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Tipranavir analogous 3-sulfonylanilidotetronic acids: new synthesis and structure-dependent anti-HIV activity

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ABSTRACT

Sulfonamide-containing tetronic acids **1**, structural analogues of the HIV-1 protease inhibitor tipranavir, were synthesised in five steps including a microwave-assisted Claisen rearrangement of cinnamyl tetronates and a modified Charette cyclopropanation of the so-formed 3-allyltetronic acids. Compounds **1** with two non-H residues (R^1, R^2) at C-5 of the tetronate core exhibited structure-dependent antiviral activity in two HIV strains. Derivatives **1c** (R^1=R^2=Me, R^3=Cl) and **1d** ($R^{1,2}$=$(CH_2)_5$, R^3=Me) were most active (IC_{50}<10 μM) in the sensitive strain HIV_{NL4-3}.

1. Introduction

Regimens with HIV protease inhibitors (PI) in combination with reverse transcriptase inhibitors continue to be the first line treatment for control of HIV-1 infections despite serious limitations such as long term drug toxicity and rapidly developing viral multidrug resistance.[1] As the precise C_2-symmetric structure of the homodimeric HIV-1 protease was known relatively early on, the rational design of inhibitors was possible.[2] Aside of peptidomimetic PI containing transition-state inserts in place of the dipeptidic cleavage sites of the substrates,[3] non-peptidic inhibitory ligands for HIV proteases were developed in steadily increasing numbers. They feature a greater oral bioavailability and slower biliary excretion when compared to peptide-derived compounds. They are also faster to synthesise and so lend themselves to a continuous development addressing the problem of resistance. In 2005, tipranavir (Aptivus®, Boehringer Ingelheim) was approved by the EMEA for clinical application in combination therapies. This sulfonamide-containing 5,6-dihydro-4-hydroxy-2-pyrone had emerged from screenings of 3-substituted coumarins and dihydropyrones and proved active even in patients no longer responding to other conventional PI.[4] Other 4-hydroxypyrones with anti-HIV activity were also reported.[5] Tipranavir analogous tetronic acids bearing 3-α-cyclopropyl groups were earlier pinpointed in patents as equally good binders to the active site of HIV-1 protease.[6,7] However, the given protocols were incomplete and failed to work in our hand.

Thus, herein, we present a conceptionally new, reliable five-step synthesis of 3-[cyclopropyl-*m*-(benzsulfonanilido)methyl]tetronic acids **1** with three variable residues (Fig. 1). We also report the structure-dependent antiviral activities of eight derivatives of **1** in two HIV strains.

2. Results and discussion

2.1. Chemistry

In contrast to dihydro-4-hydroxypyran-2-ones as occurring in tipranavir, tetronic acids cannot be directly alkylated in 3-position. The above mentioned patent literature[6] on analogues of **1** described an indirect route to achieve 3-alkylation, which comprises condensation of the respective tetronic acids with aldehydes and subsequent Grignard addition to the newly formed exocyclic double bond. We found this method to fail erratically. Scheme 1 depicts an alternative five-step synthesis of compounds **1** starting from tetronic acids **5**. These were readily prepared from the corresponding benzyl α-hydroxy carboxylates **2** and the cumulated phosphorus ylide Ph_3P=C=C=O **3**.[8] Addition of the OH group of **2** across the C=C bond of the ylide afforded an ester ylide, which in turn underwent an intramolecular Wittig alkenation to give the benzyl tetronates **4**.[9] Hydrogenolytic debenzylation then liberated the tetronic acids **5**. These were etherified in microwave with 1-(*m*-

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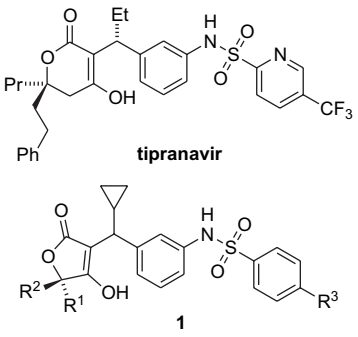
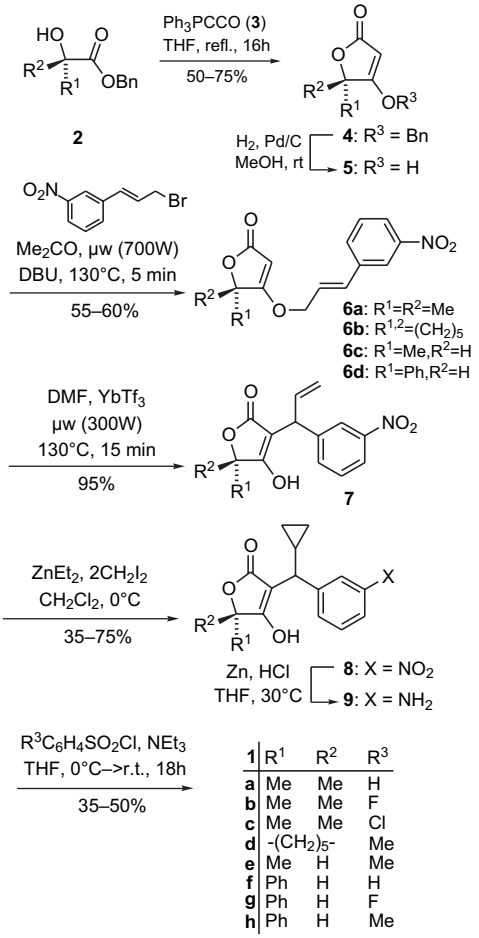


Figure 1. Structures of tipranavir and 3-[cyclopropyl-*m*-(benzsulfonanilido)methyl]-tetronic acids **1**.

nitrophenyl)allylbromide, prepared from methyl *m*-nitrocinnamoate via DIBAL-H reduction, to give the alcohol and bromination of the latter with PBr_3. When carried out in acetone in the presence of DBU under optimised conditions, i.e., by irradiating the mixture with 750 W power input for 20 s to quickly reach 130 °C and then maintaining this temperature for another 5 min by irradiating with 700 W, the product tetronates **6** were obtained in ca. 60% yield. They could be Claisen rearranged in over 90% yield by carefully controlled microwave irradiation (300 W, 130 °C, 15 min) of their solutions in DMF in the presence of catalytic amounts of ytterbium triflate. Longer periods of irradiation led to the formation of by-products originating from a follow-up Conia rearrangement.[10,11] Although the Claisen rearrangement of chiral 5-mono-substituted tetronates, e.g., **6c**,**d** proceeded with some stereoinduction it afforded unassignable mixtures of diastereoisomers of tetronic acids **7c** and **7d**, respectively. No attempts were made to separate them since the corresponding target compounds derived from them, i.e., **1e**–**h**, later showed disappointingly low anti-HIV activities in the biotests. The cyclopropanation of 3-allyltetronic acids **7** was initially planned to be carried out according to the Shi variant[12] of the Charette protocol,[13] which uses a mixture of trifluoroacetic acid, CH_2I_2 and $ZnEt_2$ in dichloromethane. While this method worked perfectly well for analogues of **7** lacking the nitro group, it was not applicable to compounds **7** themselves. However, the original Charette protocol that dispenses with trifluoroacetic acid converted alkenes **7** to the corresponding cyclopropanes **8** albeit in moderate yields. However, unreacted starting compound **7** could be recovered in each case. The reduction of the nitro group of **8** to give the corresponding aniline **9** was achieved with zinc and HCl in THF at 30 °C. After 5 min, the reaction mixture was filtered over a plug of cotton and the eluate was extracted with ethyl acetate. It should be noted that reduction of the nitro compounds **8** was also possible with $SnCl_2$ in DMF. However, removal was tedious or even impossible of the by-product Sn(II) salts, which interfere with the subsequent sulfonylation step. The susceptible crude anilines **9** were subjected to the final sulfonylation reaction without further purification. Only *p*-substituted benzenesulfonyl chlorides were employed as they were expected to lead to intrinsically more active products. Triethylamine (1 equiv at room temperature) was the auxiliary base of choice while pyridine as a base or an excess of triethylamine at higher temperature as recommended in the literature[6] gave rise to predominantly *N*,*O*-disulfonylated products. Unreacted anilines **9** could be recovered as hydrochloride salts in most cases and were subjected to a second sulfonylation step in order to double yields. The target tetronic acids **1** were finally purified for the biotests in HIV viruses by two TLC runs in order to rid them of pertinaciously adhering trace amounts of the disulfonyl adducts and residual sulfonyl chlorides.



1	R^1	R^2	R^3
a	Me	Me	H
b	Me	Me	F
c	Me	Me	Cl
d	-$(CH_2)_5$-		Me
e	Me	H	Me
f	Ph	H	H
g	Ph	H	F
h	Ph	H	Me

Scheme 1. Synthesis of 3-[cyclopropyl-*m*-(benzsulfonanilido)methyl]tetronic acids **1** from tetronic acids **5**.

2.2. Biological evaluation

Compounds **1** were tested for antiviral activity on two HIV-1 strains, the PI-sensitive HIV_{NL4-3} and a PI-resistant clone 4lig7,[14] by an assay published previously.[15] These strains were obtained by amplifying the C-terminal part of the gag gene, the entire protease (PR) and the 5′-part of the reverse transcriptase (RT) gene from the plasma of HIV-1 infected individuals by RT polymerase chain reaction (RT-PCR). The amplified part of the gag gene included two protease cleavage sites of the gag polyprotein, NC/p1 and p1/p6(gag), and two protease cleavage sites of the reading-frame-shifted gag-pol polyprotein, between NC and the transframe protein, and between the transframe protein and p6(pol). These C-terminal cleavage sites are the most frequently mutated in the context of protease inhibitor resistance. The amplicon was ligated into the molecular clone of $HIV\text{-}1_{NL4-3}$ containing a deletion of the respective genes. Bacteria were transformed with the ligation products, plasmid DNA was prepared from the bacteria and transfected into 293T cells and recombinant virus was harvested from their supernatant 2 days after transfection. The sensitivity of these recombinant virus strains towards compounds **1** was then determined with the help of an indicator cell line containing the secreted alkaline phosphatase (SEAP) gene under the control of an HIV-1 long terminal repeat (LTR).[16] When infected by HIV-1, the viral Tat protein transactivates the LTR leading to a strong increase in SEAP activity in the culture supernatant, which can be easily monitored. In our case, the indicator cells were infected with the viruses in the presence of different amounts of compounds **1** and the ensuing virus replication was monitored as a function of drug

Table 1
Drug sensitivities (IC_{50} values[a] in μM) of HIV strains NL4-3 and 4lig7[14] towards compounds **1a–d**[b] as ascertained by a published assay[15]

Compounds	NL4-3	4lig7
1a	11.4	>100
1b	55.6	>100
1c	8.8	>100
1d	8.3	72.3

[a] All assays run in duplicate; quoted IC_{50} values derived from three independent experiments and referring to the activities of the respective virus in the absence of a test compound set to 100%; SEAP activity determined 5 days later using the Phospha-light-kit (Tropix, Bedford, MA, USA).
[b] Compounds **1e–h** exhibited no activities in either strain at concentrations below 100 μM.

concentration. The concentrations inhibiting the viral activity by 50% relative to the uninhibited control (IC_{50}) for compounds **1** are listed in Table 1. They are clearly higher for NL4-3 and 4lig7 than those of approved PI such as tipranavir (6 nM/16 nM), ritonavir (37 nM/2.4 μM), nelfinavir (25 nM/2.1 μM) or saquinavir (9 nM/0.9 μM). Nonetheless, the figures revealed some tentative structure–activity relations and provided clues as to which residues should be systematically varied and in what direction in order to enhance the activity of **1**. While derivatives **1e–h** with 5-mono-substituted tetronic acid rings (R^2=H) were virtually inactive against either virus, the 5,5-dialkyl substituted analogues **1a–d** exhibited distinct activities in the PI-sensitive virus NL4-3. Among the three 5,5-dimethyltetronic acids **1a–c**, the *p*-chloro derivative proved the most active one (IC_{50}=8.8 μM) while the *p*-fluoro analogue **1b** was distinctly less active even when compared with the parent compound **1a**. 5-Spirocyclohexyltetronic acid **1d** showed the highest activity in NL4-3 and even some activity in the PI-resistant strain 4lig7 (ninefold decrease compared to NL4-3). An activity enhancement appears possible by replacing the *p*-methyl residue with a Cl substituent in analogy to **1c**. We now intend to place further electron-withdrawing and -releasing groups in *o*-, *m*- and *p*-position of the terminal arene while retaining the 5,5-dialkyl motif on the tetronic acid moiety.

3. Conclusions

We have established a short synthetic route to sulfonamide-containing tetronic acids **1**, based upon a microwave-assisted, Lewis acid-catalysed Claisen rearrangement of cinnamyl tetronates and a modified Charette cyclopropanation of the so-formed 3-allyltetronic acids. Preliminary biotests of compounds **1** revealed a distinct structure-dependency of their anti-retroviral activity against two HIV-1 strains. The 5,5-dialkyltetronic acid motif seemed to confer a higher basal activity than the 5-mono-substitution pattern. Derivatives **1c** (R^1=R^2=Me, R^3=Cl) and **1d** ($R^{1,2}$=$(CH_2)_5$, R^3=Me) were most active (IC_{50}<10 μM) against the PI-sensitive strain HIV_{NL4-3}, **1d** even noticeably so against the PI-resistant strain 4lig7. The new synthesis should be flexible enough to allow the preparation of larger arrays of analogues of **1** with variation in the pharmacological key positions R^{1-3}. In analogy to the optimisation of tipranavir, we also intend to conduct in-depth modelling studies starting with the X-ray geometry of HIV-1 protease and to co-crystallise and structurally elucidate HIV-1 protease–ligand **1** adducts and to chemically vary the positioning of R^3 as well as the (het)arene of **1**.

4. Experimental

4.1. General

Melting points were determined with a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer One FT-IR spectrophotometer. Nuclear Magnetic resonance (NMR) spectra were recorded under conditions as indicated on a Bruker Avance 300 spectrometer. Chemical shifts (δ) are given in parts per million downfield from TMS as an internal standard. Mass spectra were recorded using a Varian MAT 311A (EI). Optical rotations were recorded at 589 nm with a PERKIN–ELMER polarimeter 241. Elemental analyses were carried out with a Perkin–Elmer 2400 CHN elemental analyser. Microwave reactions were carried out in an MLS-μ-chemist or a CEM-Discover oven. For column chromatography, Merck silica gel 60 (230–400 mesh) was used. Solvents were dried, distilled and stored under argon. Starting compounds were purchased from the usual sources.

4.2. Synthesis of benzyl tetronates 4

*4.2.1. 5,5-Dimethyl-4-oxybenzyl-[5H]furan-2-one **4a**: typical procedure*

A solution of benzyl 2-hydroxyisobutyrate **2a** (6.0 g, 31.0 mmol), Ph_3PCCO (**3**) (10.3 g, 34.2 mmol) and a catalytic amount of benzoic acid (100 mg) in THF (100 mL) was stirred and heated under reflux for 24 h with exclusion of air and moisture. The solvent was evaporated and the residue was purified by column chromatography (5×30 cm; silica gel 60, cyclohexane/diethyl ether 1:1, R_f 0.65). The product obtained from the eluate was finally recrystallised from pentane/diethyl ether to give 5.2 g (71%) of **4a** as a colourless solid; mp 70 °C (lit.[17a] 70 °C); ν_{max}/cm^{-1} 2984, 1744, 1623, 1499, 1455, 1342, 1255, 1223, 1195, 934, 805, 741, 696; δ_H (300 MHz, $CDCl_3$) 1.36 (6H, s), 4.91 (1H, s), 4.93 (2H, s), 7.3 (5H, m); δ_C (75 MHz, $CDCl_3$) 24.3, 74.2, 82.3, 87.6, 127.7, 128.8, 128.9, 134.1, 171.5, 184.5; *m*/*z* (EI, 70 eV) 218 (M^+, 1%), 203 (1%), 200 (1%), 190 (1%), 174 (1%), 159 (1%), 132 (9%), 91 (100%).

*4.2.2. 4-Oxybenzyl-1-oxaspiro[4.5]dec-3-en-2-one **4b***

Analogous to the synthesis of **4a**, compound **4b** (3.23 g, 51%) was obtained from benzyl α-hydroxycyclohexylcarboxylate **2b** (4.5 g, 19.3 mmol) and ylide **3** (7.6 g, 24.1 mmol) as a colourless solid; R_f 0.71 (cyclohexane/diethyl ether 1:1); mp 93 °C (lit.[18] 94 °C); ν_{max}/cm^{-1} 2937, 1747, 1620, 1450, 1340, 1193, 981, 942, 907, 850; δ_H (300 MHz, $CDCl_3$) 1.2–2.0 (10H, m), 5.00 (1H, s), 5.04 (2H, s), 7.2–7.4 (5H, m); δ_C (75 MHz, $CDCl_3$) 21.7, 24.4, 33.1, 74.1, 84.0, 88.1, 127.7, 128.5, 129.0, 134.2, 172.1, 184.9; *m*/*z* (EI, 70 eV) 258 (M^+, 7%), 167 (7%), 132 (28%), 91 (100%).

*4.2.3. (S)-5-Methyl-4-oxybenzyl-[5H]furan-2-one **4c***

Analogous to the synthesis of **4a**, compound **4c** (6.3 g, 62%) was obtained from benzyl L-lactate **2c** (9.0 g, 50.0 mmol) and ylide **3** (15.2 g, 50.0 mmol) as a colourless solid; $[\alpha]_D^{25}$ −21.7 (*c* 1.33, MeOH); R_f 0.66 (cyclohexane/diethyl ether 1:1); mp 84 °C (lit.[19,20] 90and103–104 °C for *rac*-**4c**); ν_{max}/cm^{-1} 1727, 1626, 1293, 1126, 1083, 736, 692; δ_H (300 MHz, $CDCl_3$) 1.48 (3H, d, *J*=6.8 Hz), 4.87 (1H, q, *J*=6.8 Hz), 5.06 (2H, s), 5.12 (1H, s), 7.39 (5H, m); δ_C (75 MHz, $CDCl_3$) 17.8, 74.6, 75.5, 89.3, 127.9, 128.9, 129.1, 133.8, 172.2, 182.2; *m*/*z* (EI, 70 eV) 204 (M^+, 3%), 186 (2%), 159 (2%), 132 (14%), 91 (100%).

*4.2.4. (±)-5-Phenyl-4-oxybenzyl-[5H]furan-2-one **4d***[17a,b]

Analogous to the synthesis of **4a**, compound **4d** (3.84 g, 50%) was obtained from benzyl mandelate **2d** (7.0 g, 29.1 mmol) and ylide **3** (8.7 g, 28.9 mmol) as a colourless solid; R_f 0.69 (cyclohexane/diethyl ether 1:1); mp 93 °C; ν_{max}/cm^{-1} 1746, 1622, 1455, 1331, 1285, 1232, 1151, 1022, 695; δ_H (300 MHz, $CDCl_3$) 4.98 (1H, d, *J*=11.9 Hz), 5.06 (1H, d, *J*=11.9 Hz), 5.17 (1H, d, *J*=1.1 Hz), 5.71 (1H, d, *J*=1.1 Hz), 7.1–7.4 (10H, m); δ_C (75 MHz, $CDCl_3$) 74.4, 80.3, 89.3, 126.6, 127.5, 128.7, 128.9, 129.3, 133.7, 134.0, 172.5, 180.1; *m*/*z* (EI, 70 eV) 266 (M^+, 21%), 248 (3%), 222 (5%), 180 (17%), 175 (48%), 148 (20%), 132 (13%), 107 (100%), 105 (46%), 92 (97%), 91 (100%).

4.3. Synthesis of tetronic acids 5

*4.3.1. 5,5-Dimethyltetronic acid **5a**: typical procedure for the hydrogenolytic debenzylation*

Compound **4a** (440 mg, 2.01 mmol) was dissolved in dry methanol (20 mL), 5% Pd on charcoal (20 mg) was added and the resulting mixture was purged hydrogen gas and kept under an atmosphere (1 bar) of this for 0.2–1.0 h while stirring. After filtration over a pad of Celite, the solvent was removed in vacuo to leave colourless solid **5a** (258 mg, 99%); R_f 0.20 (ethyl acetate); mp 125 °C (from methanol) (lit.[21] 145 °C from ethyl acetate); ν_{max}/cm^{-1} 1695, 1675, 1650, 1282, 1190, 1107, 984, 798; δ_H (300 MHz, acetone-d_6) 1.60 (6H, s), 3.52 (2H, s); δ_C (75 MHz, acetone-d_6) 23.8, 36.6, 89.8, 169.1, 207.9; *m*/*z* (EI, 70 eV) 128 (M^+, 3%), 113 (3%), 100 (35%), 84 (1%), 72 (18%), 43 (100%).

*4.3.2. 4-Hydroxy-1-oxaspiro[4.5]dec-3-en-2-one **5b***

Analogous to the synthesis of **5a**, compound **5b** (321 mg, 93%) was obtained from **4b** (497 mg, 2.10 mmol) as a colourless solid; R_f 0.22 (ethyl acetate); mp 195 °C (lit.[21] 198–201 °C); ν_{max}/cm^{-1} 2939, 1684, 1673, 1546, 1312, 1293, 1267, 1242, 1206, 1201, 981, 912, 802; δ_H (300 MHz, acetone-d_6), mixture (1:2.9) of diketo and enol tautomers: 1.1–1.9 (10H, m), 3.47 (2H, s, diketo), 4.84 (1H, s, enol), 11.19 (1H, s); δ_C (75 MHz, acetone-d_6) 21.7, 24.3, 32.8, 82.7, 87.4, 171.4, 184.3; *m*/*z* (EI, 70 eV) 168 (M^+, 1%), 141 (20%), 98 (100%).

*4.3.3. (S)-5-Methyltetronic acid **5c***

Analogous to the synthesis of **5a**, compound **5c** (225 mg, 99%) was obtained from **4c** (408 mg, 2.0 mmol) as a colourless solid, $[\alpha]_D^{25}$ 20.4 (*c* 1.22, MeOH) [lit.[22] 19.3 (*c* 0.5, H_2O)]; R_f 0.20 (ethyl acetate); mp 118 °C (lit.[22] 115 °C); ν_{max}/cm^{-1} 2988, 1701, 1591, 1320, 1268, 1237, 1166, 1075, 808; δ_H (300 MHz, acetone-d_6), mixture (1:3.6) of diketo and enol tautomers: 1.42 (3H, d, *J*=6.7 Hz), 3.32 (2H, s, diketo), 4.87 (1H, q, *J*=6.7 Hz), 4.91 (1H, s, enol); δ_C (75 MHz, acetone-d_6) 17.4, 74.9, 88.2, 175.0, 182.2; *m*/*z* (EI, 70 eV) 114 (M^+, 21%), 99 (7%), 86 (39%), 69 (3%), 43 (79%), 42 (100%).

*4.3.4. (±)-5-Phenyltetronic acid **5d***

Analogous to the synthesis of **5a**, compound **5d** (88 mg, 99%) was obtained from **4d** (133 mg, 0.5 mmol) as a colourless solid; R_f 0.22 (ethyl acetate); mp 119 °C (lit.[21] 154 °C for (*R*)-**5d**); ν_{max}/cm^{-1} 2887, 1700, 1577, 1276, 1235, 1156, 1001, 769, 697; δ_H (300 MHz, acetone-d_6), mixture (1:9) of diketo and enol tautomers: 3.36 (2H, s, diketo), 5.13 (1H, s, enol), 5.85 (1H, s), 7.3–7.5 (5H, m); δ_C (75 MHz, acetone-d_6) 80.4, 88.6, 127.0, 128.7, 129.1, 135.2, 173.4, 180.6; *m*/*z* (EI, 70 eV) 176 (M^+, 13%), 148 (35%), 120 (15%), 106 (24%), 105 (100%).

4.4. Synthesis of *m*-nitrocinnamyl tetronates 6

*4.4.1. m-Nitrocinnamyl 5,5-dimethyltetronate **6a**: typical procedure for the esterification of tetronic acids*

A solution of *m*-nitrocinnamyl bromide (242 mg, 1.0 mmol) and tetronic acid **5a** (123 mg, 0.97 mmol) in acetone (20 mL) was placed in a microwave-suitable vial, treated with DBU (150 μL, 1 mmol) and immediately irradiated in an MLS microwave reactor for 20 s with 750 W and then for a further 5 min with 700 W power input at maximal 130 °C. The mixture was poured into 10% hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with brine and dried over Na_2SO_4. Evaporation of the volatiles left a brown oil that upon column chromatography (silica gel 60, cyclohexane/ethyl acetate 3:1, R_f 0.23) yielded tetronate **6a** (159 mg, 55%) as a yellow oil; ν_{max}/cm^{-1} 1744, 1624, 1525, 1343, 1261, 1219, 1197, 1112, 981, 962, 938, 909, 804, 727, 674, 657; δ_H (300 MHz, $CDCl_3$) 1.48 (6H, s), 4.75 (2H, d, *J*=6.0 Hz), 5.04 (1H, s), 6.47 (1H, dt, *J*=16.0, 6.0 Hz), 6.79 (1H, d, *J*=16.0 Hz), 7.47 (1H, dd, *J*=8.0, 8.0 Hz), 7.67 (1H, d, *J*=8.0 Hz), 8.11 (1H, d, *J*=8.0 Hz), 8.25 (1H, m); δ_C (75 MHz, $CDCl_3$) 24.4, 72.3, 82.3, 87.2, 121.2, 123.6, 124.6, 130.8, 132.6, 137.3, 148.6, 171.4, 184.4; *m*/*z* (EI, 70 eV) 289 (M^+, 42%), 276 (14%), 271 (40%), 256 (22%), 203 (23%), 175 (17%), 163 (100%), 145 (15%), 129 (55%), 128 (95%), 117 (45%), 115 (68%), 102 (18%). Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.3; H, 5.2; N, 4.8. Found: C, 62.3; H, 5.1; N, 4.7%.

*4.4.2. 4-(m-Nitrocinnamyloxy)-1-oxaspiro[4.5]dec-3-en-2-one **6b***

Analogous to the synthesis of **6a**, tetronate **6b** (192 mg, 58%) was obtained from *m*-nitrocinnamyl bromide (242 mg, 1.0 mmol) and **5b** (167 mg, 0.99 mmol); R_f 0.64 (cyclohexane/ethyl acetate 1:1), yellow oil; ν_{max}/cm^{-1} 1741, 1622, 1525, 1348, 1338, 1189, 961, 908, 729; δ_H (300 MHz, $CDCl_3$) 1.5–1.8 (10H, m), 4.69 (2H, d, *J*=5.9 Hz), 4.98 (1H, s), 6.41 (1H, dt, *J*=16.5, 5.9 Hz), 6.37 (1H, d, *J*=16.5 Hz), 7.4–7.5 (1H, m), 7.6–7.7 (1H, m), 8.0–8.1 (1H, m), 8.1–8.2 (1H, m); δ_C (75 MHz, $CDCl_3$) 21.5, 24.2, 32.9, 72.0, 83.8, 87.7, 121.0, 122.8, 124.6, 129.6, 132.2, 132.4, 137.2, 148.4, 171.7, 184.5; *m*/*z* (EI, 70 eV) 329 (M^+, 1%), 312 (1%), 285 (1%), 203 (5%), 186 (2%), 162 (88%), 145 (8%), 116 (100%), 115 (73%). Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.6; H, 5.8; N, 4.3. Found: C, 65.4; H, 5.8; N, 4.1%.

*4.4.3. m-Nitrocinnamyl (S)-5-methyltetronate **6c***

Analogous to the synthesis of **6a**, tetronate **6c** (153 mg, 56%) was obtained from *m*-nitrocinnamyl bromide (242 mg, 1.0 mmol) and **5c** (119 mg, 1.0 mmol); $[\alpha]_D^{25}$ −11.1 (*c* 1.44, MeOH); R_f 0.56 (cyclohexane/ethyl acetate 1:1), yellow oil; ν_{max}/cm^{-1} 2958, 1748, 1624, 1525, 1348, 1291,1160, 1082, 962, 907, 729; δ_H (300 MHz, $CDCl_3$) 1.43 (3H, d, *J*=6.7 Hz), 4.71 (2H, d, *J*=6.0 Hz), 4.82 (1H, q, *J*=6.7 Hz), 5.08 (1H, s), 6.42 (1H, dt, *J*=16.0, 6.0 Hz), 6.75 (1H, d, *J*=16.0 Hz), 7.47 (1H, dd, *J*=8.0, 8.0 Hz), 7.67 (1H, d, *J*=8.0 Hz), 8.06 (1H, d, *J*=8.0 Hz), 8.19 (1H, m); δ_C (75 MHz, $CDCl_3$) 17.6, 72.2, 75.3, 88.7, 121.1, 122.8, 124.5, 129.6, 132.4, 137.2, 148.4, 172.2, 181.8; *m*/*z* (EI, 70 eV) 275 (M^+, 1%), 257 (1%), 162 (26%), 116 (100%), 115 (95%), 89 (9%). Anal. Calcd for $C_{14}H_{13}NO_5$: C, 61.1; H, 4.8; N, 5.0. Found: C, 60.9; H, 4.8; N, 4.9%.

*4.4.4. m-Nitrocinnamyl 5-phenyltetronate **6d***

Analogous to the synthesis of **6a**, tetronate **6d** (184 mg, 55%) was obtained from *m*-nitrocinnamyl bromide (242 mg, 1.0 mmol) and **5b** (175 mg, 0.99 mmol); R_f 0.61 (cyclohexane/ethyl acetate 1:1), yellow oil; ν_{max}/cm^{-1} 3036, 1748, 1624, 1524, 1348, 966, 725, 699; δ_H (300 MHz, $CDCl_3$) 4.66 (1H, ddd, *J*=13.0, 7.4, 1.1 Hz), 4.75 (1H, ddd, *J*=13.0, 5.7, 1.1 Hz), 5.21 (1H, d, *J*=1.1 Hz), 5.71 (1H, s), 6.31 (1H, ddd, *J*=15.9, 7.4, 5.7 Hz), 6.56 (1H, d, *J*=15.9 Hz), 7.2–7.4 (5H, m), 7.46 (1H, dd, *J*=8.0, 8.0 Hz), 7.59 (1H, d, *J*=8.0 Hz), 8.07 (1H, ddd, *J*=8.0, 2.2, 1.1 Hz), 8.11 (1H, m); δ_C (75 MHz, $CDCl_3$) 72.3, 80.3, 88.9, 121.1, 122.8, 124.2, 126.5, 128.7, 129.3, 129.6, 132.2, 132.3, 133.8, 137.1, 148.4, 172.4, 179.9; *m*/*z* (EI, 70 eV) 337 (M^+, 6%), 320 (1%), 319 (1%), 310 (2%), 309 (2%), 260 (1%), 215 (100%), 187 (17%), 175 (9%), 162 (56%), 116 (78%), 115 (90%), 105 (100%). Anal. Calcd for $C_{19}H_{15}NO_5$: C, 67.7; H, 4.5; N, 4.2. Found: C, 67.5; H, 4.5; N, 4.1%.

4.5. Synthesis of 3-allyltetronic acids 7

*4.5.1. 4-Hydroxy-3-[1′-(m-nitrophenyl)prop-2′-en-1′-yl]-5,5-dimethyl-[5H]furan-2-one **7a**: typical procedure for the Claisen rearrangement*

A solution of tetronate **6a** (872 mg, 3.0 mmol) and a catalytic amount of $YbTf_3$ in dry DMF (6 mL) was placed in a sealed vial inside a CEM microwave appliance and irradiated for 15 min with 300 W maximal power input at 130 °C. The solution was poured into dilute hydrochloric acid, extracted with ethyl acetate, washed with brine and dried over Na_2SO_4. The solvent was evaporated and the residue applied on top of a 10 cm plug of silica gel 60. Once by-products had been washed off with cyclohexane/ethyl acetate (5:1), product **7a** was eluted with cyclohexane/ethyl acetate (1:1, R_f 0.24). Evaporation of the solvent left 825 mg (95%) of pure **7a** as a waxy solid; ν_{max}/cm^{-1}

1713, 1636, 1524, 1347, 1194, 1086, 993, 924, 785, 730; δ_H (300 MHz, $CDCl_3$) 1.49 (3H, s), 1.50 (3H, s), 4.61 (1H, d, J=7.1 Hz), 5.10 (1H, d, J=16.9 Hz), 5.29 (1H, d, J=10.2 Hz), 6.28 (1H, m), 7.43 (1H, dd, J=8.0, 8.0 Hz), 7.63 (1H, d, J=8.0 Hz), 7.99 (1H, d, J=8.0 Hz), 8.07 (1H, m); δ_C (75 MHz, $CDCl_3$) 23.9, 24.0, 42.3, 82.3, 99.4, 118.3, 121.8, 122.6, 129.4, 134.1, 136.2, 142.8, 148.3, 173.8, 180.5; *m/z* (EI, 70 eV) 289 (M^+, 18%), 272 (13%), 271 (9%), 256 (6%), 203 (14%), 186 (30%), 162 (90%), 128 (55%), 116 (100%), 115 (95%). Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.3; H, 5.2; N, 4.8. Found: C, 62.4; H, 5.1; N, 4.7%.

4.5.2. 4-Hydroxy-3-[1′-(m-nitrophenyl)prop-2′-en-1′-yl]-5-spirocyclohexyl-[5H]furan-2-one **7b**

Analogous to the synthesis of **7a**, tetronic acid **7b** (180 mg, 94%) was obtained from tetronate **6b** (190 mg, 0.57 mmol) as a colourless solid of mp 143 °C; R_f 0.24 (cyclohexane/acetone 1:1); ν_{max}/cm^{-1} 1738, 1705, 1617, 1526, 1347, 965, 908, 727; δ_H (300 MHz, $CDCl_3$) 0.9–2.1 (10H, m), 4.59 (1H, d, J=7.3 Hz), 5.06 (1H, d, J=17.2 Hz), 5.19 (1H, d, J=10.2 Hz), 6.2–6.3 (1H, m), 7.3–7.4 (1H, m), 7.4–7.6 (1H, m), 7.9–8.0 (1H, m), 8.0–8.2 (1H, m); δ_C (75 MHz, $CDCl_3$) 21.6, 24.1, 32.5, 42.3, 83.7, 99.7, 117.7, 121.6, 122.6, 129.2, 134.1, 136.2, 143.2, 148.2, 174.2, 180.9; *m/z* (EI, 70 eV) 329 (M^+, 36%), 312 (17%), 311 (11%), 301 (1%), 294 (7%), 285 (5%), 268 (8%), 230 (9%), 203 (76%), 186 (55%), 175 (14%), 167 (9%), 162 (61%), 128 (80%), 116 (89%), 115 (100%). Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.6; H, 5.8; N, 4.3. Found: C, 65.4; H, 5.7; N, 4.1%.

4.5.3. (5S)-4-Hydroxy-5-methyl-3-[1′-(m-nitrophenyl)prop-2′-en-1′-yl]-[5H]furan-2-one **7c**

Analogous to the synthesis of **7a**, tetronic acid **7c** (931 mg, 95%) was obtained as unassignable mixture of diastereomers from tetronate **6c** (981 mg, 3.56 mmol) as a colourless viscous oil; R_f 0.25 (cyclohexane/acetone 1:1); ν_{max}/cm^{-1} 2985, 1617, 1526, 1396, 1347, 1077, 731; δ_H (300 MHz, $CDCl_3$) 1.46 (3H, d, J=6.7 Hz), 4.58 (1H, d, J=7.5 Hz), 4.83 (1H, q, J=6.7 Hz), 5.10 (1H, d, J=17.1 Hz), 5.21 (1H, d, J=9.9 Hz), 6.29 (1H, m), 7.40 (1H dd, J=8.0, 8.0 Hz), 7.60 (1H, d, J=8.0 Hz), 8.01 (1H, d, J=8.0 Hz), 8.08 (1H, m); δ_C (75 MHz, $CDCl_3$) 17.8, 42.5, 75.3, 101.0, 117.7, 121.7, 122.7, 129.3, 134.1, 135.8, 143.2, 148.2, 175.4, 178.2; *m/z* (EI, 70 eV) 275 (M^+, 15%), 258 (55%), 247 (5%), 228 (10%), 220 (11%), 203 (14%), 186 (30%), 162 (90%), 128 (55%), 116 (100%), 115 (95%). Anal. Calcd for $C_{14}H_{13}NO_5$: C, 61.1; H, 4.8; N, 5.1. Found: C, 60.9; H, 4.7; N, 5.0%.

4.5.4. 4-Hydroxy-3-[1′-(m-nitrophenyl)prop-2′-en-1′-yl]-5-phenyl-[5H]furan-2-one **7d**

Analogous to the synthesis of **7a**, tetronic acid **7d** (704 mg, 95%) was obtained as unassignable mixture of diastereomers from tetronate **6d** (616 mg, 1.82 mmol) as a viscous oil; R_f 0.22 (cyclohexane/acetone 1:1); ν_{max}/cm^{-1} 3070, 3034, 1718, 1638, 1524, 1346, 1094, 1001, 913, 729, 698; δ_H (300 MHz, $CDCl_3$) 4.59 (1H, d, J=7.6 Hz), 5.09 (1H, d, J=17.2 Hz), 5.22 (1H, d, J=10.2 Hz), 5.59 (1H, s), 6.2–6.3 (1H, m), 7.1–7.3 (5H, m), 7.35 (1H, m), 7.54 (1H, m), 7.95 (1H, m), 8.08 (1H, s); δ_C (75 MHz, $CDCl_3$) 42.7, 80.2, 102.2, 118.1, 121.8, 122.6, 127.4, 129.0, 129.4, 129.8, 133.1, 134.2, 135.8, 142.9, 148.3, 174.7, 175.0; *m/z* (EI, 70 eV) 337 (M^+, 43%), 319 (9%), 246 (9%), 215 (17%), 203 (66%), 186 (35%), 176 (13%), 175 (32%), 163 (63%), 162 (12%), 157 (25%), 145 (10%), 129 (58%), 128 (99%), 127 (39%), 118 (37%), 116 (57%), 115 (100%), 105 (72%). Anal. Calcd for $C_{19}H_{15}NO_5$: C, 67.7; H, 4.5; N, 4.2. Found: C, 67.4; H, 4.7; N, 4.1%.

4.6. Synthesis of 3-(cyclopropylmethyl)tetronic acids 8

4.6.1. 4-Hydroxy-3-[cyclopropyl-(m-nitrophenyl)methyl]-5,5-dimethyl-[5H]furan-2-one **8a**: typical procedure for the cyclopropanation

A solution of $ZnEt_2$ (3.84 mL, 1 M in hexane) in dry CH_2Cl_2 (150 mL), kept at 0 °C under an argon atmosphere, was vigorously stirred and treated dropwise with a solution of CH_2I_2 (619 μL, 7.68 mmol) in the same solvent (2 mL). After 10 min, alkene **7a** (277 mg, 0.96 mmol), dissolved in dry CH_2Cl_2 (10 mL), was added dropwise. The resulting mixture was stirred at 0 °C for further 8 h and the formed precipitate was redissolved by the addition of dilute HCl. The organic phase was separated and the aqueous layer was extracted with ethyl acetate three times. The combined organic phases were washed with brine and dried over Na_2SO_4. After evaporation of the volatiles, the residue was purified by chromatography on silica gel 60 (CH_2Cl_2/acetone/cyclohexane, 40:1:1, R_f 0.21) to give **8a** (213 mg, 73%) as a brown oil; ν_{max}/cm^{-1} 1743, 1702, 1645, 1524, 1376, 1346, 1307, 1246, 1195, 1156, 1083, 784, 724, 685; δ_H (300 MHz, acetone-d_6) 0.2–0.3 (2H, m), 0.5–0.7 (2H, m), 1.45 (3H, s), 1.51 (3H, s), 1.6–1.8 (1H, m), 3.14 (1H, d, J=10.2 Hz), 7.5–7.6 (1H, m), 7.8–7.9 (1H, m), 8.0–8.1 (1H, m), 8.25 (1H, m); δ_C (75 MHz, acetone-d_6) 5.0, 6.2, 14.4, 24.5, 44.6, 81.1, 102.1, 122.0, 123.2, 130.2, 135.1, 146.7, 149.1, 172.7, 179.3; *m/z* (EI, 70 eV) 303 (M^+, 13%), 285 (21%), 262 (16%), 245 (5%), 230 (4%), 216 (7%), 189 (22%), 176 (56%), 158 (36%), 141 (23%), 130 (41%), 128 (91%), 115 (100%). Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.4; H, 5.7; N, 4.6. Found: C, 63.4; H, 5.7; N, 4.4%.

4.6.2. 4-Hydroxy-3-[cyclopropyl-(m-nitrophenyl)methyl]-5-spirocyclohexyl-[5H]furan-2-one **8b**

Analogous to the synthesis of **8a**, tetronic acid **8b** (69 mg, 35%) was obtained as a colourless solid from alkene **7b** (195 mg, 0.59 mmol), 2.37 mmol $ZnEt_2$ and CH_2I_2 (379 μL, 4.74 mmol); R_f 0.26 (CH_2Cl_2/acetone/cyclohexane, 20:1:1); mp 179 °C; ν_{max}/cm^{-1} 1692, 1588, 1518, 1346, 1295, 1267, 1232, 1149, 1098, 980, 816, 733, 685; δ_H (300 MHz, $CDCl_3$) 0.1–0.3 (2H, m), 0.4–0.7 (2H, m), 1.4–1.8 (10H, m), 1.8–2.0 (1H, m), 3.15 (1H, d, J=10.2 Hz), 7.5–7.6 (1H, m), 7.8–7.9 (1H, m), 8.0–8.1 (1H, m), 8.33 (1H, m); δ_C (75 MHz, $CDCl_3$) 5.0, 6.2, 14.5, 22.7, 25.1, 33.7, 33.8, 44.7, 82.4, 102.7, 122.0, 123.2, 130.2, 135.2, 146.9, 149.2, 172.5, 179.0; *m/z* (EI, 70 eV) 343 (M^+, 33%), 326 (16%), 302 (18%), 256 (6%), 187 (21%), 176 (53%), 158 (31%), 130 (41%), 146 (18%), 128 (58%), 115 (100%). Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.5; H, 6.2; N, 4.1. Found: C, 66.4; H, 6.4; N, 3.9%.

4.6.3. (5S)-4-Hydroxy-3-[cyclopropyl-(m-nitrophenyl)methyl]-5-methyl-[5H]furan-2-one **8c**

Analogous to the synthesis of **8a**, tetronic acid **8c** (133 mg; 40%) was obtained as a brown waxy solid from alkene **7c** (341 mg, 1.16 mmol), 5.80 mmol $ZnEt_2$ and CH_2I_2 (934 μL, 11.6 mmol); R_f 0.21 (CH_2Cl_2/acetone/cyclohexane, 20:2:1); ν_{max}/cm^{-1} 1646, 1528, 1348, 1279, 1060; δ_H (300 MHz, $CDCl_3$) 0.2–0.3 (2H, m), 0.5–0.7 (2H, m), 1.47 (3H, m), 1.6–1.8 (1H, m), 3.08 (1H, d, J=10.2 Hz), 4.84 (1H, m), 7.42 (1H, d, J=7.9 Hz), 7.76 (1H, d, J=7.9 Hz), 8.04 (1H, d, J=9.2 Hz), 8.27 (1H, d, J=7.3 Hz); δ_C (75 MHz, $CDCl_3$) 4.7, 5.7, 13.3, 17.8, 43.7, 75.4, 102.2, 121.4, 122.7, 129.0, 134.0, 144.8, 148.0, 176.3, 178.6; *m/z* (EI, 70 eV) 289 (M^+, 20%), 272 (66%), 259 (41%), 248 (51%), 176 (99%), 130 (100%), 115 (90%). Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.3; H, 5.2; N, 4.8. Found: C, 62.1; H, 5.3; N, 4.6%.

4.6.4. 4-Hydroxy-3-[cyclopropyl-(m-nitrophenyl)methyl]-5-phenyl-[5H]furan-2-one **8d**

Analogous to the synthesis of **8a**, tetronic acid **8d** (97 mg, 46%) was obtained as a brown waxy solid from alkene **7d** (206 mg, 0.61 mmol), 2.44 mmol $ZnEt_2$ and CH_2I_2 (394 μL, 4.88 mmol) as a 1:1.1 mixture of diastereomers; R_f 0.22 (CH_2Cl_2/acetone/cyclohexane, 20:2:1); ν_{max}/cm^{-1} 1722, 1649, 1524, 1347, 728; δ_H (300 MHz, $CDCl_3$) 0.2–0.3 (2H, m), 0.5–0.7 (2H, m), 1.6–1.8 (1H, m), 3.05 (1H, d, J=12.1 Hz), 5.50/5.52 (1H, s), 7.1–7.3 (5H, m), 7.38 (1H, m), 7.70 (1H, m), 8.01 (1H, d, J=8.2 Hz), 8.25 (1H, m); δ_C (75 MHz, $CDCl_3$) 4.5, 5.7, 13.2/13.5, 43.8, 80.0, 103.6, 121.4, 122.5, 127.4/127.8, 128.7, 129.6, 133.6, 134.0/134.1, 144.7/144.8, 148.0, 174.9/175.3, 182.8; *m/z* (EI, 70 eV) 351 (M^+, 35%), 334 (7%), 333 (7%), 323 (12%), 307 (8%), 278 (11%), 265 (13%), 254 (11%), 217 (22%), 202 (18%), 189 (19%), 176 (41%), 158 (25%), 149 (22%), 130 (41%), 118 (77%), 115

(76%), 105 (100%). Anal. Calcd for $C_{20}H_{17}NO_5$: C, 68.4; H, 4.9; N, 4.0. Found: C, 68.6; H, 4.9; N, 3.9%.

4.7. Synthesis of 3-sulfonylanilidotetronic acids 1

*4.7.1. 4-Hydroxy-3-[cyclopropyl-(m-benzsulfonanilido)methyl]-5,5-dimethyl-[5H]furan-2-one **1a**: typical procedure for the reduction/sulfonation*

A mixture of Zn powder (451 mg, 6.94 mmol), **8a** (516 mg, 1.71 mmol) and THF (50 mL) was treated with a solution of hydrochloric acid (1 mL, ca. 11 mmol) in THF (5 mL). After 5 min stirring, the reaction mixture was filtered over a cotton plug into a diluted aqueous $NaHCO_3$ solution. The product amine was thoroughly extracted with ethyl acetate. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The resulting brown solid amine **9a** was dissolved in dry THF (60 mL) and treated at 0 °C with a solution of benzenesulfonyl chloride (195 μL, 1.53 mmol) in THF (5 mL). Triethylamine (213 μL, 1.53 mmol) dissolved in THF (10 mL) was slowly added and the resulting mixture was stirred overnight while warming up to room temperature. The solid precipitate was filtered off and the filtrate was concentrated in vacuo. The remainder was dissolved in ethyl acetate, extracted with 5% hydrochloric acid and washed with brine. The volatiles were evaporated and the residue chromatographed twice on preparative TLC plates (CH_2Cl_2/MeOH/cyclohexane 20:1:1, R_f 0.0–0.3). The product was extracted with acetone and dried on an oil pump to yield **1a** (288 mg, 41%) as a waxy solid; R_f 0.35 (cyclohexane/acetone 1:1); δ_H (300 MHz, acetone-d_6) 0.1–0.2 (2H, m), 0.4–0.5 (1H, m), 0.5–0.6 (1H, m), 1.45 (3H, s), 1.47 (3H, s), 1.6–1.8 (1H, m), 3.88 (1H, d, J=10.2 Hz), 6.98 (1H, m), 7.0–7.2 (2H, m), 7.35 (1H, m), 7.4–7.6 (3H, m), 7.80 (2H, m), 8.98 (1H, br); δ_C (75 MHz, acetone-d_6) 4.6, 6.5, 14.5, 24.6, 24.7, 44.8, 80.7, 103.0, 119.4, 120.8, 124.6, 127.9, 129.6, 129.8, 133.5, 138.5, 140.8, 145.5, 172.5, 178.3; m/z (EI, 70 eV) 413 (M^+, 8%), 344 (9%), 295 (13%), 276 (7%), 272 (8%), 241 (4%), 212 (17%), 195 (9%), 183 (17%), 167 (16%), 139 (15%), 130 (100%). Anal. Calcd for $C_{22}H_{23}NO_5S$: C, 63.9; H, 5.6; N, 3.4. Found: C, 64.1; H, 5.7; N, 3.4%.

*4.7.2. 4-Hydroxy-3-[cyclopropyl-(m-(4′-fluorobenz)sulfonanilido)-methyl]-5,5-dimethyl-[5H]furan-2-one **1b***

Analogous to the synthesis of **1a**, tetronic acid **1b** (85 mg; 44%) was obtained as a viscous, slowly solidifying oil from crude amine **9a** (124 mg, 0.45 mmol) and 4-fluorobenzsulfonyl chloride (81 mg, 0.42 mmol); R_f 0.26 (cyclohexane/acetone 1:1); ν_{max}/cm^{-1} 3190, 3070, 2978, 2931, 1710, 1655, 1600, 1475, 1397, 1333, 1249, 1160, 1095, 1081, 1014, 936, 827, 750, 699; δ_H (300 MHz, acetone-d_6) 0.0–0.2 (2H, m), 0.3–0.6 (2H, m), 1.43 (6H, s), 1.6–1.8 (1H, m), 3.94 (1H, d, J=10.0 Hz), 6.96 (1H, m), 7.0–7.1 (1H, m), 7.20 (1H, m), 7.25 (2H, dd, J=8.7, 8.9 Hz), 7.35 (1H, m), 7.84 (2H, dd, J=5.2, 8.9 Hz), 8.90 (1H, br); δ_C (75 MHz, acetone-d_6) 3.9, 5.5, 13.7, 23.8, 23.9, 43.9, 80.2, 99.4, 116.0 (d, J=23.0 Hz), 118.5, 120.4, 124.3, 128.5, 130.1 (d, J=9.2 Hz), 136.1, 137.2, 145.9, 164.8 (d, J=251 Hz), 173.2, 181.4; m/z (EI, 70 eV) 431 (M^+, 33%), 413 (8%), 403 (6%), 387 (6%), 341 (4%), 330 (16%), 303 (11%), 286 (14%), 272 (19%), 254 (35%), 239 (12%), 208 (8%), 198 (16%), 185 (10%), 144 (100%). Anal. Calcd for $C_{22}H_{22}FNO_5S$: C, 61.2; H, 5.1; N, 4.4. Found: C, 61.0; H, 5.0; N, 4.3%.

*4.7.3. 4-Hydroxy-3-[cyclopropyl-(m-(4′-chlorobenz)sulfonanilido)-methyl]-5,5-dimethyl[5H]furan-2-one **1c***

Analogous to the synthesis of **1a**, tetronic acid **1c** (70 mg, 35%) was obtained as a viscous, slowly solidifying oil from crude amine **9a** (124 mg, 0.45 mmol) and 4-chlorobenzsulfonyl chloride (88 mg, 0.42 mmol); R_f 0.26 (cyclohexane/acetone 1:1); ν_{max}/cm^{-1} 3185, 3076, 2979, 2932, 1699, 1653, 1605, 1588, 1477, 1396, 1334, 1247, 1161, 1083, 1014, 939, 826, 754, 696; δ_H (300 MHz, acetone-d_6) 0.1–0.3 (2H, m), 0.4–0.6 (2H, m), 1.48 (6H, s), 1.6–1.8 (1H, m), 2.89 (1H, d, J=10.4 Hz), 6.92 (1H, m), 7.1–7.2 (1H, m), 7.19 (1H, m), 7.29 (1H, m), 7.47 (2H, m), 7.93 (2H, m), 9.09 (1H, br); δ_C (75 MHz, acetone-d_6) 4.7, 6.4, 14.5, 24.6, 24.7, 44.8, 80.6, 103.0, 119.8, 121.2, 125.1, 129.7, 129.9, 130.0, 138.2, 139.2, 139.6, 145.8, 172.3, 178.3; m/z (EI, 70 eV) 447 (M^+, 38%), 429 (11%), 406 (6%), 401 (11%), 388 (6%), 362 (10%), 319 (13%), 302 (6%), 297 (7%), 272 (16%), 254 (13%), 226 (12%), 202 (11%), 186 (10%), 175 (11%), 159 (11%), 144 (100%). Anal. Calcd for $C_{22}H_{22}ClNO_5S$: C, 59.0; H, 5.0; N, 3.1. Found: C, 59.2; H, 4.9; N, 3.1%.

*4.7.4. 4-Hydroxy-3-[cyclopropyl-(m-tolylsulfonanilido)methyl]-5-spirocyclohexyl-[5H]furan-2-one **1d***

Analogous to the synthesis of **1a**, tetronic acid **1d** (112 mg, 48%) was obtained as a wax from crude amine **9b** (167 mg, 0.53 mmol) and 4-toluenesulfonyl chloride (102 mg, 0.53 mmol); R_f 0.44 (cyclohexane/acetone 1:1); ν_{max}/cm^{-1} 3208, 2936, 1700, 1648, 1390, 1256, 1246, 1158, 1091, 965, 813, 706; δ_H (300 MHz, acetone-d_6) 0.1–0.2 (2H, m), 0.45 (1H, m), 0.60 (1H, m), 1.4–2.0 (11H, m), 2.32 (3H, s), 2.89 (1H, d, J=10.5 Hz), 6.99 (1H, m), 7.1–7.2 (2H, m), 7.28 (2H, m), 7.31 (1H, m), 7.68 (2H, m), 8.91 (1H, br); δ_C (75 MHz, acetone-d_6) 4.7, 6.6, 14.5, 21.4, 22.6, 22.7, 25.2, 33.6, 33.8, 44.8, 82.1, 103.3, 119.1, 120.6, 124.5, 128.1, 129.5, 130.3, 138.1, 138.7, 144.2, 145.5, 172.6, 178.3; m/z (EI, 70 eV) 467 (M^+, 16%), 453 (5%), 450 (6%), 422 (8%), 411 (8%), 387 (6%), 367 (7%), 341 (4%), 314 (10%), 270 (9%), 242 (7%), 230 (6%), 180 (9%), 155 (21%), 144 (43%), 115 (35%), 91 (100%). Anal. Calcd for $C_{26}H_{29}NO_5S$: C, 66.8; H, 6.3; N, 3.0. Found: C, 67.0; H, 6.1; N, 2.9%.

*4.7.5. (5S)-4-Hydroxy-3-[cyclopropyl-(m-tolylsulfonanilido)-methyl]-5-methyl-[5H]furan-2-one **1e***

Analogous to the synthesis of **1a**, tetronic acid **1e** (39 mg, 36%) was obtained as a viscous oil from crude amine **9c** (89 mg, 0.34 mmol) and 4-toluenesulfonyl chloride (50 mg, 0.26 mmol) as a 1:1.2 mixture of diastereomers; R_f 0.27 (cyclohexane/acetone 1:1); ν_{max}/cm^{-1} 2984, 1722, 1693, 1591, 1397, 1332, 1255, 1155, 1091, 1051, 705; δ_H (300 MHz, acetone-d_6) 0.1–0.2 (2H, m), 0.4–0.6 (2H, m), 1.39 (3H^a, d, J=6.6 Hz)/1.41 (3H^b, d, J=6.9 Hz), 1.6–1.7 (1H, m), 2.38 (3H, s), 2.82 (1H^a, J=10.2 Hz)/2.84 (1H^b, d, J=9.9 Hz), 4.68 (1H^a, q, J=6.6 Hz)/4.70 (1H^b, q, J=6.9 Hz), 6.98 (1H, d, J=7.7 Hz), 7.10 (1H, dd, J=7.7, 7.7 Hz), 7.15 (1H, m), 7.28 (2H, d, J=8.0 Hz), 7.32 (1H, m), 7.68 (2H, d, J=8.0 Hz), 9.00 (1H, br); δ_C (75 MHz, acetone-d_6) 5.0/5.1, 6.2/6.3, 14.5/14.7, 18.8/18.9, 21.4, 45.1/45.4, 74.3/74.6, 102.2, 119.1, 120.9, 124.7, 128.1, 129.4, 130.3, 137.9, 138.5, 144.2, 146.4, 174.6, 177.7; m/z (EI, 70 eV) 413 (M^+, 8%), 344 (9%), 295 (13%), 276 (7%), 272 (8%), 241 (4%), 212 (17%), 195 (9%), 183 (17%), 167 (16%), 139 (15%), 130 (100%). Anal. Calcd for $C_{22}H_{23}NO_5S$: C, 63.9; H, 5.6; N, 3.4. Found: C, 64.1; H, 5.7; N, 3.3%.

*4.7.6. 4-Hydroxy-3-[cyclopropyl-(m-benzsulfonanilido)methyl]-5-phenyl-[5H]furan-2-one **1f***

Analogous to the synthesis of **1a**, tetronic acid **1f** (65 mg, 42%) was obtained as a viscous oil from crude amine **9d** (112 mg, 0.35 mmol) and benzsulfonyl chloride (45 μL, 0.35 mmol); 1:1.5 mixture of diastereomers; R_f 0.38 (cyclohexane/acetone 1:1); ν_{max}/cm^{-1} 1724, 1685, 1330, 1155, 1092, 688; δ_H (300 MHz, acetone-d_6) 0.1–0.3 (2H, m), 0.5–0.7 (2H, m), 1.7–1.9 (1H, m), 2.92 (1H^a, d, J=10.2 Hz)/2.97 (1H^b, d, J=8.2 Hz), 5.45/5.46 (2×1H, s), 7.02 (1H, m), 7.12 (1H, m), 7.18 (1H, m), 7.2–7.6 (9H, m), 7.82 (2H, m), 8.95 (1H, br); δ_C (75 MHz, acetone-d_6) 5.1, 6.3, 14.8, 45.5, 80.1, 102.9, 119.4, 121.3, 125.1, 128.1, 128.6, 129.4, 129.5, 129.7, 129.8, 133.5, 137.1, 138.5, 141.1, 146.5, 174.7, 176.7; m/z (EI, 70 eV) 461 (M^+, 19%), 427 (5%), 337 (14%), 327 (15%), 303 (6%), 283 (25%), 256 (21%), 228 (28%), 215 (25%), 207 (28%), 186 (28%), 178 (44%), 167 (21%), 156 (31%), 152 (32%), 144 (100%). Anal. Calcd for $C_{26}H_{23}NO_5S$: C, 67.7; H, 5.0; N, 3.0. Found: C, 67.5; H, 4.8; N, 2.9%.

*4.7.7. 4-Hydroxy-3-[cyclopropyl-(m-(4′-fluorobenz)sulfonanilido)-methyl]-5-phenyl-[5H]furan-2-one **1g***

Analogous to the synthesis of **1a**, tetronic acid **1g** (69 mg, 41%) was obtained as a viscous, slowly solidifying oil from crude amine **9d**

(112 mg, 0.35 mmol) and 4-fluorobenzylsulfonyl chloride (68 mg, 0.35 mmol); 1:1.4 mixture of diastereomers; R_f 0.36 (cyclohexane/acetone 1:1); ν_{max}/cm^{-1} 1716, 1700, 1591, 1494, 1169, 1153, 699; δ_H (300 MHz, acetone-d_6) 0.0–0.3 (2H, m), 0.5–0.6 (2H, m), 1.7–1.9 (1H, m), 2.92/2.94 (2×1H, d, J=8.2 Hz), 5.25/5.29 (2×1H, s), 7.00 (1H, m), 7.11 (1H, d, J=7.6 Hz), 7.2–7.6 (7H, m), 7.41 (2H, m), 7.68 (2H, dd, J=8.7, 8.7 Hz), 8.96 (1H, br); δ_C (75 MHz, acetone-d_6) 5.2, 6.2, 14.9, 45.5, 80.4, 102.0, 116.9 (d, J=22.5 Hz), 119.5, 121.6, 125.5, 128.4, 129.2, 129.3, 129.4, 131.1 (d, J=9.2 Hz), 137.3, 138.2, 145.0, 147.4, 166.1 (d, J=207 Hz), 174.1, 176.5; m/z (EI, 70 eV) 479 (M^+, 34%), 461 (5%), 451 (4%), 343 (7%), 320 (9%), 304 (24%), 277 (14%), 246 (7%), 202 (9%), 184 (8%), 158 (13%), 144 (100%). Anal. Calcd for $C_{26}H_{22}FNO_5S$: C, 65.1; H, 4.6; N, 2.9. Found: C, 64.9; H, 4.6; N, 2.8%.

4.7.8. 4-Hydroxy-3-[cyclopropyl-(m-tolylsulfonanilido)methyl]-5-phenyl-[5H]furan-2-one ***1h***

Analogous to the synthesis of **1a**, tetronic acid **1h** (33 mg, 36%) was obtained as a viscous, slowly solidifying oil from crude amine **9d** (68 mg, 0.19 mmol) and 4-toluenesulfonyl chloride (36 mg, 0.19 mmol); 1:1.05 mixture of diastereomers; R_f 0.29 (cyclohexane/acetone 1:1); ν_{max}/cm^{-1} 1734, 1653, 1331, 1156, 1092, 702; δ_H (300 MHz, acetone-d_6) 0.0–0.3 (2H, m), 0.4–0.6 (2H, m), 1.7–1.9 (1H, m), 2.30/2.31 (2×3H, s), 2.90 (1H^a, d, J=9.5 Hz), 2.94 (1H^b, d, J=9.3 Hz), 5.25/5.28 (2×1H, s), 6.9–7.4 (10H, m), 7.41 (1H, m), 7.69 (2H, m), 8.90 (1H, br); δ_C (75 MHz, acetone-d_6) 4.2, 5.3, 13.9/14.0, 21.9, 44.3/44.5, 79.5, 100.1, 117.9, 118.0, 120.2, 124.1, 127.1, 127.2, 127.5, 128.2, 128.3, 129.3, 129.5, 136.9, 137.0, 137.2, 137.5, 143.2, 146.2, 174.7, 177.9; m/z (EI, 70 eV) 475 (M^+, 19%), 447 (2%), 351 (4%), 321 (5%), 302 (8%), 272 (8%), 259 (10%), 229 (8%), 178 (12%), 155 (17%), 144 (32%), 130 (49%), 115 (29%), 105 (36%), 91 (100%). Anal. Calcd for $C_{27}H_{25}NO_5S$: C, 68.2; H, 5.3; N, 2.9. Found: C, 68.0; H, 5.1; N, 3.0%.

4.8. HIV-1 drug sensitivity assay[15]

Indicator CEMx174-SEAP cells in 96 well plates (2500/well) were treated in triplicates with the test compounds **1** (0, 0.01, 0.1, 1, 10, 100 μM) and 2 h later were infected with either PI-sensitive HIV_{NL4-3} or PI-resistant 4lig7 viruses at a concentration equivalent to 15,000 relative light units (RLU). The infectious dose for each virus was estimated beforehand by infecting CEMx174-SEAP cells with 1, 5, 10 or 20 μL virus-containing supernatant. The minimal volume of this supernatant that had resulted in at least 15,000 RLU in a 15 μL volume of supernatant of CEMx174-SEAP cells 3 days after infection was determined as described[15] using a Phospha-light-kit (Tropix, Bedford, MA, USA). Five days after the cells had been treated with compounds **1**, the SEAP activity was determined in the same way and IC_{50} values were calculated from the means of two independent runs with the activities of untreated infected cells set to 100%.

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14. Sequences of the PR genes of the two viruses are given underneath. For deviations from the HIV-1 consensus B (Los Alamos) and interpretations of effects of commercial protease inhibitors refer to www.hiv-grade.de.
NL4–3:CCTCAGATCACTCTTTGGCAGCGACCCCTCGTCACAATAAAGATAGGGGGGC
AATTAAAGGAAGCTCTATTAGATACAGGAGCAGATGATACAGTATTAGAAGAAATGA
ATTTGCCAGGAAGATGGAAACCAAAAATGATAGGGGGAATTGGAGGTTTTATCAAA
GTAAGACAGTATGATCAGATACTCATAGAAATCTGCGGACATAAAGCTATAGGTACAG
TATTAGTAGGACCTACACCTGTCAACATAATTGGAAGAAATCTGTTGACTCAGATTGG
CTGCACTTTAAATTTTCCCATTAGTCCTATTGAGACTGTACCAGTAAAATTAAAGCCAG
GAATGGATGGCCCAAAAGTTAAACAATGGCCATTGACAGAAGAAAAAATAAAAGCA
TTAGTAGAAATTTGTACAGAAATGGAAAAGGAAGGAAAAATTTCAAAAATTGGGCCT
GAAAATCCATACAATACTCCAGTATTTGCCATAAAGAAAAAAGACAGTACTAAATGGA
GAAAATTAGTAGATTTCAGAGAACTTAATAAGAGAACTCAAGATTTCTGGGAAGTTCA
ATTAGGAATsCCACATCCTGCAGGGTTAAAACAGAAAAAATCAGTAACAGTACTGGAT
GTGGGCGATGCATATTTTTCAGTTCCCTTAGATAAAGACTTCAGGAAGTATACTGCATT
TACCATACCTAGTATAAACAATGAGACACCAGGGATTAGATATCAGTACAATGTGCTT
CCACAGGGATGGAAAGGATCACCAGCAATATTCCAGTGTAGCATGACAAAAATCTTA
GAGCCTTTTAGAAAACAAAATCCAGACGTAGTCATCTATCAATACATGGATGATTTGT
ATGTAGGATCTGACTTAGAAATAGGGCAGCATAGAACAAAAATAGAGGAACTGAGAC
AACATCTGTTGAGGTGGGGATTTACCACACCAGACAAAAAACATCAGAAAGAACCTC
CATTCCTTTGGATGGGTTATGAACTCCATCCTGATAAATGGACAGTACAGCCTATAGT
GCTGCCAGAAAAGGACAGCTGGACTGTCAATGACATACAGAAATTAGTGGGAAAATT
GAATTGGGCAAGTCAGATTTATGCAGGGATTAAAGTAAGGCAATTATGTAAACTTCTT
AGGGGAACCAAAGCACTAACAGAAGTAGTACCACTAACAGAAGAAGCAGAGCTAGA
ACTGGCAGAAAACAGGGAGATTCTAAAAGAACCGGTACATGGAGTGTATTATGACCC
ATCAAAAGACTTAATAGCAGAAATACAGAAGCAGGGGCAAGGCCAATGGACATATCA
AATTTATCAAGAGCCATTTAGAAATCTGAAAACAGGAAAGTATGCAAGAATGAAGGG
TGCCCACACTAATGATGTGAAACAATTAACAGAGGCAGTACAAAAAA.
4lig7:CCTCAGATCACTCTTTGGCAACGACCCCTCGTCACAATAAAGATAGGAGGGCAA
CTAATTGAAGCCCTATTAGATACAGGAGCAGATGATACAGTATTAGAGGATATAAATT
TGCCAGGGAGATGGAAGCCAAAAATAATAGGGGGAATTGGAGGTTTTATCAAAGTA
AGACAGTATGACCAAGTACCCATAGAAATCTGTGGACACAAAGTTATGAGTACAGTAT
TAGTAGGACCTACACCTGTCAACGTAATtGGCAGAAAcCTGAtGACCCAGATCGGCTG
CACTTTAAACTTTCCCATtAGTCCTATtGAAACTGTACCAGTAAAATTAAAGCCAGGAA
TGGATGGCCCAAAAGTTAAACAATGRCCMTTGACAGaASWWAAWATMMAAGCAT
TAGTAGAAATTTGTACAGAGTTGGAGAAGGATGGAAAAATTTCAAAAATTGGGCCTG
AAAATCCATACAATACTCCAATATTTGCCATAAAGAAAAAAGACAGTGATAAATGGAG
AAAGTTAGTAGACTTCAGAGAACTTAATAAGAGAACTCAAGACTTCTGGGAAGTTCAA
TTAGGAATACCACATCCTGCAGGGTTAAAACAGAAAAAATCAGTAACAATACTGGAT
GTGGGTGATGCATATTTTTCAATTCCCTTAGACAAAGACTTCAGGAAGTATACTGCATT
TACCATACCTAGTACAAACAATGAGACACCAGGGATAAGATATCAATATAATGTGCTT
CCACAGGGATGGAAAGGATCACCAGCAATATTCCAAAGTAGCATGACAAAGATCTTA
GAGCCTTTTAGAAAACAATATCCAGACATAGTTATCTATCAATACGTGGATGATTTGTA
TGTAGGATCTGACTTAGAAATAGGACAGCATAGGACAATGATAAAGGAACTCAGACA
ATATCTGTGGAAGTGGGGGTTTTACACACCAGATAGAAAACATCAGCAAGAACCTCC
ATTCCGTTGGATGGGCTATGAACTCCACCCTGACAAATGGACAGTACAGCCTATAAAG
CTGCCAGATAAAGACAGCTGGACTGTCAATGACATACAGAAGTTAGTGGGAAAATTA
AATTGGGCAAGCCAGATTTATGCAGGGATTAAAGTAAAGCAATTATGTAAACTCCTTA
AGGGAACCAAGTCACTAACAGAAGTTGTACCACTAACAAAAGAAGCAGAGCTAGAAC
TGGCAGAAAACAGGGAGATTCTAAAAGAACCGGTACATGGAGTGTATTATGACCCAT
CAAAAGACTTAATAGCAGAA.
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