CF} = 31.5), 79.81 (CH), 124.23 (q, J_{CF} = 282.0), 173.17 (C). – ^{19}F NMR (282.2 MHz): δ = –78.42 (d, J_{HF} = 6.7). – MS: *m/z* (%) = 201 (100), 169 (25), 123 (80), 103 (68), 87 (23), 71 (52), 69 (22), 57 (88), 43 (39), 41 (46), 29 (25). – $C_{10}H_{17}F_3O_4$ (258.23): calcd. C 46.51, H 6.64; found C 46.78, H 6.52.

(2R,4R,5S,6R)-Isomer **11**: A solution of **5a** (0.75 g, 2.1 mmol) in THF (20 ml) with 3 N HCl was stirred at room temp. for one weak. The mixture was extracted several times with Et_2O, and the combined org. extracts were dried ($MgSO_4$). After evaporation of the volatile components in high vacuum, the crude product was recrystallized from hexanes to yield 0.41 g (55%) of pure **11**; m.p. 165.0–166.5°C. – $[\alpha]_D^{rt}$ = –6.0 (*c* = 0.97, C_2H_5OH). – IR ($CHCl_3$): $\tilde{\nu}$ = 3425 cm^{-1} (br.), 2930 (s), 2855 (s), 1765 (s), 1730 (m), 1460 (m), 1430 (m), 1400 (m), 1380 (m), 1340 (m), 1290 (m), 1260 (m), 1150 (s), 1040 (m). – ^1H NMR (300 MHz): δ = 0.81–0.94 (m, 2H, cyclohex.), 1.06–1.32 (m, 8H, cyclohex.), 1.54–1.91 (m, 11H, cyclohex.), 2.12 (d, *J* = 11.5, 1H), 2.92 (dd, J_1 = 2.5, J_2 = 2.5, 5-H), 3.42 (dd, J_1 = 10.1, J_2 = 2.3, 6-H), 4.19 (qd, J_1 = 6.4, J_2 = 2.7, 4-H), 4.43 (d, *J* = 5.2, 2-H), 8.0–10.0 (br., 1H, COOH). – ^{13}C NMR (75 MHz): δ = 25.18 (CH_2), 25.32 (CH_2), 25.49 (CH_2), 26.18 (CH_2), 26.61 (CH_2), 26.99 (CH_2), 27.77 (CH_2), 29.36 (CH_2), 39.69 (CH), 41.67 (CH), 41.82 (CH), 76.41 (q, J_{CF} = 32.5), 82.68 (CH), 106.68 (CH), 122.20 (q, J_{CF} = 280.0), 169.36 (C). – ^{19}F NMR (282.2 MHz): δ = –76.86 (d, J_{HF} = 6.3). – MS: *m/z* (%) = 364 (1) [M^+ + 1], 281 (100), 235 (35), 217 (24), 111 (21), 95 (84), 83 (36), 81 (16), 79 (10), 69 (5), 55 (36), 41 (22). – $C_{18}H_{27}F_3O_4$ (364.40): calcd. C 59.33, H 7.47; found C 59.07, H 7.28.

Crystal Structure Determination of **4a**[11]: ENRAF-Nonius CAD4 diffractometer, Mo-K_α radiation, λ = 0.7107 Å, graphite monochromator, *T* = 293 K. Crystal data: $C_{14}H_{23}F_3O_4$, M_r = 312.32, orthorhombic space group $P2_12_12_1$, *a* = 9.7079(10), *b* = 10.518(3), *c* = 15.637(6) Å, α = 90.00, β = 90.00, γ = 90.00°, *V* = 1596.6(8) Å^3, *Z* = 4, D_{calc} = 1.299 g/cm^{-3}, *F*(000) = 664, μ(Mo-K_α) = 0.115 mm^{-1}, 1981 unique reflexions, 1384 "observed" with $I > 3\sigma(I)$, *R* = 0.0374. The structure was solved with SHELX-86[12] and refined by full-matrix least-squares techniques with SHELX-76[13] by using anisotropic displacement parameters for all non-hydrogen atoms. The presentation of the structure was possible by using the program PLUTO[14].

Crystal Structure Determination of **7**[11]: ENRAF-Nonius CAD4 diffractometer, Mo-K_α radiation, λ = 0.7107 Å, graphite monochromator, *T* = 85 K. Crystal data: $C_{14}H_{26}O_4$, M_r = 258.35, orthorhombic space group $P2_12_12_1$, *a* = 9.457(2), *b* = 10.601(4), *c* = 15.222(9) Å, α = 90.00, β = 90.00, γ = 90.00°, *V* = 1526.1(1.2) Å^3, *Z* = 4, D_{calc} = 1.123 g/cm^{-3}, *F*(000) = 616, μ(Mo-K_α) = 0.09 mm^{-1}, 1905 unique reflexions, 1634 "observed" with $I > 3\sigma(I)$, *R* = 0.032. The structure was solved with SHELX-86[12] and refined by full-matrix least-squares techniques with SHELX-76[13] by using anisotropic displacement parameters for all non-hydrogen atoms. The presentation of the structure was possible by using the program PLUTO[14].

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[287/93]