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Bioactive butenolides from *Streptomyces antibioticus* TÜ 99: absolute configurations and synthesis of analogs

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Abstract—The four furanones (butenolides) **1**–**4**, which had been isolated from the fermentation broth of *Streptomyces antibioticus* TÜ 99 and in preliminary tests had been shown to be biologically active, were synthesized by reaction of the readily available furanones **9** or **16** with 2-methylpropanal or 2-methylbutanal. In addition, a series of analogs was prepared in a similar way from **16** using different aldehydes. The hitherto unknown absolute configurations of the natural products **1**–**4** as well as those of all the analogs prepared were determined with Mosher's NMR method and/or X-ray crystallography. Some of the compounds synthesized proved to be active in the quorum sensing system of *Chromobacterium violaceum*.

1. Introduction

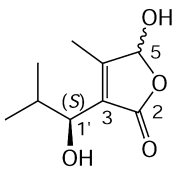
In the 1960s, the strain *Streptomyces antibioticus* TÜ 99 was characterized with respect to the metabolites produced and was shown to yield chlorothricin and bromothricin,[1] the juglomycins A and B, ketomycin,[2] the nikkomycins Z and J,[1] as well as nocardamine. Later, the strain was reinvestigated using HPLC with photoconductivity detection,[3] which led to the discovery of four new metabolites, the substituted butenolides **1**–**4**. These butenolides (furanones) showed in preliminary tests an antibiotic activity against *Pseudomonas* as well as a weak inhibition of the chitinase from *Serratia marcescens*. However, only small amounts could be isolated which did neither allow a determination of the absolute configurations nor permit a more detailed investigation of the biological properties. Therefore, synthetic routes to this class of molecules were sought.[4]

2. Results and discussion

2.1. Syntheses

The synthetic pathway sought not only should yield the natural metabolites **1**–**4** but should allow the introduction of different side chains at C(3). Deliberately, a non-stereoselective approach was used, since stereoisomers of biologically active natural products often allow interesting conclusions with respect to structure-activity relationships. The hemiacetalic compounds **1** and **3** epimerize in solution to mixtures of stereoisomers, which makes their isolation and characterization tedious; therefore, the first synthetic targets were compounds **2** and **4**, which lack the C(5) OH group.

Cycloaddition of diazomethane to the commercially



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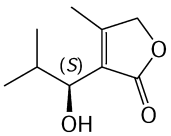

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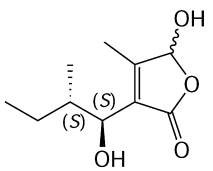

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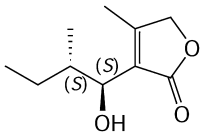

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Keywords: butenolides; 2(5*H*)-furanones; *Streptomyces antibioticus*; Mosher esters; quorum sensing.

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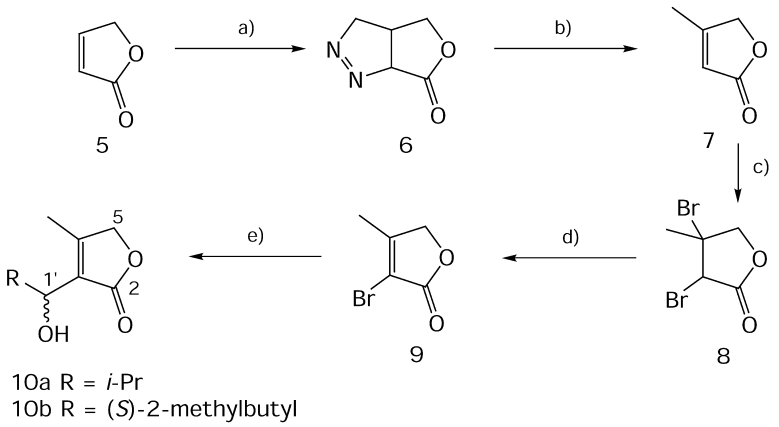
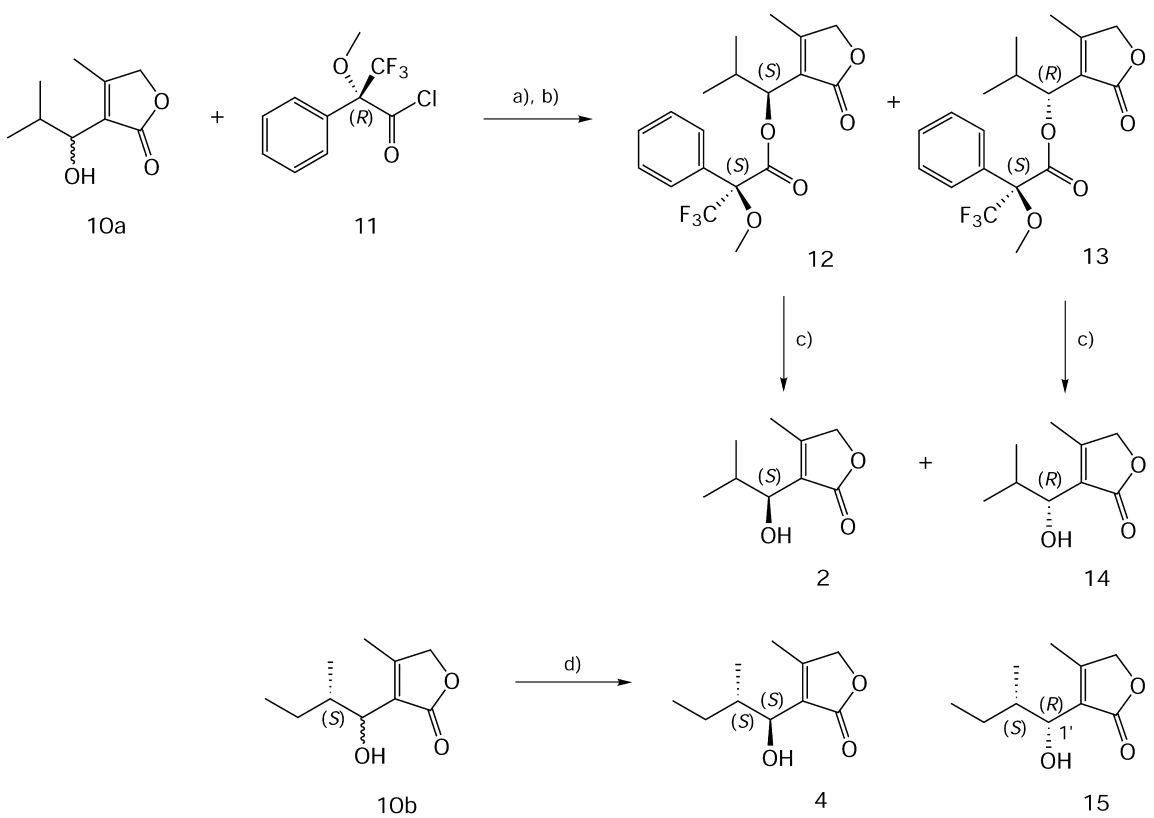


Scheme 1. (a) Et_2O, diazomethane, rt, 90%. (b) Dioxane, 130°C, 87%. (c) CH_2Cl_2, Br_2, 40°C, 87%. (d) CH_2Cl_2, *sym*-collidine, rt, 92%. (e) THF/pentane/Et_2O, *tert*-BuLi, 2-methylpropanal for **10a**/(*S*)-2-methylbutanal for **10b**, −120°C, 57–60%.

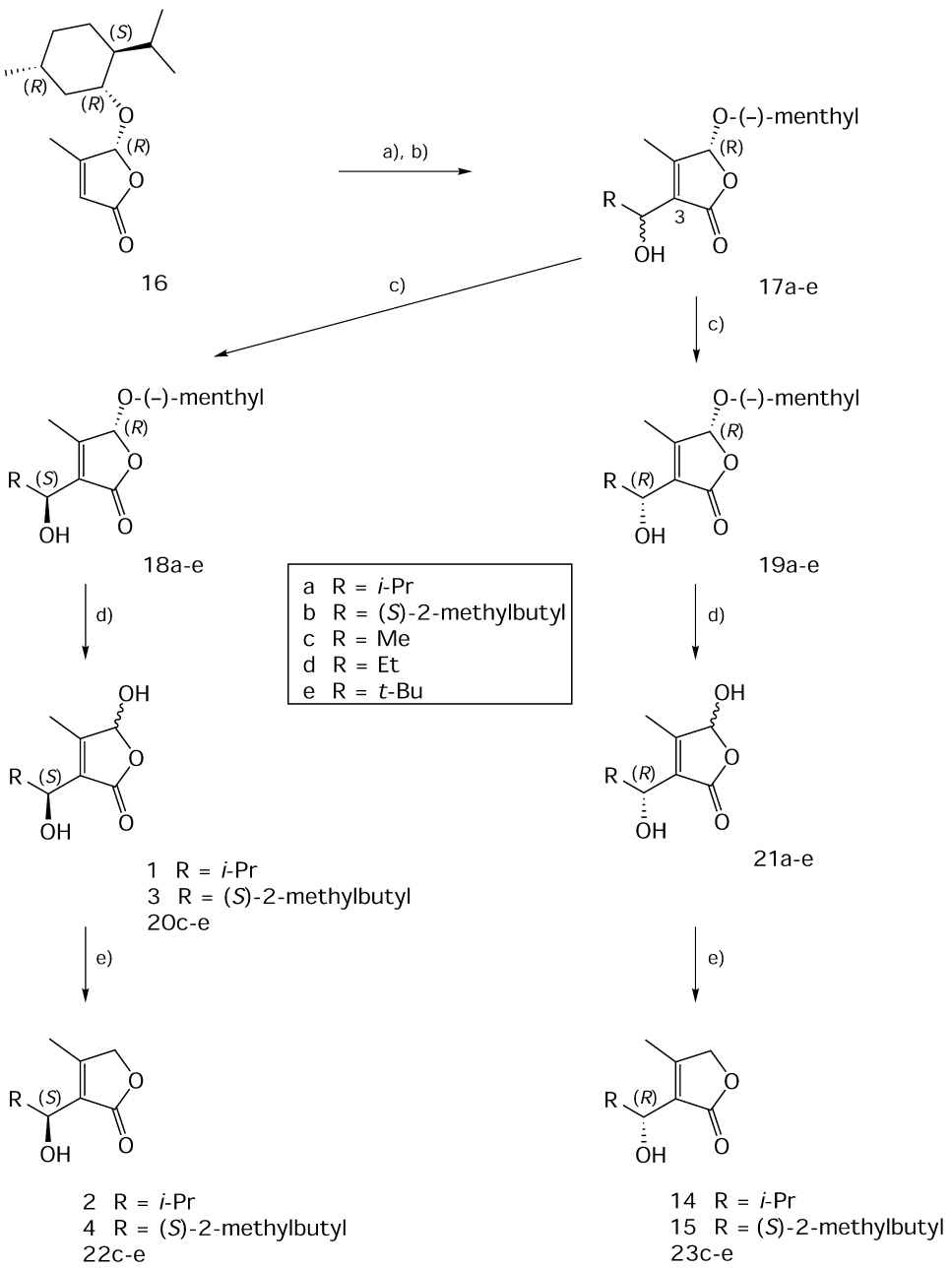
available 2(5*H*)-furanone (**5**) followed by elimination of nitrogen gave the methylated furanone **7** (Scheme 1), which was then transformed to **8** and subsequently to **9** by a bromination–dehydrobromination process. Halogen-metal exchange with *tert*-butyllithium gave a nucleophile, which now could be added to suitable aldehydes. Reaction with 2-methylpropanal or (*S*)-2-methylbutanal gave the racemate **10a** and the pair of diastereomers **10b**, respectively.

Racemate **10a** was esterified with (*R*)-Mosher acid chloride (**11**) to give **12** and **13** (Scheme 2), which could be separated by HPLC. Saponification then yielded the natural product **2** and its enantiomer **14**. Since **10b** was a mixture of diastereomers, direct separation by HPLC could be achieved to give natural product **4** and its 1′-epimer **15**.

To alleviate the problem of epimerization, the synthesis of compounds **1** and **3** was started with the menthyl ether **16** (Scheme 3) which is easily accessible in optically pure form[5] from the condensation product of propanal with glyoxylic acid and (−)-menthol, and where the hemiacetalic OH group is blocked. Ether **16** was treated with LDA, which, aided by the large protecting menthyl group, led to abstraction of H–C(3) rather than of the more activated H–C(5); the nucleophile thus obtained was reacted with a variety of aldehydes to give the diastereomeric mixtures



Scheme 2. (a) Pyridine, CCl_4, rt. (b) HPLC RP-C18, water/MeOH 3:7. (c) Dioxane, 1.2 M NaOH in water, 80°C, 1 h. (d) HPLC RP-C18, water/THF 87:13.



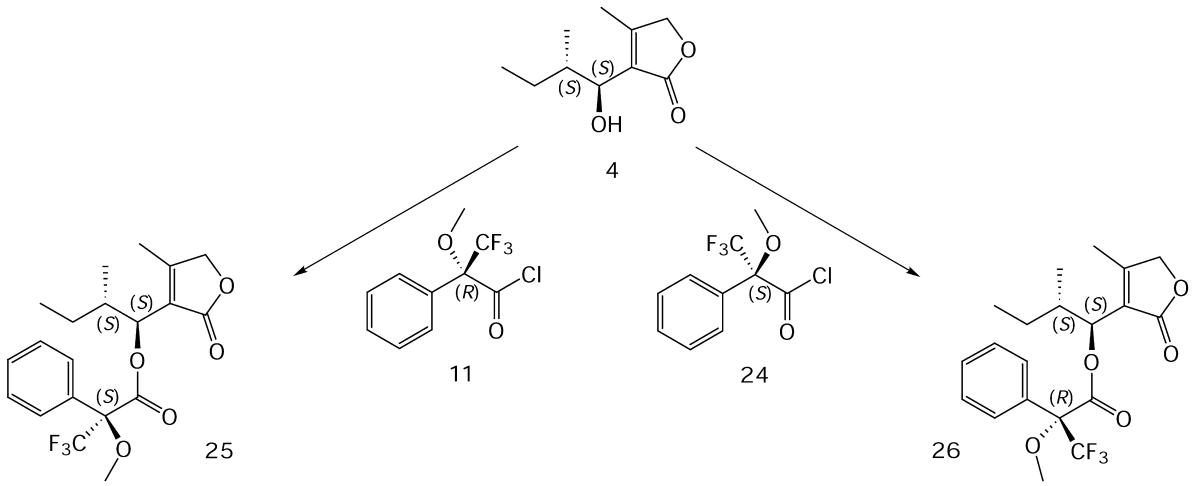
Scheme 3. (a) THF, LDA (1.1 equiv.), −78°C, 30 min. (b) Aldehyde, −78°C, 30 min. (c) Flash chromatography SiO_2. (d) CH_2Cl_2, BBr_3, −78°C. (e) MeOH, $NaBH_4$, 0°C.

17a–e, which were separated by flash chromatography into the epimers **18a–e** and **19a–e**. After removal of the menthyl group with boron tribromide,[6] compounds **1**, **3**, **20c–e** and **21a–e** were obtained, respectively; their reduction with $NaBH_4$ gave eventually **2**, **4**, **22c–e**, **14**, **15**, and **23c–e**, respectively. The synthetic products **1–4** were identical with the natural products originally isolated from the fermentation broth.

2.2. Determination of the configurations

The absolute configuration at C(2′) of metabolites **3** and **4** was determined at an early stage of the project by GC comparison of the natural product **4** with the two product mixtures obtained from the bromofuranone **9** with (*S*)-2-methylbutanal and with (*RS*)-2-methylbutanal, respectively. The natural product **4** showed the same retention time as one of the products obtained from (*S*)-2-methylbutanal. Therefore, the C(2′) configuration of **4** had to be (*S*). The same had to be true for **3**, since this compound could be obtained from **4** by reduction with sodium borohydride.

The absolute configurations at C(1′) were determined with Mosher's empirical NMR method for secondary alcohols.[7] Whereas derivatives **12** and **13**, which were used in the resolution of the racemate **10a**, were directly suited for the NMR analysis, compound **4** had to be esterified once with (*R*)-Mosher acid chloride (**11**) and once with (*S*)-Mosher acid chloride (**24**) to give **25** and **26**, respectively (Scheme 4).



Scheme 4.

According to Mosher[7] the preferred conformation for esters of α-methoxy-α-trifluoromethylphenylacetic acid (MTPA, Mosher's acid) is such that all the bonds between the CF_3 group and the hydrogen at the OH bearing carbon of the alcohol part lie more or less in one plane (the 'MTPA plane'[8]). In this arrangement (Fig. 1), the phenyl group of the MTPA part shields the protons of that alcohol part which is in an eclipsed position to it. Thus, a comparison of the chemical shifts of **12** with the corresponding values for **13** will reveal the absolute configurations. The chemical shift differences $\Delta\delta=\delta_{12}-\delta_{13}$ are compiled in Table 1. They are negative for the protons of the isopropyl group and positive for the protons of the furanone part. This is a proof for the (*S*)-configuration at C(1′) of **12**; the same must hold for the synthetic product **2**. In a similar way, chemical shift comparison of **25** and **26** (Table 1) led to the conclusion that **25** had the (*S*) configuration at C(1′), which then must also be the configuration of the synthetic compound **4**. In both pairs of isomers, the proton at C(2′) shows an unusual behavior. The chemical shift differences observed are opposite to what is expected. Preliminary calculations suggested that the furanone ring adopts different orientations in **12** and **13**, which might lead to different shieldings of H–C(2′) by the furanone carbonyl group in the two isomers.[9]

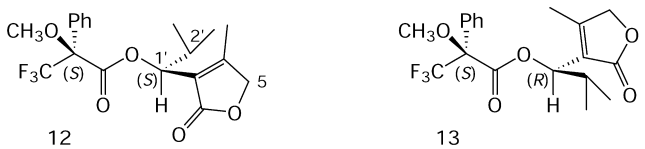


Figure 1. Preferred conformations for the Mosher esters **12** and **13** (the torsion angles shown around the bonds leading to the furanone and to the isopropyl group, respectively, are arbitrary).

Table 1. Chemical shifts and chemical shift differences for selected protons of the Mosher esters **12**, **13**, **25**, and **26**

	δ of **12** (ppm)	δ of **13** (ppm)	Δδ (ppm)	δ of **25** (ppm)	δ of **26** (ppm)	Δδ (ppm)
H_a–C(5)	4.92	4.61	+0.08	4.60	4.69	−0.09
H_b–C(5)	4.65	4.57	+0.08	4.56	4.65	−0.09
CH_3–C(4)	2.21	1.89	+0.32	1.90	2.11	−0.21
CH_3–C(2′)	0.81	0.87	−0.06	0.83	0.77	+0.06
CH_3–C(2′)	0.85	1.02	−0.17			
H–C(2′)	2.49	2.42	+0.07	2.24	2.33	−0.10
H_a–C(3′)				1.63	1.43	+0.20
H_b–C(3′)				1.20	1.03	+0.17
H–C(4′)				0.90	0.80	+0.10

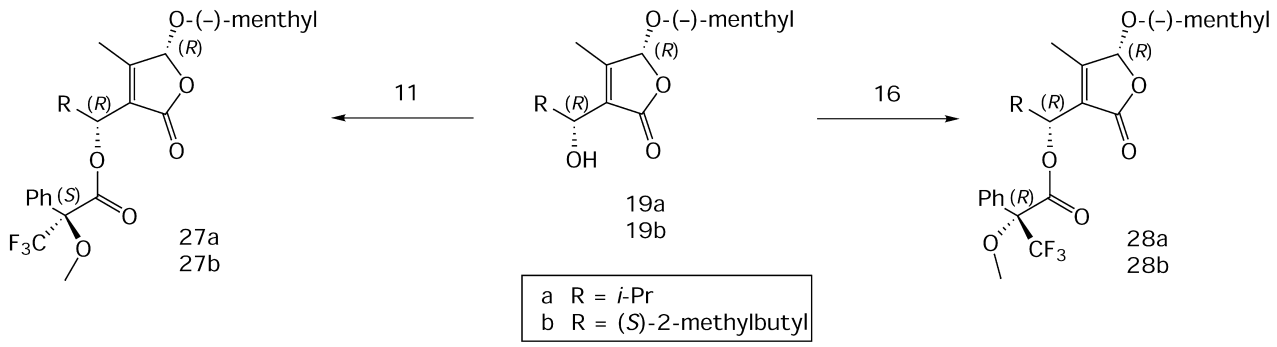
The correlation between the synthetic products **1**–**4** and the metabolites originally isolated was made by comparison of the NMR spectra and the specific rotations. Since metabolite **2** had been isolated in such a small quantity that the specific rotation could not be determined, a tiny amount of the natural product was esterified with (*R*)-Mosher's acid chloride (**11**); the derivative obtained was identical to **12** by 600 MHz ^{1}H NMR and HPLC.

The configurations in the pairs **18a/19a** and **18b/19b** were determined again with Mosher's method: compounds **19a** and **19b** were each derivatized once with (*R*)-Mosher's acid chloride (**11**) and once with (*S*)-Mosher's acid chloride (**24**) (Scheme 5). The resulting pairs of esters **27a/28a** and **27b/28b** were subjected to NMR analysis as described above (see chemical shifts in Section 4), which led to the absolute configurations shown in the schemes.

Finally, compounds **13**, **18c**,**e**, **19d**, **25**, **27a**, and **27b** gave crystals that were suitable for X-ray structure determinations. For **18c**,**e**, and **19d** these crystal structures were the anchoring points for the absolute configurations in the corresponding series of compounds, whereas in the cases of **13**, **25**, **27a**,**b** corroboration of the configurational assignments made from the NMR measurements was obtained. In addition, the crystal structures of the MTPA esters confirmed that the preferred solution conformation (Fig. 1), which is the basis of Mosher's method for the determination of absolute configurations, is also present in the crystal, although the 'MTPA plane' is in some cases somewhat distorted. The structure of **13** (Fig. 2) is shown as an example. To our knowledge, the 'MTPA plane' has so far only rarely been visualized by X-ray structure determinations.[8]

2.3. Biological activity

A selection of the compounds prepared were tested for their



Scheme 5.

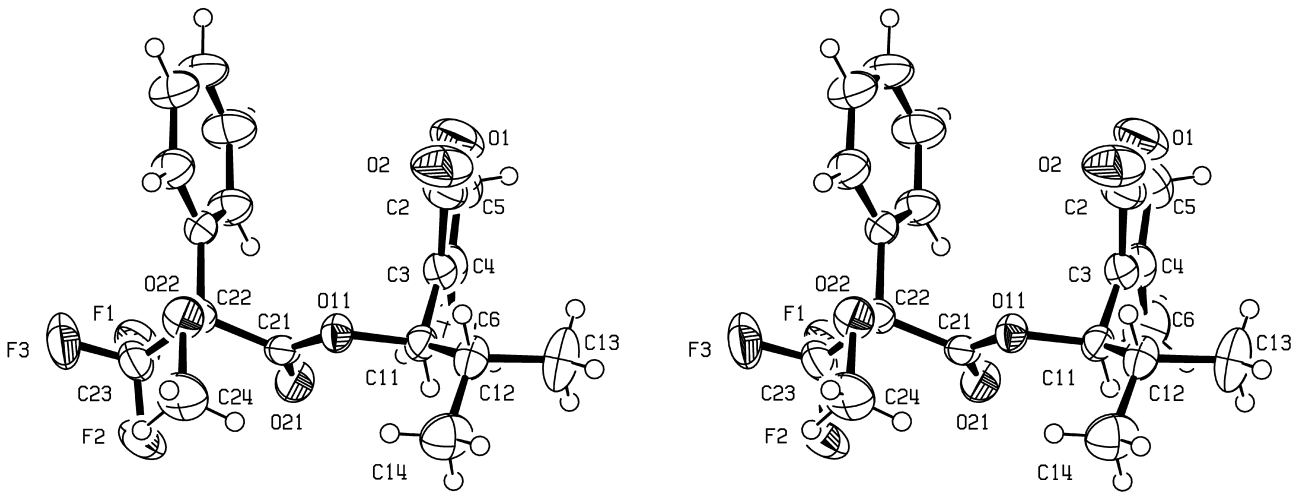
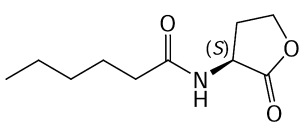


Figure 2. Crystal structure of **13**, stereo view.

biological properties. The weak antimicrobial activity detected in preliminary tests[3] with the natural products **1**–**4** could not be confirmed; none of the compounds tested with the agar diffusion method at a concentration of 1 mg/ml showed any activity against a variety of microorganisms (6 Gram positive bacteria, 3 Gram negative bacteria, and 6 fungi).[10] However, some of the compounds proved to interfere with the quorum sensing system of the *Chromobacterium violaceum* mutant CV026.[11] Furanones **21c**,**d**,**e** were found to inhibit violacein production when administered together with an optimal concentration of *N*-hexanoylhomoserine lactone (**29**), the natural signaling compound of *C. violaceum*. In contrast, the natural metabolites **3** and **4** and their diastereoisomers **21b** and **15** proved to be activators: they showed a synergistic effect when administered together with a suboptimal concentration of *N*-hexanoylhomoserine lactone.[12]



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3. Conclusion

An easy access was found to the natural butenolides **1**–**4** and to their analogs and stereoisomers. Unfortunately, the antimicrobial activity observed earlier[3] for the natural products **1**–**4** could not be confirmed. However, the interesting behavior in the quorum sensing system of *Chromobacterium violaceum* displayed by some of the furanones described makes this class of compounds a valuable target for further investigations.

4. Experimental

4.1. General information

Chemicals were bought from Fluka AG, Merck GmbH, Acros Organics, and Aldrich Chemical Company, Inc. Flash chromatography: silica gel 60 (0.040–0.063 mm) from Merck and from Macherey–Nagel. All solvents for flash chromatography were distilled solvents of a technical quality. THF was freshly distilled over Na under Ar before use. The removal of solvents was done under vacuum in a rotary evaporater. Mp: Büchi 535 apparatus or Kofler hot stage, uncorrected. Optical rotations: Perkin–Elmer 141 (10 cm cell) and Perkin–Elmer 341 (10 cm cell) at 20°C. NMR Spectra: Varian Gemini 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz), Varian VXR 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) Bruker VRX 500 (^{1}H: 500 MHz, ^{13}C 125 MHz); chemical shifts (δ) in ppm downfield from TMS (δ=0.0) as internal standard; coupling constants J in Hz; in ^{13}C NMR spectra of Mosher esters, the resonances of the CF_3 and of the 4°

carbon next to it were not always clearly observed due to the splitting by J_{CF} and long relaxation times. MS: VG 70–250 (EI, 70 eV) spectrometer and Finnigan MAT 312 (FAB-MS, matrix: 3-nitrobenzyl alcohol (NBA)). Elemental analyses were performed by the Microanalytical Laboratory of the Departement Chemie, Universität Basel. MPLC: System Büchi B680 with B687 gradient former, B688 pump and B684 fraction collector; detection: Knauer variable wavelength ultraviolet light detector. Preparative HPLC: System Waters 600 with a pump model 510 (250 μl pump head), a Photodiode Array Detector 991, and Millenium V 2.01 software from Waters. All solvents were HPLC quality.

4.2. X-Ray structure determinations

Crystals of the compounds under investigation were mounted on a Nonius KappaCCD or CAD4 diffractometer. Data collection and integration of the data sets were carried out using the Nonius collect suite.[13] The structures were solved using direct methods using the program SIR92.[14] Least squares refinement was carried out using the program CRYSTALS.[15] Plots were produced using Ortep3 for Windows.[16] Chebychev polynomial weights[17] were used to complete the refinement. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication. CCDC-numbers: **13**: 187135; **18c**: 187134; **18e**: 187132; **19d**: 187133; **25**: 187136; **27a**: 187130; **27b**: 187131. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.3. Syntheses

4.3.1. 3,3a,4,6a-Tetrahydrofuro[3,4,-*c*]pyrazol-6-one 6. A solution of diazomethane (3.00 g, 71.0 mmol) in Et_2O (300 ml) was added with careful stirring to (5*H*)-furan-2-one (4.79 g, 57.0 mmol). The reaction mixture was left overnight at rt. Then, the excess diazomethane was destroyed with a 5% solution of benzoic acid in Et_2O. The precipitated product was filtered off, washed with Et_2O, dried and recrystallized from warm THF to yield **6** (6.48 g, 51.4 mmol, 90%) as colorless prisms. Mp 109.5–110.5°C (Lit.,[18] 110.0–110.5°C). ^{1}H NMR (400 MHz, $CDCl_3$): 5.58 (ddd, J=9.3, 2.2, 2.0 Hz, 1H, H–C(6a)); 4.88 (ddd, J=18.6, 8.0, 2.0 Hz, 1H, H_a–C(3)); 4.83 (ddd, J=18.6, 3.7, 2.2 Hz, 1H, H_b–C(3)); 4.58 (dd, J=9.8, 8.7 Hz, 1H, H_a–C(4)); 3.87 (dd, J=9.8, 4.8 Hz, 1H, H_b–C(4)); 3.14 (m, 1H, H–C(3a)). ^{13}C NMR (75 MHz, $CDCl_3$): 168.7; 93.2; 86.4; 73.0; 31.0. EI-MS: 70 (12), 69 (100), 68 (80), 55 (16), 54 (14), 53 (13), 42 (58), 41 (81), 40 (67), 39 (82), 39 (14).

4.3.2. 4-Methylfuran-2(5*H*)-one 7. A solution of **6** (2.50 g, 19.8 mmol) in dioxane (25 ml) was heated for 1 h at 70°C. The temperature of the oil bath was incrementally raised by 20°C/h up to 130°C. Then, the reaction was refluxed for 48 h. After cooling down, the solvent was distilled off under reduced pressure; vacuum distillation of the crude product gave **7** (1.69 g, 17.2 mmol, 87%) as a colorless, hygroscopic liquid. Bp 101–103°C [12 mbar] (Lit.,[19] 105–107°C [15 mbar]). ^{1}H NMR (300 MHz, $CDCl_3$): 5.86–5.83 (m, 1H, H–C(3)); 4.74–4.72 (m, 2H, H–C(5)); 2.15–2.13 (m, 3H, H_3C–C(4)). ^{13}C NMR (75 MHz, $CDCl_3$): 174.2; 166.2; 116.4; 74.0; 14.1. EI-MS: 98 (45, M^+), 84 (10), 70 (10), 69 (100), 68 (20), 41 (59), 40 (34), 39 (41), 38 (14).

4.3.3. 3,4-Dibromo-4,5-dihydro-4-methylfuran-2(3*H*)-one 8. To a solution of **7** (3.14 g, 32.0 mmol) in CH_2Cl_2 (15 ml), a solution of bromine (3.50 ml, 10.9 g, 68.1 mmol) in $CHCl_3$ (5 ml) was added over 30 min at rt under protection from light with an aluminum sheet. The resulting mixture was refluxed for 24 h. After cooling, the excess of bromine was removed by bubbling argon through the solution. After the addition of saturated $NaHCO_3$ solution (20 ml), the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, and the solvent was evaporated. Flash chromatography (gradient hexane/CH_2Cl_2 1:1 ∅ 1:3 ∅ CH_2Cl_2) afforded **8** (7.18 g, 27.8 mmol, 87%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): 4.68 (s, 1H, H–C(3)); 4.59 (d, J=10.9 Hz, 1H, H_a–C(5)); 4.44 (d, J=10.9 Hz, 1H, H_b–C(5)); 2.06 (s, 3H, H_3C–C(4)). ^{13}C NMR (75 MHz, $CDCl_3$): 170.5; 78.0; 61.8; 47.9; 25.3. EI-MS: 260 (1), 258 (2), 256 (1, M^+), 135 (63), 133 (66), 121 (13), 119 (12), 81 (12), 79 (12), 69 (28), 53 (100), 51 (11), 50 (11), 41 (52).

4.3.4. 3-Bromo-4-methylfuran-2(5*H*)-one 9. 2,4,6-Trimethylpyridine (9.20 ml, 8.43 g, 69.6 mmol) was added to a solution of **8** (5.98 g, 23.2 mmol) in CH_2Cl_2 (250 ml). After stirring for 1.5 h at rt, the reaction mixture was successively washed two times with 10% H_2SO_4 solution (100 ml), two times with saturated $NaHCO_3$ solution (100 ml) and once with brine (100 ml). The combined organic phase was dried over Na_2SO_4, filtered and the solvent evaporated. Flash chromatography with a gradient hexane/CH_2Cl_2 1:4 ∅ CH_2Cl_2 afforded **9** (3.78 g, 21.4 mmol, 92%) as yellow prisms. Mp 65–66°C. (Lit.,[20] 64–65°C). ^{1}H NMR (300 MHz, $CDCl_3$): 4.76 (q, J=0.9 Hz, 2H, H–C(5)); 2.13 (t, J=0.9 Hz, 3H, H_3C–C(4)). ^{13}C NMR (75 MHz, $CDCl_3$): 169.2; 160.6; 108.9; 73.4; 13.9. EI-MS: 178 (33), 176 (34, M^+), 149 (94), 147 (100), 121 (62), 119 (80), 117 (16), 97 (20), 93 (12), 81 (19), 79 (20), 68 (10), 67 (63), 66 (18), 53 (45), 52 (12), 51 (33), 50 (41), 49 (15), 41 (22). Anal. calcd for $C_5H_5BrO_2$ (177.00): C 33.93, H 2.85, O 18.08; found: C 33.75, H 2.95, O 18.14.

4.3.5. 3-[(*RS*)-1-Hydroxy-2-methylpropyl]-4-methylfuran-2(5*H*)-one 10a. A solution of **9** (710 mg, 4.01 mmol) in a mixture of absolute THF (60 ml), pentane (15 ml) and absolute Et_2O (15 ml) under argon was cooled to −120°C (EtOH/N_2). Under vigorous stirring, a 1.3 M solution of *tert*-butyllithium in hexane (3.09 ml, 4.01 mmol) was quickly added. After 1 min, 2-methylpropanal (366 μl, 289 mg, 4.01 mmol) was added. The reaction mixture was allowed to warm up to −10°C over 3 h, and the reaction was quenched with a saturated $(NH_4)_2SO_4$ solution (30 ml). The two-phase system was acidified with conc. HCl to pH 2–3. The aqueous phase was separated and extracted two times with CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4, filtered and the solvent evaporated. A first purification with MPLC (LiChroPrep 25–40; eluent A, 95% water/5% MeOH, eluant B, MeOH; gradient 0 min (100:0), 10 min (100:0), 60 min (0:100); t_R=38–40 min) followed by HPLC (Eurospher 100-7 RP-C18; water/THF (85:15), t_R=19–22 min) afforded **10a** (387 mg, 2.27 mmol, 57%) as

a colorless, viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): 4.70 (d, J=17.3 Hz, 1H, H_a–C(5)); 4.67 (d, J=17.3 Hz, 1H, H_b–C(5)); 4.14 (d, J=8.0 Hz, 1H, H–C(1′)); 3.13 (br, 1H, HO–C(1′)); 2.09 (s, 3H, H_3C–C(4)); 2.08–1.97 (m, 1H, H–C(2′)); 1.05 (d, J=6.7 Hz, 3H, H–C(3′)); 0.84 (d, J=6.8 Hz, 3H, H_3C–C(2′)). ^{13}C NMR (75 MHz, $CDCl_3$): 174.3; 158.5; 127.4; 72.8; 72.4; 33.9; 18.8; 18.5; 12.5. FAB-MS (NBA): 172 (10), 171 (100, $[M+H]^+$), 153 (62), 71 (10), 57 (25), 55 (16), 43 (30), 41 (13). Anal. calcd for $C_9H_{14}O_3$ (170.21): C 63.51, H 8.29, O 28.20; found: C 63.11, H 8.11, O 28.31.

4.3.6. (1*S*)-1-(4-Methyl-2-oxo-2,5-dihydrofuran-3-yl)-2-methylpropyl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 12 and (1*R*)-1-(4-methyl-2-oxo-2,5-dihydrofuran-3-yl)-2-methylpropyl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 13. (2*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyl chloride ((*R*)-Mosher's acid chloride, **11**) (100 mg, 0.396 mmol) was dissolved at rt in abs. pyridine (1 ml) under argon. A solution of **10a** (48.2 mg, 0.283 mmol) in abs. CCl_4 (1 ml) was added at rt and the resulting mixture was stirred at this temperature for 24 h. Then, 3-dimethylamino-1-propylamine (84.0 μl, 68.5 mg, 0.671 mmol) was added and the resulting solution was stirred for further 15 min. After the addition of Et_2O (5 ml), the solution was washed with cold 1N HCl, saturated $NaHCO_3$ solution, and brine. The combined organic phases were dried over Na_2SO_4, filtered, and the solvent was evaporated. Purification and separation of the diastereoisomers with HPLC (Eurospher 100-7 RP-C18; water/MeOH 30:70; t_R **12**=16.5–20.0 min, t_R **13**=20.5–21.5 min) gave **12** (34.6 mg, 0.090 mmol, 32%) and **13** (37.4 mg, 0.097 mmol, 34%) as cubes.

Data of (1*S*)-1-(4-Methyl-2-oxo-2,5-dihydrofuran-3-yl)-2-methylpropyl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**12**). Mp 85.7–88.2°C. $[\alpha]_D^{20}$=−60.0 (c=1.04, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): 7.53–7.37 (m, 5H, phenyl); 5.35 (d, J=9.2 Hz, 1H, H–C(1′)); 4.69 (d, J=17.3 Hz, 1H, H_a–C(5)); 4.65 (d, J=17.3 Hz, 1H, H_b–C(5)); 3.52 (s, 3H, H_3CO–C(2″)); 2.53–2.44 (m, 1H, H–C(2′)); 2.21 (s, 3H, H_3C–C(4)); 0.85 (d, J=6.6 Hz, 3H, H–C(3′)); 0.81 (d, J=6.8 Hz, 3H, H_3C–C(2′)). ^{13}C NMR (75 MHz, $CDCl_3$): 171.9; 166.2; 162.9; 131.9; 129.7; 128.4; 127.3; 123.8; 123.3 (q, $^1J_{CF}$=287 Hz); 84.5 (q, $^2J_{CF}$=28 Hz); 75.6; 72.5; 55.6; 29.9; 18.7; 18.4; 12.7. FAB-MS (NBA): 387 (10, $[M+H]^+$), 189 (12), 153 (100), 57 (22), 55 (15), 43 (24), 41 (13). Anal. calcd for $C_{19}H_{21}F_3O_5$ (386.37): C 59.06, H 5.48, O 20.71; found: C 58.85, H 5.71, O 20.70.

Data of (1*R*)-1-(4-Methyl-2-oxo-2,5-dihydrofuran-3-yl)-2-methylpropyl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**13**). Mp 87.2–90.4°C. $[\alpha]_D^{20}$=−2.9 (c=2.18, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): 7.47–7.37 (m, 5H, phenyl); 5.41 (d, J=9.0 Hz, 1H, H–C(1′)); 4.61 (d, J=17.3 Hz, 1H, H_a–C(5)); 4.57 (d, J=17.3 Hz, 1H, H_b–C(5)); 3.55 (s, 3H, H_3CO–C(2″)); 2.49–2.34 (m, 1H, H–C(2′)); 1.89 (s, 3H, H_3C–C(4)); 1.02 (d, J=6.6 Hz, 3H, H–C(3′)); 0.87 (d, J=6.8 Hz, 3H, H_3C–C(2′)). ^{13}C NMR (75 MHz, $CDCl_3$): 172.0; 166.1; 162.0; 131.8; 129.7; 128.4; 127.3; 124.0; 123.2 (q, $^1J_{CF}$=287 Hz); 84.6 (q, $^2J_{CF}$=28 Hz); 75.8; 72.4; 55.7; 30.5; 18.9; 18.5; 12.5. FAB-MS (NBA): 387 (10, $[M+H]^+$), 189 (13), 153 (100), 57 (14), 55 (10), 43 (17), 41 (10). Anal. calcd for $C_{19}H_{21}F_3O_5$ (386.37): C 59.06, H 5.48, O 20.71; found: C 59.05, H 5.55, O 20.70. Crystal data: crystallized from hexane/CH_2Cl_2; M_r: 386.37 g/mol; crystal system: orthorhombic; space group: $P2_12_12_1$; a: 9.402(1) Å; b: 10.634(2) Å; c: 19.152(4) Å; α: 90°; β: 90°; γ: 90°; V: 1914.9(5) Å^3; Z: 4; F(000): 808; density: 1.34 g/cm^{-3}; μ: 0.11 mm^{-1}; crystal size: 0.30×0.50×0.70 mm^3; temperature: 293 K; radiation type: Mo Kα wavelength: 0.71073 λ; instrument: CAD4; θ_{max}: 30.44°; no. of measured reflections: 2795; no. of independent reflections: 2782; no. of reflections in refinement: 2100; no. of variables: 245; final R: 0.0385; final R_w: 0.0424; weighting scheme: Chebychev polynomial; last max/min in difference map: 0.21/−0.22 eÅ^{-3}; CCDC-number; 187135.

4.3.7. 3-[(1*S*)-1-Hydroxy-2-methylpropyl]-4-methylfuran-2(5*H*)-one 2. Compound **12** (35 mg, 0.091 mmol) was dissolved in a mixture of dioxane (12 ml) and 1.2 M NaOH in water (12 ml). The solution was heated at 80°C for 1 h. After cooling, the mixture was acidified (pH ~3) with diluted HCl and extracted 3× with Et_2O (60 ml). The combined organic phases were dried over Na_2SO_4, filtered, and the solvent was evaporated. Purification with HPLC (Eurospher 100-7 RP-C18; eluent: water/MeOH gradient 0 min (50:50) 30 min (0:100); t_R **2**=9.4 min) gave **2** (8.00 mg, 0.047 mmol, 52%) as a colorless oil. $[\alpha]_D^{20}$=−16.5 (c=1.00, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): 4.71 (d, J=17.3 Hz, 1H, H_a–C(5)); 4.66 (d, J=17.3 Hz, 1H, H_b–C(5)); 4.14 (d, J=7.9 Hz, 1H, H–C(1′)); 3.13 (br, 1H, HO–C(1′)); 2.09 (s, 3H, H_3C–C(4)); 2.08–1.98 (m, 1H, H–C(2′)); 1.04 (d, J=6.7 Hz, 3H, $(H_3C)_2$–C(2′)); 0.84 (d, J=6.7 Hz, 3H, $(H_3C)_2$–C(2′)). ^{13}C NMR (125 MHz, $CDCl_3$): 174.2; 158.5; 127.3; 72.7; 72.3; 33.7; 18.7; 18.3; 12.4. EI-MS: 152 (10), 128 (23), 127 (100), 110 (36), 109 (12), 99 (24), 82 (32), 53 (14), 43 (29), 41 (17), 39 (15). Anal. calcd for $C_9H_{14}O_3$ (170.21): C 63.51, H 8.29, O 28.20; found: C 63.22, H 8.33, O 28.27.

4.3.8. 3-[(1*R*)-1-Hydroxy-2-methylpropyl]-4-methylfuran-2(5*H*)-one 14. Same procedure as for **2**. Compound **13** (42.0 mg, 0.109 mmol) afforded **14** (10.0 mg, 0.059 mmol, 54%) as a colorless oil. $[\alpha]_D^{20}$=+17.0 (c=1.00, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): 4.71 (d, J=17.3 Hz, 1H, H_a–C(5)); 4.66 (d, J=17.3 Hz, 1H, H_b–C(5)); 4.14 (t, J=8.7 Hz, 1H, H–C(1′)); 3.10 (d, J=9.4 Hz, 1H, HO–C(1′)); 2.08 (s, 3H, H_3C–C(4)); 2.08–2.00 (m, 1H, H–C(2′)); 1.05 (d, J=6.7 Hz, 3H, $(H_3C)_2$–C(2′)); 0.84 (d, J=6.7 Hz, 3H, $(H_3C)_2$–C(2′)). ^{13}C NMR (125 MHz, $CDCl_3$): 174.2; 158.3; 127.4; 72.7; 72.4; 33.8; 18.8; 18.4; 12.4. EI-MS: 152 (12), 128 (23), 127 (100), 110 (36), 109 (13), 99 (24), 82 (31), 53 (14), 43 (29), 41 (18), 39 (15). Anal. calcd for $C_9H_{14}O_3$ (170.21): C 63.51, H 8.29, O 28.20; found: C 63.21, H 8.38, O 28.60.

4.3.9. Mixture 10b: 3-[(1*S*,2*S*)-1-hydroxy-2-methylbutyl]-4-methylfuran-2(5*H*)-one 4 and 3-[(1*R*,2*S*)-1-hydroxy-2-methylbutyl]-4-methylfuran-2(5*H*)-one 15. Compound **9** (400 mg, 2.26 mmol) was coupled with (*S*)-2-methylbutanal[21] (237 μl, 195 mg, 2.26 mmol) using the procedure given for **10a** to yield mixture **10b**. A first purification with MPLC (LiChroPrep 25–40; eluent A, 95% water/5% MeOH, eluant B, MeOH; gradient 0 min (100:0),

10 min (100:0), 60 min (0:100); t_R **10b**=44–46 min) followed by a separation with HPLC (Eurospher 100-7 RP-C18; water/THF (87:13), t_R **4**=18.0–19.5 min and t_R **15**=19.5–22.0 min) afforded **4** (182 mg, 0.998 mmol, 44%) and **15** (74.2 mg, 0.403 mmol, 18%) as colorless oils.

Data of 3-[(1*S*,2*S*)-1-hydroxy-2-methylbutyl]-4-methylfuran-2(5*H*)-one (**4**). $[\alpha]_D^{20}=-34.0$ (c=1.35, MeOH) (nat. prod.[3]: $[\alpha]_D^{23}=-10.4$ (c=0.31, MeOH)). ^{1}H NMR (500 MHz, $CDCl_3$): 4.71 (d, J=17.3 Hz, 1H, H_a–C(5)); 4.66 (d, J=17.3 Hz, 1H, H_b–C(5)); 4.21 (t, J=8.3 Hz, 1H, H–C(1′)); 2.09 (s, 3H, H_3C–C(4)); 1.88–1.81 (m, 1H, H–C(2′)); 1.80–1.73 (m, 1H, H_a–C(3′)); 1.25–1.15 (m, 1H, H_b–C(3′)); 0.93 (t, J=7.5 Hz, 3H, H–C(4′)); 0.79 (d, J=6.8 Hz, 3H, H_3C–C(2′)). ^{13}C NMR (125 MHz, $CDCl_3$): 174.3; 158.5; 127.4; 72.7; 70.9; 39.9; 24.6; 14.9; 12.4; 10.7. EI-MS: 128 (31), 127 (100), 110 (65), 99 (21), 82 (42), 53 (13), 43 (15), 41 (21), 39 (14). Anal. calcd for $C_{10}H_{16}O_3$ (184.24): C 65.19, H 8.75, O 26.05; found: C 65.17, H 8.79, O 26.10.

Data of 3-[(1*R*,2*S*)-1-hydroxy-2-methylbutyl]-4-methylfuran-2(5*H*)-one (**15**) $[\alpha]_D^{20}=+17.0$ (c=1.00, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): 4.70 (d, J=17.3 Hz, 1H, H_a–C(5)); 4.65 (d, J=17.3 Hz, 1H, H_b–C(5)); 4.29 (t, J=8.5 Hz, 1H, H–C(1′)); 3.06 (d, J=9.2 Hz, 1H, HO–C(1′)); 2.08 (s, 3H, H_3C–C(4)); 1.80–1.71 (m, 1H, H–C(2′)); 1.43–1.34 (m, 1H, H_a–C(3′)); 1.30–1.10 (m, 1H, H_b–C(3′)); 1.00 (d, J=6.7 Hz, 3H, H_3C–C(2′)); 0.91 (t, J=7.4 Hz, 3H, H–C(4′)). ^{13}C NMR (125 MHz, $CDCl_3$): 174.3; 158.1; 127.5; 72.7; 71.0; 40.4; 25.6; 14.6; 12.5; 11.5. EI-MS: 128 (40), 127 (100), 110 (67), 99 (23), 82 (47), 53 (15), 43 (19), 41 (24), 39 (15). Anal. calcd for $C_{10}H_{16}O_3$ (184.24): C 65.19, H 8.75, O 26.05; found: C 65.21, H 8.80, O 26.32.

4.3.10. Mixture 17a: (5*R*)-3-[(1*R*)-1-hydroxy-2-methylpropyl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}-4-methylfuran-2(5*H*)-one 18a and (5*R*)-3-[(1*S*)-1-hydroxy-2-methylpropyl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}-4-methylfuran-2(5*H*)-one 19a. A solution of freshly distilled diisopropylamine (1.83 ml, 1.30 g, 12.8 ml) in freshly distilled THF (90 ml) was cooled to 0°C under argon. *n*-BuLi in hexane (8.60 ml, 12.8 mmol) was added dropwise over 30 min and the resulting solution was stirred for 30 min at 0°C. Then, the mixture was cooled to −78°C and a solution of **16**[5] (2.70 g, 10.7 mmol) in THF (5 ml) was added dropwise during 30 min and the resulting solution was stirred for 30 min with the apparition of an orange color. Freshly distilled 2-methylpropanal (1.07 ml, 0.85 g, 11.8 mmol) was added dropwise during 30 min and the solution was stirred for further 30 min. After warm-up to −20°C, the reaction was quenched with saturated NH_4Cl solution (50 ml) and the mixture was extracted three times with CH_2Cl_2 (150 ml), washed with saturated $NaHCO_3$ solution, brine and water, dried over $MgSO_4$, filtered and the solvent evaporated. Flash chromatography with CH_2Cl_2 afforded 2.70 g (8.33 mmol, 78%) of the mixture **17a**. A second flash chromatography with AcOEt/hexane 1:5 as eluent afforded **18a** (1.43 g, 4.41 mmol, 41%) as colorless plates and **19a** (1.27 g, 3.92 mmol, 37%) as colorless plates, too.

Data of (5*R*)-3-[(1*R*)-1-hydroxy-2-methylpropyl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}-4-methylfuran-2(5*H*)-one (**18a**). Mp 82.0–83.5°C. $[\alpha]_D^{20}=-130.5$ (c=1.00, $CHCl_3$, stab. 1% EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): 5.75 (s, 1H, H–C(5)); 4.13 (t, J=8.4 Hz, 1H, H–C(1″)); 2.89 (d, J=9.1 Hz, 1H, HO–C(1″)); 2.05–1.97 (m, 1H, H–C(2″)); 1.99 (s, 3H, H_3C–C(4)); 1.04 (d, J=6.6 Hz, 3H, $(H_3C)_2$–C(2″)); 0.84 (d, J=6.9 Hz, 3H, $(H_3C)_2$–C(2″)). Menthyl resonances: 3.63; 2.16–2.12; 2.12–2.08; 1.72–1.67; 1.67–1.63; 1.36; 1.29–1.22; 1.07–0.99; 1.03–0.98; 0.96; 0.91–0.82; 0.88; 0.80. ^{13}C NMR (125 MHz, $CDCl_3$): 171.6; 156.4; 129.9; 100.6; 72.4; 33.9; 18.8; 18.3; 11.7. Menthyl resonances: 79.4; 47.7; 40.4; 34.2; 31.4; 25.2; 23.1; 22.2; 20.8; 15.7. EI-MS: 281 (10), 168 (15), 152 (64), 144 (17), 143 (38), 141 (27), 140 (12), 139 (77), 138 (11), 137 (12), 127 (71), 126 (56), 123 (11), 97 (28), 95 (27), 83 (100), 81 (36), 71 (20), 69 (65), 67 (15), 57 (33), 55 (59), 43 (64), 41 (52), 39 (11). Anal. calcd for $C_{19}H_{32}O_4$ (324.46): C 70.33, H 9.94, O 19.72; found: C 70.54, H 10.04, O 19.48.

Data of (5*R*)-3-[(1*S*)-1-hydroxy-2-methylpropyl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}-4-methylfuran-2(5*H*)-one (**19a**). Mp 51.5–53.0°C. $[\alpha]_D^{20}=-111.0$ (c=1.00, $CHCl_3$, stab. 1% EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): 5.70 (s, 1H, H–C(5)); 4.09 (dd, J=9.7 Hz, 8.1, 1H, H–C(1″)); 2.97 (d, J=9.7 Hz, 1H, HO–C(1″)); 2.05–1.98 (m, 1H, H–C(2″)); 1.96 (s, 3H, H_3C–C(4)); 1.04 (d, J=6.6 Hz, 3H, $(H_3C)_2$–C(2″)) 0.84 (d, J=6.9 Hz, 3H, $(H_3C)_2$–C(2″)). Menthyl resonances: 3.62; 2.14–2.08; 2.08–2.05; 1.77–1.66; 1.66–1.63; 1.46–1.36; 1.28–1.21; 1.07–0.94; 1.03–0.98; 0.95; 0.91–0.82; 0.80. ^{13}C NMR (125 MHz, $CDCl_3$): 171.7; 156.3; 129.7; 100.8; 72.6; 34.1; 18.8; 18.5; 11.8. Menthyl resonances: 79.4; 47.7; 40.4; 34.2; 31.4; 25.5; 23.3; 22.2; 20.8; 16.0. EI-MS: 281 (11), 168 (11), 152 (59), 144 (11), 143 (44), 141 (25), 140 (12), 139 (85), 137 (11), 127 (66), 126 (43), 123 (12), 97 (28), 95 (24), 83 (100), 81 (34), 71 (19), 69 (62), 67 (14), 57 (33), 55 (54), 43 (59), 41 (49). Anal. calcd for $C_{19}H_{32}O_4$ (324.46): C 70.33, H 9.94, O 19.72; found: C 70.56, H 9.86, O 19.68.

4.3.11. Mixture 17b: (5*R*)-3-[(1*S*,2*S*)-1-hydroxy-2-methylbutyl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}-4-methylfuran-2(5*H*)-one 18b and (5*R*)-3-[(1*R*,2*S*)-1-hydroxy-2-methylbutyl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}-4-methylfuran-2(5*H*)-one 19b. Same procedure as for **17a**. **16** (15.0 g, 59.6 mmol) was coupled with (*S*)-methylbutanal[21] (4.73 g, 65.4 mmol). The second flash chromatography was performed with a mixture of *tert*-butyl methyl ether/hexane 1:4 as eluant and afforded **18b** (3.80 g, 11.2 mmol, 19%) as colorless star-shaped crystals and **19b** (4.60 g, 13.6 mmol, 23%) as colorless star-shaped crystals, too.

Data of (5*R*)-3-[(1*S*,2*S*)-1-hydroxy-2-methylbutyl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}-4-methylfuran-2(5*H*)-one (**18b**). Mp 61.5–63.5°C. $[\alpha]_D^{20}=-153.5$ (c=1.00, $CHCl_3$, stab. 1% EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): 5.75 (s, 1H, H–C(5)); 4.18 (t, J=8.5 Hz, 1H, H–C(1″)); 2.81 (d, J=9.2 Hz, 1H, HO–C(1″)); 1.98 (s, 3H, H_3C–C(4)); 1.86–1.74 (m, 2H, H–C(2″), H_a–C(3″)); 1.29–1.23 (m, 1H, H_b–C(3″)); 0.93

(t, J=7.3 Hz, 3H, H–C(4″)); 0.79 (d, J=7.0 Hz, 3H, H_3C–C(2″)). Menthyl resonances: 3.63; 2.16–2.12; 2.12–2.08; 1.72–1.67; 1.67–1.62; 1.46–1.37; 1.23–1.15; 1.09–1.00; 1.00–0.96; 0.96; 0.91–0.82; 0.88; 0.80. ^{13}C NMR (125 MHz, $CDCl_3$): 171.7; 156.3; 130.0; 100.6; 71.2; 40.1; 24.7; 15.0; 11.7; 11.0. Menthyl resonances: 79.4; 47.7; 40.4; 34.2; 31.4; 25.2; 23.1; 22.2; 20.8; 15.8. EI-MS: 281 (12), 182 (11), 166 (21), 144 (30), 143 (34), 139 (73), 137 (11), 127 (48), 126 (53), 110 (16), 97 (25), 95 (17), 83 (100), 81 (26), 71 (11), 69 (51), 67 (11), 57 (48), 55 (44), 43 (26), 41 (38). Anal. calcd for $C_{20}H_{34}O_4$ (338.49): C 70.97, H 10.12, O 18.91; found: C 70.92, H 10.23, O 18.92.

Data of (5*R*)-3-[(1*R*,2*S*)-1-hydroxy-2-methylbutyl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}-4-methylfuran-2(5*H*)-one (**19b**). Mp 51.0–52.5°C. $[\alpha]_D^{20}$=−117.5 (c=1.00, $CHCl_3$, stab. 1% EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): 5.70 (s, 1H, H–C(5)); 4.26 (t, J=7.3 Hz, 1H, H–C(1″)); 3.01 (d, J=9.1 Hz, 1H, HO–C(1″)); 2.15–2.09 1.98 (s, 3H, H_3C–C(4)); 1.79–1.72 (m, 2H, H–C(2″), H_a–C(3″)); 1.46–1.36 (m, 1H, H_b–C(3″)); 0.99 (d, J=6.7 Hz, 3H, H_3C–C(2″)); 0.90 (t, J=7.4 Hz, 3H, H–C(4″)). Menthyl resonances: 3.63; 2.15–2.09; 2.08–2.05; 1.77–1.71; 1.71–1.64; 1.46–1.36; 1.29–1.22; 1.11–1.05; 1.05–1.00; 0.96; 0.91–0.82; 0.88; 0.81. ^{13}C NMR (125 MHz, $CDCl_3$): 171.7; 156.1; 129.9; 100.8; 71.1; 40.6; 25.4; 14.4; 11.7; 11.5. Menthyl resonances: 79.4; 47.6; 40.4; 43.2; 31.4; 25.5; 23.3; 22.2; 20.7; 15.9. EI-MS: 281 (12), 182 (12), 166 (18), 144 (19), 143 (34), 139 (71), 127 (40), 126 (40), 110 (13), 97 (26), 95 (17), 83 (100), 81 (25), 71 (10), 69 (50), 67 (11), 57 (47), 55 (44), 43 (25), 41 (37). Anal. calcd for $C_{20}H_{34}O_4$ (338.49): C 70.97, H 10.12, O 18.91; found: C 70.92, H 10.28, O 18.91.

4.3.12. Mixture 17c: (5*R*)-3-[(1*S*)-1-hydroxyethyl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}-4-methylfuran-2(5*H*)-one 18c and (5*R*)-3-[(1*R*)-1-hydroxyethyl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}-4-methylfuran-2(5*H*)-one 19c. Same procedure as for **17a**. **16** (15.0 g, 59.6 mmol) was coupled with acetaldehyde (4.70 ml, 83.3 mmol). Two flash chromatographies were performed with a mixture of *tert*-butyl methyl ether/AcOEt/hexane 1:4:15 as eluent and afforded **18c** (4.00 g, 13.5 mmol, 23%) as colorless cubes and **19c** (3.20 g, 10.8 mmol, 18%) as colorless cubes, too.

Data of (5*R*)-3-[(1*S*)-1-hydroxyethyl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}-4-methylfuran-2(5*H*)-one (**18c**). Mp 101.0–101.6°C. $[\alpha]_D^{20}$=−162.0 (c=1.00, $CHCl_3$, stab. 1% EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): 5.69 (s, 1H, H–C(5)); 4.70 (dq, J=7.2 Hz, 6.8, 1H, H–C(1″)); 2.87 (d, J=8.0 Hz, 1H, HO–C(1″)); 2.01 (s, 3H, H_3C–C(4)); 1.47 (d, J=6.7 Hz, 3H, H–C(2″)). Menthyl resonances: 3.62; 2.17–2.08; 1.72–1.64; 1.46–1.37; 1.29–1.21; 1.08–0.85; 0.96; 0.88; 0.80. ^{13}C NMR (125 MHz, $CDCl_3$): 171.4; 154.7; 131.6; 100.8; 63.0; 22.6; 11.4. Menthyl resonances: 79.5; 47.7; 40.4; 34.2; 31.4; 25.1; 23.0; 22.2; 20.9; 15.7. EI-MS: 141 (27), 140 (11), 139 (14), 138 (24), 137 (23), 124 (100), 113 (14), 99 (33), 95 (29), 83 (36), 81 (52), 69 (31), 67 (15), 57 (17), 55 (31), 43 (53), 41 (25). Anal. calcd for $C_{17}H_{28}O_4$ (296.41): C 68.89, H 9.52, O 21.59; found: C 68.96, H 9.27, O 21.70.

Data of (5*R*)-3-[(1*R*)-1-hydroxyethyl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}-4-methylfuran-2(5*H*)-one (**19c**). Mp 86.9–87.3°C. $[\alpha]_D^{20}$=−118.5 (c=1.00, $CHCl_3$, stab. 1% EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): 5.69 (s, 1H, H–C(5)); 4.68 (dq, J=8.1 Hz, 6.8, 1H, H–C(1″)); 2.92 (d, J=6.7 Hz, 1H, HO–C(1″)); 2.00 (s, 3H, H_3C–C(4)); 1.48 (d, J=6.7 Hz, 3H, H–C(2″)). Menthyl resonances: 3.62; 2.16–2.08; 1.72–1.64; 1.46–1.37; 1.29–1.21; 1.09–0.85; 0.96; 0.88; 0.81. ^{13}C NMR (125 MHz, $CDCl_3$): 171.3; 154.6; 131.4; 101.0; 63.1; 22.8; 11.4. Menthyl resonances: 79.7; 47.7; 40.5; 34.2; 31.4; 25.1; 23.0; 22.2; 20.9; 15.7. EI-MS: 141 (25), 140 (11), 139 (14), 138 (23), 137 (20), 124 (100), 113 (12), 99 (33), 95 (26), 83 (42), 81 (48), 69 (33), 67 (15), 57 (18), 55 (31), 43 (43), 41 (26). Anal. calcd for $C_{17}H_{28}O_4$ (296.41): C 68.89, H 9.52, O 21.59; found: C 68.87, H 9.57, O 21.63.

4.3.13. Mixture 17d: (5*R*)-3-[(1*S*)-hydroxypropyl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}-4-methylfuran-2(5*H*)-one 18d and (5*R*)-3-[(1*R*)-hydroxypropyl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}-4-methylfuran-2(5*H*)-one 19d. Same procedure as for **17a**. **16** (15.0 g, 59.6 mmol) was coupled with propionaldehyde (6.10 ml, 83.3 mmol). Two flash chromatographies were performed with a mixture of *tert*-butyl methyl ether/AcOEt/hexane 1:4:15 as eluent and afforded **18d** (2.20 g, 7.10 mmol, 12%) as colorless cubes and **19d** (2.60, g 8.38 mmol, 14%) as colorless cubes, too.

Data of (5*R*)-3-[(1*S*)-1-hydroxypropyl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}-4-methylfuran-2(5*H*)-one (**18d**). Mp 116.3–116.5°C. $[\alpha]_D^{20}$=−156.0 (c=1.00, $CHCl_3$, stab. 1% EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): 5.72 (s, 1H, H–C(5)); 4.41 (td, J=8.3 Hz, 7.2, 1H, H–C(1″)); 2.81 (d, J=8.8 Hz, 1H, HO–C(1″)); 1.99 (s, 3H, H_3C–C(4)); 1.89–1.80 (m, 1H, H_a–C(2″)); 1.76–1.69 (m, 1H, H_b–C(2″)); 0.94 (t, J=7.4 Hz, 3H, H–C(3″)). Menthyl resonances: 3.62; 2.16–2.08; 1.69–1.62; 1.47–1.37; 1.29–1.22; 1.08–0.93; 0.96; 0.87; 0.80. ^{13}C NMR (125 MHz, $CDCl_3$): 171.4; 155.7; 130.4; 100.7; 68.3; 29.6; 11.4; 9.9. Menthyl resonances: 79.5; 47.7; 40.4; 34.2; 31.4; 25.1; 23.0; 22.2; 20.9; 15.7. EI-MS: 281 (14), 155 (25), 154 (15), 143 (30), 139 (55), 138 (100), 127 (30), 126 (11), 97 (14), 95 (26), 95 (26), 83 (63), 81 (48), 69 (40), 67 (11), 57 (48), 57 (48), 55 (43), 43 (26), 41 (42). Anal. calcd for $C_{18}H_{30}O_4$ (310.44): C 69.64, H 9.74, O 20.62; found: C 69.51, H 9.56, O 20.50.

Data of (5*R*)-3-[(1*R*)-1-hydroxypropyl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}-4-methylfuran-2(5*H*)-one (**19d**). Mp 91.6–91.9°C. $[\alpha]_D^{20}$=−121.0 (c=1.00, $CHCl_3$, stab. 1% EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): 5.70 (s, 1H, H–C(5)); 4.40 (td, J=9.2, 7.1 Hz, 1H, H–C(1″)); 2.91 (d, J=9.3 Hz, 1H, HO–C(1″)); 1.98 (s, 3H, H_3C–C(4)); 1.90–1.81 (m, 1H, H_a–C(2″)); 1.78–1.71 (m, 1H, H_b–C(2″)); 0.94 (t, J=7.3 Hz, 3H, H–C(3″)). Menthyl resonances: 3.63; 2.14–2.08; 1.71–1.62; 1.47–1.37; 1.29–1.22; 1.07–0.92; 0.96; 0.88; 0.81. ^{13}C NMR (125 MHz, $CDCl_3$): 171.5; 155.7; 130.3; 100.9; 68.4; 29.8; 11.5; 9.8. Menthyl resonances: 79.6; 47.7; 40.4; 34.2; 31.4; 25.3; 23.2; 22.2; 20.8; 15.8. EI-MS: 281 (11), 155 (24), 154 (13), 143 (37), 139 (64), 138 (100), 137 (19), 127 (32), 97 (15), 95 (27), 83 (77), 81 (52), 69 (41), 67 (11), 57

(49), 55 (42), 43 (20), 41 (35). Anal. calcd for $C_{18}H_{30}O_4$ (310.44): C 69.64, H 9.74, O 20.62; found: C 69.40, H 9.69, O 20.64.

4.3.14. Mixture 17e: (5*R*)-3-[(1*S*)-hydroxy-2,2-dimethylpropyl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}-4-methylfuran-2(5*H*)-one 18e and (5*R*)-3-[(1*R*)-hydroxy-2,2-dimethylpropyl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}-4-methylfuran-2(5*H*)-one 19e. Similar procedure as for **17a**. **16** (15.1 g, 59.0 mmol) was coupled with 2,2-dimethylpropanal (8.50 ml, 77.0 mmol) at −110°C (diethyl ether/hexane 1:4, liquid N_2. The second flash chromatography was performed with a mixture of AcOEt/hexane 1:9 as eluent and afforded **18e** (4.0 g, 12 mmol, 20%) as colorless needles and **19e** (4.0 g, 12 mmol, 20%) as colorless needles, too.

Data of (5*R*)-3-[(1*S*)-hydroxy-2,2-dimethylpropyl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}-4-methylfuran-2(5*H*)-one (**18e**). Mp 112.7–113.6°C. $[\alpha]_D^{20}=-153.5$ (c=1.00, $CHCl_3$, stab. 1% EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): 5.75 (s, 1H, H–C(5)); 4.18 (s, J=8.7 Hz, 1H, H–C(1″)); 3.36 (d, J=8.6 Hz, 1H, HO–C(1″)); 1.99 (s, 3H, H_3C–C(4)); 0.95 (s, 9H, $(H_3C)_3$–C(2″)). Menthyl resonances: 3.62; 2.10–2.06; 1.72–1.63; 1.48–1.35; 1.30–1.21; 1.12–0.85; 0.95; 0.88; 0.80. ^{13}C NMR (125 MHz, $CDCl_3$): 172.6; 158.0; 129.3; 100.9; 75.7; 38.2; 26.4; 13.0. Menthyl resonances: 79.8; 48.2; 40.8; 34.6; 31.9; 25.7; 23.6; 22.6; 21.2; 16.2. EI-MS: 282 (16), 281 (13), 166 (16), 144 (82), 143 (31), 139 (72), 127 (47), 126 (100), 97 (18), 95 (14), 83 (85), 81 (21), 69 (36), 57 (65), 55 (38), 43 (21), 41 (36). Anal. calcd for $C_{20}H_{34}O_4$ (338.49): C 70.97, H 10.12, O 18.91; found: C 71.01, H 10.04, O 18.77.

Data of (5*R*)-3-[(1*R*)-hydroxy-2,2-dimethylpropyl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}-4-methylfuran-2(5*H*)-one (**19e**). Mp 85.5–86.8°C. $[\alpha]_D^{20}=-108.5$ (c=1.00, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): 5.68 (s, 1H, H–C(5)); 4.17 (s, J=9.5 Hz, 1H, H–C(1″)); 3.53 (d, J=9.5 Hz, 1H, HO–C(1″)); 1.97 (s, 3H, H_3C–C(4)); 0.95 (s, 9H, $(H_3C)_3$–C(2″)). Menthyl resonances: 3.64; 2.15–2.03; 1.72–1.63; 1.47–1.37; 1.29–1.23; 1.09–0.85; 0.96; 0.88; 0.81. ^{13}C NMR (125 MHz, $CDCl_3$): 172.2; 157.2; 128.7; 100.6; 75.4; 37.7; 26.0; 12.7. Menthyl resonances: 79.4; 47.8; 40.4; 34.4; 31.5; 25.8; 23.7; 22.2; 20.7; 16.2. EI-MS: 282 (17), 281 (13), 166 (13), 144 (89), 143 (31), 139 (70), 127 (45), 126 (100), 97 (19), 95 (17), 83 (92), 81 (23), 69 (40), 57 (69), 55 (42), 43 (22), 41 (40). Anal. calcd for $C_{20}H_{34}O_4$ (338.49): C 70.97, H 10.12, O 18.91; found: C 70.93, H 10.06, O 18.88.

4.3.15. 5-Hydroxy-3-[(1*S*)-1-hydroxy-2-methylpropyl]-4-methylfuran-2(5*H*)-one 1. 18a (4.00 g, 12.3 mmol) was dissolved in absolute CH_2Cl_2 (200 ml) under argon. The solution was cooled to −78°C and boron tribromide (6.00 ml, 61.7 mmol) was added over 30 min, and the resulting mixture was stirred for 2 h at this temperature. The solution was allowed to warm up to −25°C and saturated $NaHCO_3$ solution (100 ml) was added. After warming up to rt, the mixture was extracted with AcOEt. The combined organic phases were dried over $MgSO_4$, filtered, and the solvent was evaporated. Flash chromatography with AcOEt/hexane 1:1 afforded **1** (1.80 g, 9.68 mmol, 79%) as colorless amorphous solid. This amorphous product was crystallized from AcOEt/hexane to afford **1** (1.60 g, 8.60 mmol, 70%, mixture of epimers) as colorless plates. Mp 103.5–105.0°C. $[\alpha]_D^{20}=-16.0$ (c=1.00, MeOH) (nat. prod.[3]: $[\alpha]_D^{23}=-14.6$ (c=0.31, MeOH)). ^{1}H NMR (500 MHz, $CDCl_3$): 5.90–5.85 (m, 2×1H, H–C($5^{1\text{ and }2}$)); 5.25 (d, J=9.3 Hz, 1H, HO–C($55^{1\text{ or }2}$)); 5.05 (d, J=9.3 Hz, 1H, HO–C($5^{2\text{ or }1}$)); 4.15–4.05 (m, 2×1H, H–C($1'^{1\text{ and }2}$)); 3.33 (br, 1H, HO–C($1'^{1\text{ or }2}$)); 3.09 (br, 1H, HO–C($1'^{2\text{ or }1}$)); 2.08 (s, 3H, H_3C–C($4^{1\text{ or }2}$)); 2.06 (s, 3H, H_3C–C($4^{2\text{ or }1}$)); 2.05–1.95 (m, 2×1H, H–C($2'^{1\text{ and }2}$)); 1.04 (d, J=6.6 Hz, 3H, $(H_3C)_2$–C($2'^{1\text{ or }2}$)); 1.03 (d, J=6.6 Hz, 3H, $(H_3C)_2$–C($2'^{2\text{ or }1}$)); 0.85 (d, J=6.8 Hz, 3H, $(H_3C)_2$–C($2'^{1\text{ or }2}$)); 0.83 (d, J=6.8 Hz, 3H, $(H_3C)_2$–C($2'^{2\text{ or }1}$)). ^{13}C NMR (125 MHz, $CDCl_3$): 172.1; 172.0; 158.5; 129.7; 129.2; 98.9; 98.8; 72.3; 72.2; 33.9; 33.5; 18.7; 18.5; 18.4; 11.9; 11.6. EI-MS: 168 (12), 153 (32), 143 (23), 135 (20), 126 (38), 125 (17), 109 (10), 99 (21), 98 (18), 97 (27), 71 (40), 70 (10), 69 (30), 67 (11), 55 (13), 53 (10), 44 (43), 43 (100), 42 (11), 41 (54), 39 (30). Anal. calcd for $C_9H_{14}O_4$ (186.21): C 58.05, H 7.58, O 34.37; found: C 58.06, H 7.58, O 34.40.

4.3.16. 5-Hydroxy-3-[(1*S*,2*S*)-1-hydroxy-2-methylbutyl]-4-methylfuran-2(5*H*)-one 3. Same procedure as for **1**. **18b** (2.00 g, 5.92 mmol) was treated with boron tribromide (1.90 ml, 17.8 mmol). The resulting mixture was stirred for 2 h. Then, additional boron tribromide (1.90 ml, 17.8 mmol) was added and the mixture was stirred for another 2 h. The flash chromatography afforded **3** (970 mg, 4.85 mmol, 82%, mixture of epimers) as a colorless yellowish oil. $[\alpha]_D^{20}=-21.0$ (c=0.51, MeOH) (nat. prod.[3]: $[\alpha]_D^{24}=-21.9$ (c=0.45, MeOH)). ^{1}H NMR (500 MHz, $CDCl_3$): 6.70–6.30 (br, 2×1H, HO–C($5^{1\text{ and }2}$)); 5.90 (s, 1H, H–C($5^{1\text{ or }2}$)); 5.88 (s, 1H, H–C($5^{2\text{ or }1}$)); 4.22 (d, J=8.3 Hz, 1H, H–C($1'^{1\text{ or }2}$)); 4.17 (d, J=8.7 Hz, 1H, H–C($1'^{2\text{ or }1}$)); 3.70–3.30 (br, 2×1H, HO–C($1'^{1\text{ and }2}$)); 2.07 (s, 3H, H_3C–C($4^{1\text{ or }2}$)); 2.05 (s, 3H, H_3C–C($4^{2\text{ or }1}$)); 1.90–1.80 (m, 2×1H, H–C($2'^{1\text{ and }2}$)); 1.80–1.70 (m, 1H, H_a–C($3'^{1\text{ and }2}$)); 1.22–1.14 (m, 1H, H_b–C($3'^{1\text{ and }2}$)); 0.92 (t, J=7.3 Hz, 3H, H–C($4'^{1\text{ or }2}$)); 0.92 (t, J=7.4 Hz, 3H, H–C($4'^{2\text{ or }1}$)); 0.79 (d, J=6.8 Hz, 3H, H_3C–C($2'^{1\text{ or }2}$)); 0.75 (d, J=6.8 Hz, 3H, H_3C–C($2'^{2\text{ or }1}$)). ^{13}C NMR (125 MHz, $CDCl_3$): 172.4; 172.0; 159.3; 159.2; 129.4; 129.2; 98.8; 98.7; 70.7; 70.5; 39.6; 39.0; 24.8; 24.7; 14.8; 14.7; 11.8; 11.6; 10.8; 10.7. EI-MS: 144 (11), 143 (61), 127 (10), 126 (100), 125 (28), 98 (12), 97 (30), 69 (27), 57 (13), 41 (29), 39 (13). Anal. calcd for $C_{10}H_{16}O_4$ (200.24): C 59.98, H 8.05, O 31.96; found: C 60.04, H 8.14, O 31.95.

4.3.17. 5-Hydroxy-3-[(1*S*)-1-hydroxyethyl]-4-methylfuran-2(5*H*)-one 20c. Same procedure as for **1**. **18c** (1.00 g, 3.38 mmol) was treated with boron tribromide (0.974 ml, 10.1 mmol). The resulting mixture was stirred for 2 h. Then, additional boron tribromide (0.974 ml, 10.1 mmol) was added and the mixture was stirred for another 2 h. The flash chromatography afforded **20c** (330 mg, 1.90 mmol, 62%, mixture of epimers). Colorless cubes (Et_2O/hexane). Mp 101.0–102.5°C. $[\alpha]_D^{20}=-10.3$ (c=1.00, MeOH). ^{1}H NMR (500 MHz, d_6-DMSO): 7.68 (2s, 2×1H, HO–C($5^{1\text{ and }2}$)); 5.80 (m, 2×1H,

H–C($5^{1\text{ and }2}$)); 5.11–5.07 (m, 1H, H–C($1'^{1\text{ or }2}$)); 4.55–4.49 (m, 1H, H–C($1'^{2\text{ or }1}$)); 3.37–3.37 (m, 2×1H, HO–C($1'^{1\text{ and }2}$)); 2.04 (2s, 2×3H, H_3C–C($4^{1\text{ and }2}$)); 1.27 (2d, J=6.6 Hz, 2×3H, H–C($2'^{1\text{ and }2}$)). ^{13}C NMR (125 MHz, d_6-DMSO): 170.6; 157.6; 131.0; 98.0; 97.9; 61.3; 22.2; 11.4. EI-MS: 143 (25), 140 (19), 125 (18), 124 (11), 112 (11), 97 (35), 71 (20), 69 (50), 67 (32), 66 (10), 53 (17), 45 (13), 44 (49), 43 (100), 41 (59), 40 (13), 39 (46). Anal. calcd for $C_7H_{10}O_4$ (158.15): C 53.16, H 6.37, O 40.47; found: C 53.30, H 6.32, O 40.53.

4.3.18. 5-Hydroxy-3-[(1*S*)-1-hydroxypropyl]-4-methylfuran-2(5*H*)-one 20d. Same procedure as for **1**. **18d** (1.00 g, 3.38 mmol) was treated with boron tribromide (0.930 ml, 9.68 mmol). The resulting mixture was stirred for 2 h. Then, additional boron tribromide (0.930 ml, 9.68 mmol) was added and the mixture was stirred for another 2 h. The flash chromatography afforded **20d** (350 mg, 2.03 mmol, 63%). Colorless cubes (Et_2O/hexane). Mp 77.0–78.5°C. $[\alpha]_D^{20}$=−18.7 (c=1.00, MeOH). ^1H NMR (500 MHz, d_6-DMSO): 7.68 (m, 2×1H, HO–C($5^{1\text{ and }2}$)); 5.86–5.77 (m, 2×1H, H–C($5^{1\text{ and }2}$)); 5.08–5.04 (m, 1H, H–C($1'^{1\text{ or }2}$)); 4.32–4.24 (m, 1H, H–C($1'^{2\text{ or }1}$)); 3.36 (s, 1H, HO–C($1'^{1\text{ or }2}$)); 3.35 (s, 1H, HO–C($1'^{2\text{ or }1}$)); 2.02 (2s, 2×3H, H_3C–C($4^{1\text{ and }2}$)); 1.61 (2q, J=7.1 Hz, 2×2H, H–C($2'^{1\text{ and }2}$)); 0.82 (2t, J=7.4 Hz, 2×3H, H–C($3'^{1\text{ and }2}$)). ^{13}C NMR (125 MHz, d_6-DMSO): 170.7; 158.6, 130.0; 98.0; 97.9; 66.4; 66.3; 28.5; 11.5; 9.7. EI-MS: 154 (25), 143 (67), 139 (40), 125 (74), 115 (14), 111 (13), 97 (100), 95 (10), 83 (17), 81 (13), 79 (15), 71 (14), 69 (68), 67 (20), 57 (40), 53 (20), 51 (12), 44 (28), 43 (29), 41 (79), 39 (53). Anal. calcd for $C_8H_{12}O_4$ (172.18): C 55.81, H 7.03, O 37.17; found: C 55.80, H 6.89, O 37.26.

4.3.19. 5-Hydroxy-3-[(1*S*)-1-hydroxy-2,2-dimethylpropyl]-4-methylfuran-2(5*H*)-one 20e. Same procedure as for **1**. **18e** (1.00 g, 2.96 mmol) reacted with boron tribromide (0.860 ml, 8.86 mmol). The resulting mixture was stirred for 2 h. Then, additional boron tribromide (0.860 ml, 8.86 mmol) was added and the mixture was stirred for another 2 h. Flash chromatography with AcOEt/hexane 1:2 afforded **20e** (482 mg, 2.41 mmol, 81%). Colorless cubes (EtOH). Mp 162.3–162.7°C. $[\alpha]_D^{20}$=−41.5 (c=1.00, MeOH). ^1H NMR (500 MHz, d_6-DMSO): 7.75 (d, J=7.5 Hz, 1H, HO–C(5^1)); 7.66 (d, J=8.5 Hz, 1H, HO–C(5^2)); 5.93 (d, J=7.5 Hz, 1H, H–C($5^{1\text{ or }2}$)); 5.80 (d, J=8.5 Hz, 1H, H–C($5^{2\text{ or }1}$)); 5.12 (d, J=4.9 Hz, 1H, HO–C($1'^{1\text{ and }2}$)); 4.14 (d, J=4.7 Hz; 1H, H–C($1'^{1\text{ or }2}$)); 4.11 (d, J=4.5 Hz, 1H, H–C($1'^{2\text{ or }1}$)); 2.09 (s, 3H, H_3C–C($4^{1\text{ and }2}$)); 0.90 (s, 9H, $(H_3C)_3$–C($2'^{1\text{ or }2}$)); 0.89 (s, 9H, $(H_3C)_3$–C($2'^{2\text{ or }1}$)). ^{13}C NMR (125 MHz, d_6-DMSO): 172.7; 172.4; 161.1; 160.4; 130.2; 98.9; 98.8; 73.8; 73.7; 38.1; 38.0; 26.9; 13.9; 13.7. EI-MS: 167 (32), 149 (43), 144 (11), 127 (10), 126 (100), 98 (17), 97 (15), 70 (12), 69 (26), 57 (85), 55 (11), 44 (12), 43 (19), 41 (68), 39 (34). Anal calcd for $C_{10}H_{16}O_4$ (200.23): C 59.98, H 8.05, O 31.96; found: C 60.08, H 7.98, O 32.04.

4.3.20. 5-Hydroxy-3-[(1*R*)-1-hydroxy-2-methylpropyl]-4-methylfuran-2(5*H*)-one 21a. Same procedure as for **1**. **19a** (4.00 g, 12.3 mmol) was treated with boron tribromide (6.00 ml, 61.7 mmol), and the flash chromatography afforded **21a** (1.90 g, 10.2 mmol, 83%) as colorless amorphous solid. This amorphous product was crystallized from AcOEt/hexane to afford **21a** (1.70 g, 9.14 mmol, 75%, mixture of epimers) as colorless plates. Mp 105.0–106.5°C. $[\alpha]_D^{20}$=+16.0 (c=1.00, MeOH). ^1H NMR (500 MHz, $CDCl_3$): 5.90–5.85 (m, 2×1H, H–C($5^{1\text{ and }2}$)); 5.23 (d, J=8.9 Hz, 1H, HO–C($5^{1\text{ or }2}$)); 5.01 (d, J=7.4 Hz, 1H, HO–C($5^{2\text{ or }1}$)); 4.15–4.08 (m, 2×1H, H–C($1'^{1\text{ and }2}$)); 3.33 (d, J=9.2 Hz, 1H, HO–C($1'^{1\text{ or }2}$)); 3.08 (d, J=8.4 Hz, 1H, HO–C($1'^{2\text{ or }1}$)); 2.08 (s, 3H, H_3C–C($4^{1\text{ or }2}$)); 2.06 (s, 3H, H_3C–C($4^{2\text{ or }1}$)); 2.05–1.95 (m, 2×1H, H–C($2'^{1\text{ and }2}$)); 1.04 (d, J=6.6 Hz, 3H, $(H_3C)_2$–C($2'^{1\text{ or }2}$)); 1.03 (d, J=6.6 Hz, 3H, $(H_3C)_2$–C($2'^{2\text{ or }1}$)); 0.85 (d, J=6.8 Hz, 3H, $(H_3C)_2$–C($2'^{1\text{ or }2}$)); 0.83 (d, J=6.8 Hz, 3H, $(H_3C)_2$–C($2'^{2\text{ or }1}$)). ^{13}C NMR (125 MHz, $CDCl_3$): 172.1; 172.0; 158.5; 158.5; 129.8; 129.2; 98.9; 98.8; 72.3; 72.2; 33.9; 33.6; 18.7; 18.5; 18.4; 11.9; 11.6. EI-MS: 168 (17), 153 (44), 143 (20), 135 (29), 126 (33), 125 (15), 110 (10), 99 (23), 98 (18), 97 (34), 71 (38), 69 (30), 67 (11), 55 (13), 53 (11), 44 (40), 43 (100), 42 (11), 41 (54), 39 (31). Anal. calcd for $C_9H_{14}O_4$ (186.21): C 58.05, H 7.58, O 34.37; found: C 58.09, H 7.62, O 34.37.

4.3.21. 5-Hydroxy-3-[(1*R*,2*S*)-1-hydroxy-2-methylbutyl]-4-methylfuran-2(5*H*)-one 21b. Same procedure as for **1**. **19b** (2.00 g, 5.92 mmol) was treated with boron tribromide (1.90 ml, 17.8 mmol). The resulting mixture was stirred for 2 h. Then, additional boron tribromide (1.90 ml, 17.8 mmol) was added and the mixture was stirred for another 2 h. The flash chromatography afforded **21b** (950 mg, 4.50 mmol, 76%, mixture of epimers) as colorless yellowish needles. Mp 79.5–81.0°C. $[\alpha]_D^{20}$=+5.0 (c=1.00, MeOH). ^1H NMR (500 MHz, $CDCl_3$): 6.00–5.85 (m, 2×1H, H–C($5^{1\text{ and }2}$)); 4.30 (d, J=6.9 Hz, 1H, H–C($1'^{1\text{ or }2}$)); 4.24 (d, J=7.4 Hz, 1H, H–C($1'^{2\text{ or }1}$)); 3.70–3.30 (2br, 2×1H, HO–C($1'^{1\text{ and }2}$)); 3.00–2.50 (br, 2×1H, HO–C($5^{1\text{ and }2}$)); 2.08 (s, 3H, H_3C–C($4^{1\text{ or }2}$)); 2.06 (s, 3H, H_3C–C($4^{2\text{ or }1}$)); 1.81–1.70 (m, 2×1H, H–C($(2'^{1\text{ and }2})$); 1.42–1.30 (m, 2×1H, H_a–C($3'^{1\text{ and }2}$)); 1.12–1.00 (m, 2×1H, H_b–C($3'^{1\text{ and }2}$)); 0.99 (d, J=6.7 Hz, 3H, H_3C–C($2'^{1\text{ or }2}$)); 0.97 (d, J=6.7 Hz, 3H, H_3C–C($2'^{2\text{ or }1}$)); 0.90 (t, J=7.3 Hz, 3H, H–C($4'^{1\text{ or }2}$)); 0.89 (t, J=7.3 Hz, 3H, H–C($4'^{2\text{ or }1}$)). ^{13}C NMR (125 MHz, $CDCl_3$): 172.4; 172.2; 158.9; 129.6; 129.3; 98.9; 98.8; 70.7; 40.0; 39.7; 25.4; 14.4; 14.3; 11.9; 11.6; 11.4; 11.3. EI-MS: 153 (10), 144 (11), 143 (56), 127 (10), 126 (100), 125 (28), 98 (13), 97 (31), 69 (30), 57 (16), 41 (33), 39 (16). Anal. calcd for $C_{10}H_{16}O_4$ (200.24): C 59.98, H 8.05, O 31.96; found: C 60.06, H 8.03, O 32.19.

4.3.22. 5-Hydroxy-3-[(1*R*)-1-hydroxyethyl]-4-methylfuran-2(5*H*)-one 21c. Same procedure as for **1**. **19c** (1.00 g, 3.38 mmol) was treated with boron tribromide (0.974 ml, 10.1 mmol). The resulting mixture was stirred for 2 h. Then, additional boron tribromide (0.974 ml, 10.1 mmol) was added and the mixture was stirred for another 2 h. The flash chromatography afforded **21c** (300 mg, 1.90 mmol, 56%, mixture of epimers). Colorless cubes (Et_2O/hexane). Mp 103.0–104.5°C. $[\alpha]_D^{20}$=+7.6 (c=1.00, MeOH). ^1H NMR (500 MHz, d_6-DMSO): 7.68 (d, J=8.1 Hz, 1H, HO–C(5^1)); 7.68 (d, J=7.9 Hz, 1H, HO–C(5^2)); 5.81 (d, J=7.9 Hz, 1H, H–C($5^{1\text{ or }2}$)); 5.79 (d, J=8.1 Hz, 1H, H–C($5^{2\text{ or }1}$)); 5.10–5.08 (m, 1H,

H–C($1'^{1\text{ or }2}$)); 4.55–4.49 (m, 1H, H–C($1'^{2\text{ or }1}$)); 3.36 (2s, 2×1H, HO–C($1'^{1\text{ and }2}$)); 2.04 (s, 3H, H_3C–C($4^{1\text{ or }2}$)); 2.03 (s, 3H, H_3C–C($4^{2\text{ or }1}$)); 1.27 (d, J=6.6 Hz, 3H, H–C($2'^{1\text{ or }2}$)); 1.26 (d, J=6.6 Hz, 3H, H–C($2'^{2\text{ or }1}$)). ^{13}C NMR (125 MHz, d_6-DMSO): 170.6; 170.5; 157.6; 131.1; 131.0; 98.0; 97.9; 61.3; 61.2; 22.3; 22.2; 11.4. EI-MS: 143 (55), 140 (22), 125 (39), 114 (11), 112 (13), 111 (10), 98 (19), 97 (66), 95 (10), 83 (11), 71 (19), 69 (72), 68 (10), 67 (33), 66 (12), 53 (16), 45 (26), 44 (33), 43 (100), 41 (72), 40 (15), 39 (53), 38 (10). Anal. calcd for $C_7H_{10}O_4$ (158.15): C 53.16, H 6.37, O 40.47; found: C 53.19, H 6.23, O 40.32.

4.3.23. 5-Hydroxy-3-[(1*R*)-1-hydroxypropyl]-4-methylfuran-2(5*H*)-one 21d. Same procedure as for **1**. **19d** (1.00 g, 3.38 mmol) was treated with boron tribromide (0.930 ml, 9.68 mmol). The resulting mixture was stirred for 2 h. Then, additional boron tribromide (0.930 ml, 9.68 mmol) was added and the mixture was stirred for another 2 h. The flash chromatography afforded **21d** (350 mg, 2.03 mmol, 63%). Colorless cubes (Et_2O/hexane). Mp 79.5–81.0°C. $[\alpha]_D^{20}$=+15.6 (c=1.00, MeOH). ^{1}H NMR (500 MHz, d_6-DMSO): 7.69 (d, J=7.9 Hz, 1H, HO–C(5^1)); 7.68 (d, J=8.1 Hz, 1H, HO–C(5^2)); 5.84 (d, J=7.8 Hz, 1H, H–C($5^{1\text{ or }2}$)); 5.80 (d, J=8.1 Hz, 1H, H–C($5^{2\text{ or }1}$)); 5.09–5.03 (m, 1H, H–C($1'^{1\text{ or }2}$)); 4.32–4.24 (m, 1H, H–C($1'^{2\text{ or }1}$)); 3.36 (2s, 2×1H, HO–C($1'^{1\text{ and }2}$)); 2.03 (s, 3H, H_3C–C($4^{1\text{ or }2}$)); 2.02 (s, 3H, H_3C–C($4^{2\text{ or }1}$)); 1.61 (2qd, J=6.8, 3.1 Hz, 2×2H, H–C($2'^{1\text{ and }2}$)); 0.82 (t, J=7.3 Hz, 3H Hz, H–C($3'^{1\text{ or }2}$)); 0.81 (t, J=7.3 Hz, 3H, H–C($3'^{2\text{ or }1}$)). ^{13}C NMR (125 MHz, d_6-DMSO): 170.8; 170.7; 158.6; 158.5; 130; 129.9; 98.0; 97.9; 66.4; 66.3; 28.5; 28.4; 11.6; 11.5; 9.8; 9.7. EI-MS: 154 (30), 143 (66), 139 (47), 126 (10), 125 (72), 115 (13), 111 (14), 98 (11), 97 (100), 95 (12), 83 (19), 81 (14), 79 (17), 71 (15), 69 (69), 67 (23), 57 (43), 55 (13), 53 (22), 51 (13), 44 (32), 43 (30), 41 (82), 39 (57). Anal. calcd for $C_8H_{12}O_4$ (172.18): C 55.81, H 7.03, O 37.17; found: C 55.97, H 6.84, O 37.22.

4.3.24. 5-Hydroxy-3-[(1*R*)-1-hydroxy-2,2-dimethylpropyl]-4-methylfuran-2(5*H*)-one 21e. Same procedure as for **1**. **19e** (1.00 g, 2.96 mmol) was treated with boron tribromide (0.860 ml, 8.86 mmol). The resulting mixture was stirred for 2 h. Then, additional boron tribromide (0.860 ml, 8.86 mmol) was added and the mixture was stirred for another 2 h. Flash chromatography with AcOEt/hexane 1:2 afforded **21e** (330 mg, 1.65 mmol, 66%). Colorless cubes (EtOH). Mp 162.0–162.7°C. $[\alpha]_D^{20}$=+39.0 (c=1.00, MeOH). ^{1}H NMR (500 MHz, d_6-DMSO): 7.71 (d, J=7.5 Hz, 1H, HO–C(5^1)); 7.62 (d, J=8.6 Hz, 1H, HO–C(5^2)); 5.90 (dd, J=7.5 Hz, 0.6, 1H, H–C($5^{1\text{ or }2}$)); 5.76 (dd, J=8.5 Hz, 0.2, 1H, H–C($5^{2\text{ or }1}$)); 5.08 (d, J=4.8 Hz, 1H, HO–C($1'^{1\text{ and }2}$)); 4.11 (d, J=4.6 Hz; 1H, H–C($1'^{1\text{ or }2}$)); 4.07 (d, J=4.3 Hz, 1H, H–C($1'^{2\text{ or }1}$)); 2.06 (s, 3H, H_3C–C($4^{1\text{ or }2}$)); 2.05 (s, 3H, H_3C–C($4^{2\text{ or }1}$)); 0.86 (s, 9H, $(H_3C)_3$–C($2'^{1\text{ or }2}$)); 0.85 (s, 9H, $(H_3C)_3$–C($2'^{2\text{ or }1}$)). ^{13}C NMR (125 MHz, d_6-DMSO): 172.7; 172.4; 161.1; 160.0; 130.2; 98.9; 98.8; 73.8; 73.7; 38.1; 38.0; 26.9; 13.9; 13.7. EI-MS: 144 (14), 126 (100), 97 (11), 69 (16), 57 (50), 41 (29), 39 (12). Anal. calcd for $C_{10}H_{16}O_4$ (200.23): C 59.98, H 8.05, O 31.96; found: C 60.20, H 7.89, O 31.71.

4.3.25. 3-[(1*S*)-1-Hydroxy-2-methylpropyl]-4-methylfuran-2(5*H*)-one 2. 1 (750 mg, 4.03 mmol) was dissolved in absolute MeOH (20 ml) under argon and the solution was cooled to 0°C. Sodium borohydride (620 mg, 16.1 mmol) was added in portions, and the mixture was stirred for 45 min at rt. The reaction was quenched with water and extracted three times with AcOEt. The combined organic phases were dried over $MgSO_4$, filtered, and the solvent was evaporated. Flash chromatography with *tert*-butyl methyl ether afforded **2** (400 mg, 2.35 mmol, 58%) as a colorless liquid. For the characterization, see above.

4.3.26. 3-[(1*S*,2*S*)-1-Hydroxy-2-methylbutyl]-4-methylfuran-2(5*H*)-one 4. Same procedure as for **2**. **3** (1.00 g, 5.00 mmol) was reduced with sodium borohydride (720 mg, 20.0 mmol). Purification afforded **4** (500 mg, 2.72 mmol, 54%) as a colorless oil. For the characterization, see above.

4.3.27. 3-[(1*S*)-1-Hydroxyethyl]-4-methylfuran-2(5*H*)-one 22c. Same procedure as for **2**. **20c** (200 mg, 1.27 mmol) was reduced with sodium boron hydride (192 mg, 5.06 mmol). Purification afforded **22c** (120 mg, 0.845 mmol, 66%) as an oil. $[\alpha]_D^{20}$=−30.2 (c=1.00, $CHCl_3$, stab. 1% EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): 4.72 (q, J=6.3 Hz, 1H, H–C($1'$)); 4.65 (s, 2H, H–C(5)); 3.31 (s, 1H, HO–C($1'$)); 2.12 (s, 3H, H_3C–C(4)); 1.46 (d, J=6.6 Hz, 3H, H–C($2'$)). ^{13}C NMR (125 MHz, $CDCl_3$): 174.0; 157.3; 128.7; 72.6; 62.7; 22.4; 12.1. EI-MS: 127 (100), 124 (16), 99 (58), 96 (15), 95 (13), 71 (12), 69 (13), 67 (27), 53 (24), 45 (14), 43 (51), 41 (30), 39 (26). Anal. calcd for $C_7H_{10}O_3$ (142.16): C 59.14, H 7.09, O 33.77; found: C 58.80, H 6.89, O 33.84.

4.3.28. 3-[(1*S*)-1-Hydroxypropyl]-4-methylfuran-2(5*H*)-one 22d. Same procedure as for **2**. **20d** (200 mg, 1.16 mmol) was reduced with sodium borohydride (177 mg, 4.65 mmol). The purification afforded **22d** (150 mg, 0.961 mmol, 83%) as an oil. $[\alpha]_D^{20}$=−40.5 (c=1.00, $CHCl_3$, stab. 1% EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): 4.68–4.64 (m, 2H, H–C(5)); 4.44 (t, J=6.6 Hz, 1H, H–C($1'$)); 3.31 (s, 1H, HO–C($1'$)); 2.11 (s, 3H, H_3C-(4)); 1.84 (dquin., J=13.8 Hz, 7.4, 1H, H_a–C($2'$)); 1.73 (ddq, J=13.8 Hz, 7.4, 6.6, 1H, H_b–C($2'$)); 0.93 (t, J=7.4 Hz, 3H, H–C($3'$)). ^{13}C NMR (125 MHz, $CDCl_3$): 174.0; 158.2; 127.7; 72.6; 67.9; 29.2; 12.1; 9.7. EI-MS: 138 (11), 127 (100), 99 (41), 71 (10), 53 (19), 43 (22), 41 (16), 39 (14). Anal. calcd for $C_8H_{12}O_3$ (156.18): C 61.52, H 7.74, O 30.73; found: C 61.30, H 7.73, O 31.28.

4.3.29. 3-[(1*S*)-1-Hydroxy-2,2-dimethylpropyl]-4-methylfuran-2(5*H*)-one 22e. Same procedure as for **2**. **20e** (200 mg, 1.00 mmol) was reduced with sodium borohydride (200 mg, 5.28 mmol). The purification afforded **22e** (134 mg, 73%) as a colorless solid. Mp 77–78°C. $[\alpha]_D^{20}$=−28.4 (c=1.00, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): 4.73 (d, J=17.5 Hz, 1H, H_a–C(5)); 4.65 (d, J=17.5 Hz, 1H, H_b–C(5)); 4.20 (d, J=9.5 Hz, 1H, H–C($1'$)); 3.66 (d, J=9.5 Hz, 1H, HO–C($1'$)); 2.08 (s, 3H, CH_3–C(4)); 0.96 (s, 9H, $(CH_3)_3$–C($2'$)). ^{13}C NMR (125 MHz, $CDCl_3$): 174.8; 159.3; 126.3; 75.2; 72.8; 37.8; 25.9; 13.3. EI-MS (70 eV): 151 (13), 128 (80), 127 (64), 110 (100), 99 (12), 82 (65), 57 (49), 53 (13), 43 (18), 41 (35), 39,

(19). FAB-MS (NBA): 186 (10), 185 (100), 167 (82), 137 (14), 136 (10), 127 (14), 77 (14), 57 (12), 41 (12), 39 (13). FAB-MS (NBA+KCl): 223 (46), 186 (10), 185 (100), 167 (91), 137 (10), 127 (16), 57 (16), 43 (13), 41 (13), 39 (30). Anal. calcd for $C_{10}H_{16}O_3$ (184.24): C 65.19, H 8.75, O 26.05; found: C 64.97, H 8.78, O 26.12.

4.3.30. 3-[(1*R*)-1-Hydroxy-2-methylpropyl]-4-methylfuran-2(5*H*)-one 14. Same procedure as for **2**. **21a** (750 mg, 4.03 mmol) was reduced with sodium borohydride (620 mg, 16.1 mmol). Purification afforded **14** (400 mg, 2.35 mmol, 58%) as colorless needles. Mp 42.5–43.0°C. $[\alpha]_D^{20}$=+17.0 (*c*=1.00, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): 4.71 (d, *J*=17.3 Hz, 1H, H_a–C(5)); 4.66 (d, *J*=17.3 Hz, 1H, H_b–C(5)); 4.14 (t, *J*=8.7 Hz, 1H, H–C(1′)); 3.10 (d, *J*=9.4 Hz, 1H, HO–C(1′)); 2.08 (s, 3H, H_3C–C(4)); 2.08–2.00 (m, 1H, H–C(2′)); 1.05 (d, *J*=6.7 Hz, 3H, $(H_3C)_2$–C(2′)); 0.84 (d, *J*=6.7 Hz, 3H, $(H_3C)_2$–C(2′)). ^{13}C NMR (125 MHz, $CDCl_3$): 174.2; 158.3; 127.4; 72.7; 72.4; 33.8; 18.8; 18.4; 12.4. EI-MS: 152 (12), 128 (23), 127 (100), 110 (36), 109 (13), 99 (24), 82 (31), 53 (14), 43 (29), 41 (18), 39 (15). Anal. calcd for $C_9H_{14}O_3$ (170.21): C 63.51, H 8.29, O 28.20; found: C 63.21, H 8.38, O 28.60.

4.3.31. 3-[(1*R*,2*S*)-1-Hydroxy-2-methylbutyl]-4-methylfuran-2(5*H*)-one (15). Same procedure as for **2**. **21b** (1.00 mg, 5.00 mmol) was reduced with sodium borohydride (720 mg, 20.0 mmol). Purification afforded **15** (530 mg, 2.88 mmol, 58%) as a colorless solid. Mp 91.0–92.0°C. $[\alpha]_D^{20}$=+17.0 (*c*=1.00, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): 4.70 (d, *J*=17.3 Hz, 1H, H_a–C(5)); 4.65 (d, *J*=17.3 Hz, 1H, H_b–C(5)); 4.29 (t, *J*=8.5 Hz, 1H, H–C(1′)); 3.06 (d, *J*=9.2 Hz, 1H, HO–C(1′)); 2.08 (s, 3H, H_3C–C(4)); 1.80–1.71 (m, 1H, H–C(2′)); 1.43–1.34 (m, 1H, H_a–C(3′)); 1.30–1.10 (m, 1H, H_b–C(3′)); 1.00 (d, *J*=6.7 Hz, 3H, H_3C–C(2′)); 0.91 (t, *J*=7.4 Hz, 3H, H–C(4′)). ^{13}C NMR (125 MHz, $CDCl_3$): 174.3; 158.1; 127.5; 72.7; 71.0; 40.4; 25.6; 14.6; 12.5; 11.5. EI-MS: 128 (40), 127 (100), 110 (67), 99 (23), 82 (47), 53 (15), 43 (19), 41 (24), 39 (15). Anal. calcd for $C_{10}H_{16}O_3$ (184.24): C 65.19, H 8.75, O 26.05; found: C 65.21, H 8.80, O 26.32.

4.3.32. 3-[(1*R*)-1-Hydroxyethyl]-4-methylfuran-2(5*H*)-one 23c. Same procedure as for **2**. **21c** (200 mg, 1.27 mmol) was reduced with sodium borohydride (192 mg, 5.06 mmol). Purification afforded **23c** (120 mg, 0.845 mmol, 66%) as an oil. $[\alpha]_D^{20}$=+29.7 (*c*=1.00, $CHCl_3$, stab. 1% EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): 4.72 (q, *J*=6.6 Hz, 1H, H–C(1′)); 4.65 (s, 2H, H–C(5)); 3.26 (s, 1H, HO–C(1′)); 2.12 (s, 3H, H_3C–C(4)); 1.47 (d, *J*=6.6 Hz, 3H, H–C(2′)). ^{13}C NMR (125 MHz, $CDCl_3$): 174.0; 157.2; 128.8; 72.6; 62.7; 22.4; 12.1. EI-MS: 127 (100), 124 (27), 99 (56), 81 (10), 71 (12), 69 (14), 67 (39), 53 (27), 45 (13), 43 (50), 41 (36), 39 (30). Anal. calcd for $C_7H_{10}O_3$ (142.16): C 59.14, H 7.09, O 33.77; found: C 58.86, H 6.99, O 33.90.

4.3.33. 3-[(1*R*)-1-Hydroxypropyl]-4-methylfuran-2(5*H*)-one 23d. Same procedure as for **2**. **21d** (200 mg, 1.16 mmol) was reduced with sodium borohydride (177 mg, 4.65 mmol). Purification afforded **23d** (140 mg, 0.897 mmol, 77%) as an oil. $[\alpha]_D^{20}$=+41.7 (*c*=1.00, $CHCl_3$, stab. 1% EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): 4.68–4.64 (m, 2H, H–C(5)); 4.44 (t, *J*=6.6 Hz, 1H, H–C(1′)); 3.21 (s, 1H, HO–C(1′)); 2.11 (s, 3H, H_3C-(4)); 1.85 (dquin., *J*=13.8, 7.4 Hz, 1H, H_a–C(2′)); 1.73 (ddq, *J*=13.8, 7.4, 6.6 Hz, 1H, H_b–C(2′)); 0.93 (t, *J*=7.4 Hz, 3H, H–C(3′)). ^{13}C NMR (125 MHz, $CDCl_3$): 174.0; 158.1; 127.7; 72.6; 68.0; 29.3; 12.1; 9.7. EI-MS: 138 (11), 127 (100), 99 (41), 71 (10), 53 (20), 43 (23), 41 (17), 39 (15). Anal. calcd for $C_8H_{12}O_3$ (156.18): C 61.52, H 7.74, O 30.73; found: C 61.37, H 7.74, O 31.19.

4.3.34. 3-[(1*R*)-1-Hydroxy-2,2-dimethylpropyl]-4-methylfuran-2(5*H*)-one 23e. Same procedure as for **2**. **21e** (200 mg, 1.00 mmol) was reduced with sodium borohydride (200 mg, 5.28 mmol). The purification afforded **23e** (118 mg, 64%) as a colorless solid. Mp 77–78°C. $[\alpha]_D^{20}$=+27.0 (*c*=1.00, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): 4.73 (d, *J*=17.0 Hz, 1H, H_a–C(5)); 4.65 (d, *J*=17.5 Hz, 1H, H_b–C(5)); 4.20 (d, *J*=9.5 Hz, 1H, H–C(1′)); 3.65 (d, *J*=10 Hz, 1H, HO–C(1′)); 2.08 (s, 3H, CH_3–C(4)); 0.96 (s, 9H, $(CH_3)_3$–C(2′)). ^{13}C NMR (125 MHz, $CDCl_3$): 174.8; 159.3; 126.3; 75.2; 72.8; 37.8; 25.9; 13.3. EI-MS (70 eV): 151 (13), 128 (81), 127 (65), 123 (11), 110 (100), 99 (12), 82 (64), 57 (49), 53 (13), 43 (17), 41 (35), 39, (18). FAB-MS (NBA): 185 (100), 167 (82), 137 (10), 127 (12), 57 (11), 41 (11), 39 (10). FAB-MS (NBA+KCl): 223 (39), 185 (100), 167 (92),137 (14), 127 (15), 57 (17), 43 (11), 41 (13), 39 (13). Anal. calcd for $C_{10}H_{16}O_3$ (184.24): C 65.19, H 8.75, O 26.05; found: C 65.24, H 8.75, O 26.34.

4.3.35. (1*S*,2*S*)-2-Methyl-1-(4-methyl-2-oxo-2,5-dihydrofuran-3-yl)butyl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 25. Same procedure as for **12**. (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride ((*R*)-Mosher's acid chloride, **11**) (35 mg, 0.140 mmol) was reacted with **4** (18.4 mg, 0.100 mmol). Purification by HPLC (Eurospher 100-7 RP-C18; water/MeOH 25:75; t_R **25**=13.5–15.0 min) afforded **25** (22.5 mg, 0.056 mmol, 56%) as colorless plates. Mp 84.3–85.2°C. $[\alpha]_D^{20}$=−57.2 (*c*=1.18, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): 7.55–7.34 (m, 5H, phenyl); 5.44 (d, *J*=9.4 Hz, 1H, H–C(1′)); 4.69 (d, *J*=17.3 Hz, 1H, H_a–C(5)); 4.65 (d, *J*=17.3 Hz, 1H, H_b–C(5)); 3.52 (s, 3H, H_3CO–C(2″)); 2.40–2.26 (m, 1H, H–C(2′)); 2.11 (s, 3H, H_3C–C(4)); 1.49–1.36 (m, 1H, H_a–C(3′)); 1.10–0.95 (m, 1H, H_b–C(3′)); 0.80 (t, *J*=7.4 Hz, 3H, H–C(4′)); 0.77 (d, *J*=6.9 Hz, 3H, H_3C–C(2′)). ^{13}C NMR (75 MHz, $CDCl_3$): 172.0; 166.2; 162.9; 132.0; 129.6; 128.4; 127.3; 123.8; 123.3 (q, $^1J_{CF}$=287 Hz); 84.5 (q, $^2J_{CF}$=27 Hz); 74.0; 72.4; 55.6; 35.6; 24.6; 14.5; 12.7; 10.2. FAB-MS (NBA): 401 (8, $[M+H]^+$), 189 (12), 168 (10), 167 (100), 43 (13). Anal. calcd for $C_{20}H_{23}F_3O_5$ (400.40): C 60.00, H 5.79, O 19.98; found: C 59.98, H 5.84, O 20.12.

4.3.36. (1*S*,2*S*)-2-Methyl-1-(4-methyl-2-oxo-2,5-dihydrofuran-3-yl)butyl (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 26. Same procedure as for **12** (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride ((*S*)-Mosher's acid chloride, **24**) (35 mg, 0.140 mmol) was reacted with **4** (18.4 mg, 0.100 mmol). Purification by HPLC (Eurospher 100-7 RP-C18; water/MeOH 25:75; t_R **26**=12.0–14.0 min) afforded **26** (25.2 mg, 0.063 mmol,

63%) as colorless plates. Mp 86.2–88.6°C. $[\alpha]_D^{20}=-12.8$ (c=1.43, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): 7.47–7.35 (m, 5H, phenyl); 5.50 (d, J=9.1 Hz, 1H, H–C(1′)); 4.60 (d, J=17.3 Hz, 1H, H_a–C(5)); 4.56 (d, J=17.3 Hz, 1H, H_b–C(5)); 3.54 (s, 3H, H_3CO–C(2″)); 2.28–2.19 (m, 1H, H–C(2′)); 1.90 (s, 3H, H_3C–C(4)); 1.70–1.56 (m, 1H, H_a–C(3′)); 1.28–1.12 (m, 1H, H_b–C(3′)); 0.90 (t, J=7.4 Hz, 3H, H–C(4′)); 0.83 (d, J=6.9 Hz, 3H, H_3C–C(2′)). ^{13}C NMR (75 MHz, $CDCl_3$): 172.0; 166.1; 162.1; 131.8; 129.7; 128.4; 127.3; 124.0; 123.2 (q, $^1J_{CF}$=287 Hz); 84.4 (q, $^2J_{CF}$=27 Hz); 74.3; 72.4; 55.6; 36.3; 24.6; 14.6; 12.5; 10.5. FAB-MS (NBA): 401 (8, $[M+H]^+$), 189 (12), 168 (11), 167 (100), 57 (16), 55 (11), 43 (19), 41 (12). Anal. calcd for $C_{20}H_{23}F_3O_5$ (400.40): C 60.00, H 5.79, O 19.98; found: C 59.69, H 6.03, O 20.37.

4.3.37. (1*R*)-1-[(5*R*)-5-{[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl]oxy}-4-methyl-2-oxo-2,5-dihydrofuran-3-yl]-2-methylpropyl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 27a. Same procedure as for **12**. **19a** (143 mg, 0.441 mmol) was esterified with **11** (200 mg, 0.794 mmol). Flash chromatography with AcOEt/hexane 1:5 afforded **27a** (190 mg, 0.352 mmol, 80%). Colorless prisms (AcOEt/hexane). Mp 103.5–105.0°C. $[\alpha]_D^{20}=-84.0$ (c=1.00, $CHCl_3$, stab. 1% EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): 7.50–7.34 (m, 5H, phenyl); 5.69 (s, 1H, H–C(5)); 5.37 (d, J=9.1 Hz, 1H, H–C(1″)); 3.55 (s, 3H, H–C(3″)); 2.44–2.35 (m, 1H, H–C(2″)); 1.82 (s, 3H, H_3C–C(4)); 1.03 (d, J=6.6 Hz, 3H, $(H_3C)_2$–C(2″)); 0.87 (d, J=6.7 Hz, 3H, $(H_3C)_2$–C(2″)). Menthyl resonances: 3.62; 2.13–2.09; 2.11–2.06; 1.72–1.67; 1.68–1.63; 1.46–1.36; 1.29–1.22; 1.07–0.99; 1.03–0.93; 0.95; 0.91–0.82; 0.88;0.80. ^{13}C NMR (125 MHz, $CDCl_3$): 169.4; 166.1; 160.2; 131.8; 129.6; 128.4; 127.3; 126.4; 123.1 (q, $^1J_{CF}$=288 Hz); 100.0; 75.6; 55.7; 30.5; 19.0; 18.4; 11.9. Menthyl resonances: 79.1; 47.8; 40.3; 34.2; 31.4; 25.4; 23.3; 22.3; 20.8; 15.9. EI-MS: 190 (12), 189 (100), 169 (26), 152 (19), 151 (22), 83 (30), 69 (17), 55 (16), 43 (12), 41 (10). Anal. calcd for $C_{29}H_{39}F_3O_6$ (540.63): C 64.43, H 7.27, O 17.76; found: C 64.19, H 7.28, O 17.88.

4.3.38. (1*R*,2*S*)-1-[(5*R*)-5-{[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl]oxy}-4-methyl-2-oxo-2,5-dihydrofuran-3-yl]-2-methylbutyl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 27b. Same procedure as for **12**. **19b** (150 mg, 0.444 mmol) was esterified with **11** (200 mg, 0.794 mmol). Flash chromatography with AcOEt/hexane 1:5 afforded **27b** (130 mg, 0.234 mmol, 53%) as colorless cubes. Mp 117.0–118.0°C. $[\alpha]_D^{20}=-86.0$ (c=1.00, $CHCl_3$, stab. 1% EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): 7.46–7.33 (m, 5H, phenyl); 5.67 (s, 1H, H–C(5)); 5.51 (d, J=8.4 Hz, 1H, H–C(1″)); 3.54 (s, 3H, H–C(3″)); 2.19–2.10 (m, 1H, H–C(2″)); 1.79 (s, 3H, H_3C–C(4)); 1.38–1.30 (m, 1H, H_a–C(3″)); 1.12–0.90 (m, 1H, H_b–C(3″)); 0.99 (d, J=6.6 Hz, 3H, H_3C–C(2″)); 0.90 (t, J=7.4 Hz, 3H, H–C(4″)). Menthyl resonances: 3.61; 2.12–2.05; 1.73–1.64; 1.46–1.36; 1.28–1.22; 1.12–0.90; 0.95; 0.91–0.82; 0.88; 0.80. ^{13}C NMR (125 MHz, $CDCl_3$): 169.5; 166.1; 160.0; 131.8; 129.5; 128.4; 127.3; 126.5; 123.1 (q, $^1J_{CF}$=288 Hz); 100.0; 74.5; 55.7; 36.9; 25.2; 15.1; 11.9; 11.0. Menthyl resonances: 79.1; 47.8; 40.3; 34.2; 31.4; 25.4; 23.3; 22.2; 20.8; 15.9. EI-MS: 190 (13), 189 (100), 183 (47), 166 (15), 165 (24), 110 (12), 83 (33), 69 (16), 57 (12), 55 (15). Anal. calcd for $C_{30}H_{41}F_3O_6$ (554.65): C 64.97, H 7.45, O 17.31; found: C 65.04, H 7.59, O 17.03.

4.3.39. (1*R*)-1-[(5*R*)-5-{[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl]oxy}-4-methyl-2-oxo-2,5-dihydrofuran-3-yl]-2-methylpropyl (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 28a. Same procedure as for **12**. **19a** (143 mg, 0.441 mmol) was esterified with **24** (200 mg, 0.794 mmol). Flash chromatography with AcOEt/hexane 1:5 afforded **28a** (190 mg, 0.352 mmol, 80%) as a pale yellow oil. $[\alpha]_D^{20}=-22.5$ (c=1.00, $CHCl_3$, stab. 1% EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): 7.50–7.35 (m, 5H, phenyl); 5.74 (s, 1H, H–C(5)); 5.35 (d, J=9.4 Hz, 1H, H–C(1″)); 3.51 (s, 3H, H–C(3″)); 2.48–2.39 (m, 1H, H–C(2″)); 2.02 (s, 3H, H_3C–C(4)); 0.85 (d, J=6.6 Hz, 3H, $(H_3C)_2$–C(2″)); 0.84 (d, J=7.0 Hz, 3H, $(H_3C)_2$–C(2″)). Menthyl resonances: 3.64; 2.14–2.09; 2.11–2.05; 1.72–1.66; 1.68–1.63; 1.46–1.36; 1.29–1.22; 1.07–0.99; 1.03–0.93; 0.95; 0.91–0.82; 0.88; 0.81. ^{13}C NMR (125 MHz, $CDCl_3$): 169.4; 166.2; 161.2; 132.0; 129.6; 128.4; 127.3; 126.2; 123.1 (q, $^1J_{CF}$=289 Hz); 100.1; 75.4; 55.5; 30.3; 18.7; 18.3; 12.0. Menthyl resonances: 79.2; 47.7; 40.3; 34.2; 31.4; 25.5; 23.3; 22.2; 20.7; 15.9. EI-MS: 190 (12), 189 (100), 169 (24), 152 (19), 151 (24), 123 (11), 105 (13), 83 (32), 77 (10), 69 (18), 55 (18), 43 (12), 41 (11). Anal. calcd for $C_{29}H_{39}F_3O_6$ (540.63): C 64.43, H 7.27, O 17.76; found: C 64.51, H 7.37, O 17.79.

4.3.40. (1*R*,2*S*)-1-[(5*R*)-5-{[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl]oxy}-4-methyl-2-oxo-2,5-dihydrofuran-3-yl]-2-methylbutyl (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 28b. Same procedure as for **12**. **19b** (150 mg, 0.444 mmol) was esterified with **24** (200 mg, 0.794 mmol). Flash chromatography with AcOEt/hexane 1:5 afforded **28b** (140 mg, 0.253 mmol, 57%) as a colorless oil. $[\alpha]_D^{20}=-23.0$ (c=1.00, $CHCl_3$, stab. 1% EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): 7.50–7.47 (m, 5H, phenyl); 5.73 (s, 1H, H–C(5)); 5.48 (d, J=8.8 Hz, 1H, H–C(1″)); 3.51 (s, 3H, H–C(3″)); 2.24–2.16 (m, 1H, H–C(2″)); 2.00 (s, 3H, H_3C–C(4)); 1.35–1.28 (m, 1H, H_a–C(3″)); 1.05–1.00 (m, 1H, H_b–C(3″)); 0.87 (t, J=7.4 Hz, 3H, H–C(4″)); 0.83 (d, J=6.6 Hz, 3H, H_3C–C(2″)). Menthyl resonances: 3.63; 2.14–2.09; 2.08–2.04; 1.72–1.63; 1.46–1.36; 1.28–1.23; 1.09–1.00; 1.05–1.00; 0.95; 0.91–0.82; 0.88; 0.81. ^{13}C NMR (125 MHz, $CDCl_3$): 169.5; 166.1; 160.9; 131.9; 129.6; 128.4; 127.3; 126.3; 123.3 (q, $^1J_{CF}$=289 Hz); 100.1; 84.4 (q); 74.4; 55.5; 36.6; 25.0; 14.8; 12.1; 10.9. Menthyl resonances: 79.2; 47.7; 40.4; 34.2; 31.4; 25.5; 23.3; 22.2; 20.7; 16.0. EI-MS: 190 (12), 189 (100), 183 (43), 166 (16), 165 (24), 110 (12), 83 (40), 69 (18), 57 (13), 55 (18), 41 (11). Anal. calcd for $C_{30}H_{41}F_3O_6$ (554.65): C 64.97, H 7.45, O 17.31; found: C 65.10, H 7.68, O 17.29.

4.4. Determination of the C(2′) configuration of 4

Furanone **9** was reacted once with (*S*)-2-methylbutanal[21] and once with (*RS*)-2-methylbutanal according to the procedure given for **10b**. The product mixture was subjected to GC: Carlo Erba HRGC 5000, permethylated β-cyclodextrin column 25 m×0.22 mm (Chrompack), He, Split 50:1, isothermal 138°C. Retention times (min) and, in parentheses, peak areas (%):

Products from **9** and (*RS*)-2-methylbutanal	29.8 (31)	30.2 (19)	30.7 (19)	32.5 (31)
Products from **9** and (*S*)-2-methylbutanal	–	30.2 (38)	–	32.5 (62)
Metabolite **4**	–	30.2 (100)	–	–

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