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ORIGINAL PAPER

Improved and scalable synthesis of building blocks for the modular synthesis of teraryl-based alpha-helix mimetics

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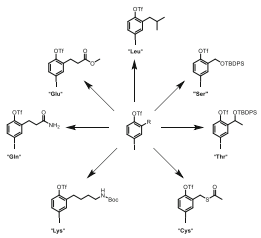
Abstract The modular synthesis of teraryl-based alpha-helix mimetics can be accomplished by sequential Suzuki-couplings of arylboronic acid building blocks with 4-iodophenyltriflate core-fragments. We report about new synthetic accesses to core fragments featuring the side chains of Leu, Lys, Cys, Glu, Gln, Ser, and Thr starting from simple phenol precursors.

Graphical abstract



Keywords Baeyer–Villiger oxidation · Claisen rearrangement · Iodination · Peptidomimetics · Protein–protein interactions · Wittig reaction

Introduction

Over the last two decades, protein–protein interactions (PPIs) have been recognized as one of the main factors in controlling protein function in living cells. The number of different PPIs in human cells is estimated to be ~65,000 [1–3], with α-helices playing a role in ~60 % of the interaction sites [4, 5]. For the study and pharmaceutical intervention of PPIs, tool compounds are needed, which allow the control of the particular interaction of a specific target protein [6]. As short peptides have limitations as drugs due to their conformational instability, their poor proteolytic stability, and bioavailability, strategies have been pursued to overcome these limitations [7] by using stapled peptides [8], β-peptides [9, 10], β-hairpins [11], or α-helix mimetics [12–30] addressing the so called "hot spots" at the protein interaction area responsible for a significant amount of the overall binding energy. Hamilton and co-workers have presented a quite general approach of mimicking α-helices by suitable positioning of amino acid side chains around a terarylic scaffold [31], which has been successfully applied for the design of inhibitors of several PPIs. As α-helix-based PPIs are such a frequent phenomenon, which provides numerous opportunities for controlling cellular events by small molecules, we have started a program to produce a comprehensive library of teraryl-based α-helix mimetics, taking advantage of a highly modular and convergent strategy developed in our laboratory, in which a central iodophenyltriflate-core exhibiting leaving groups with differentiated reactivity is decorated with pyridine boronic acids using Pd-catalyzed cross-coupling reactions (Fig. 1) [32–34]. With a set of 2 × 18 building blocks, any representative of the 5670 permutations of α-helix mimetics featuring the proteinogenic amino acids should be accessible within a day.

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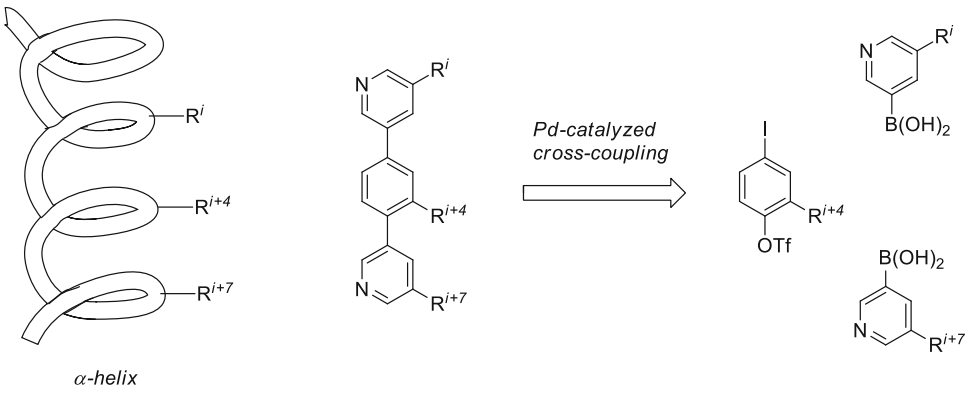


Fig. 1 Peptidomimetic design and synthetic strategy

While we are currently in the final steps of providing a comprehensive set of building blocks, we have also recognized that several of our originally published synthetic routes toward 4-iodophenyltriflates are not of sufficient efficiency regarding steps and overall yields to provide the desired building blocks in the gram quantities required for library synthesis. In this manuscript, we report about second generation syntheses of essential 4-iodophenyltriflate core fragments, which are much shorter and higher yielding than the previously reported routes and present routes to building blocks featuring the amino acid side chain functionality in a form more suitable for long-term storage and subsequent teraryl assembly [32].

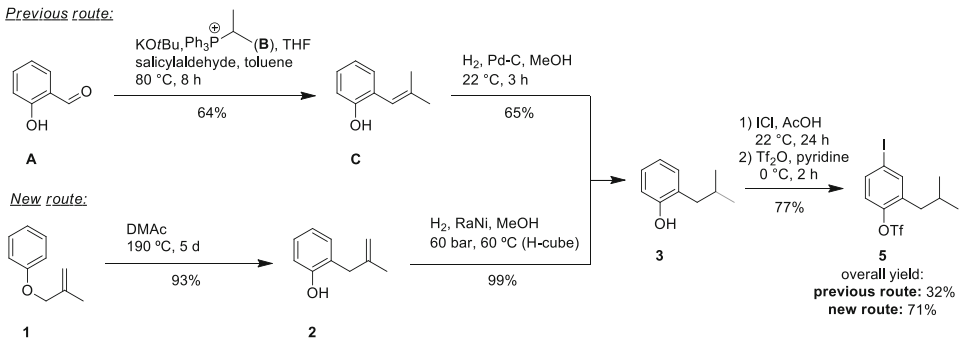
Results and discussion

The synthesis of 4-iodophenyltriflates can be accomplished by iodination of 2-substituted phenols, followed by triflation of the HO-group. For most amino acid side chains, the corresponding 2-substituted phenols have to be prepared from commercially available starting materials [32].

In our original publication for synthesizing, the Leu core fragment a Wittig reaction was used to introduce the *iso*-butyl side chain (Scheme 1, previous route) [32]. In addition to its poor atom economy, this route was also hampered by low yields for the formation of a sensitive destabilized ylide product **B**. Especially upon scale-up hydrolysis of phosphonium-salt **B** was observed resulting from adventitious water introduced by hygroscopic KO*t*Bu.

In order to overcome these limitations, we envisioned to use a Claisen-rearrangement of phenyl-methallyl ether **1** to introduce the side chain in the ortho-position (Scheme 1, new route) [43]. The use of *N*,*N*-dimethylformamide (DMF) as a solvent resulted in only 75 % conversion due to thermic decomposition of DMF. When the thermally more robust *N*,*N*-dimethyl acetamide (DMAc) was used as solvent, the reaction reached 95 % conversion. Product **2** could be isolated by a simple extractive workup, in which through a base/acid-switch unconsumed starting material and DMAc were removed. Although isomerization of the double bond to the thermodynamically more stable, higher substituted double bond **C** was observed to some extent, this had no further consequences as in the next step the double bonds of the mixture of **2** and **C** were hydrogenated with an H-cube flow reactor with Raney-Ni (RaNi) as catalyst leading to the same saturated product **3**. With this reaction sequence, the desired Leu-core unit fragment **5**

Scheme 1



could be isolated in 71 % overall yield (4 steps) using inexpensive reagents, which compares well to our initial route (32 % overall yield over 5 linear steps including synthesis of reagent **B**).

A common precursor for several core unit fragments containing polar amino acid side chains in its protected form is compound **8**, which results from iodination and triflation of salicylic aldehyde **6**. Under the initial reaction conditions full conversion could be detected only after 8 days including several additions of ICl. The central role of **8** in our synthetic scheme made it necessary to optimize its synthesis. By changing the solvent from AcOH to dichloromethane (DCM), the iodination occurred faster and 91 % conversion was detected after 48 h (Table 1) [37].

Intermediate **8** could be further converted in an improved procedure to the protected Cys-core fragment **11** (Scheme 2) [32]. Similarly, we gained access to the Ser-core unit **12** and Thr-core unit **14**, which we now have protected as *tert*-butyldiphenylsilyl (TBDPS) ethers to avoid decomposition of the triflate under storage conditions.

In our previous publication, the Glu- and Gln-core unit fragments were planned to be accessed from a common nitrile-containing precursor **F** (Scheme 3) [32]. In the last step, nitrile **F** should be converted either to the carboxylic acid ester **18** or to the amide **22**. Despite considerable effort, we have not been able to perform these transformations with **F** and only observed decomposition of the starting material. In this paper, we present a solution to this problem by introducing the individual side chains earlier in the synthesis (Scheme 3). Gln-core unit **22** could be accessed by transforming the iodinated and triflated aldehyde **8** to amide **21** via Wittig reaction. The orchestration of the sequence of events turned out to be crucial, as any attempt to introduce the triflate on a substrate with already installed primary amide side chain was accompanied by dehydration leading to a nitrile [38].

The second key step was the reduction of the double bond in **21**. As catalytic hydrogenation with Pd would have resulted in the dehalogenation of the iodide, we chose diimide reduction instead, which is distinguished by functional group tolerance toward halogens. Among the possible precursors for diimide generation, we selected potassium azadicarboxylate (PADA) **20** [39]. No degradation-products of the precursor remain in the reaction and unreacted PADA **20** can be removed simply by filtration as this salt is insoluble in the organic solvent used for the reaction [40]. Gln-core unit fragment **22** was isolated in 46 % overall yield (4 steps).

The Glu-core unit fragment **18** was accessible starting from dihydrocoumarine (**15**) (Scheme 3). After iodination [41], the lactone was converted to the corresponding methyl ester **17** via transesterification followed by triflation under standard conditions. The Glu-core unit fragment **18** was isolated in its ester protected form in 78 % overall yield (3 steps).

With the two routes presented in Scheme 3, we have now described for the first time the core-fragments for Gln **22** and in its protected form for Glu **18**.

An important amino acid side chain representing hot spot interactions at PPI interfaces is Lys. The original route for the synthesis of the Lys-building block **30** started from dihydrocoumarine (**15**), which was reduced to the corresponding lactol. Taking advantage of the equilibrium between lactol and open chain aldehyde allowed a Henry-reaction leading to **G**, whose hydroxy-function was removed by $NaBH_3CN$ in MeOH under reflux temperature (Scheme 4). After iodination and introduction of the triflate group, in the final step, the nitro-group was reduced to the corresponding amine **I** with Fe in 2 M aqueous HCl at RT (quantitative conversion) [32]. This long linear reaction sequence and a low overall yield of 9 % made an improved reaction route necessary, in which we also planned to present the Lys-building block in its Boc-protected form to

Table 1 Different methods for iodination of **7** [35–37]

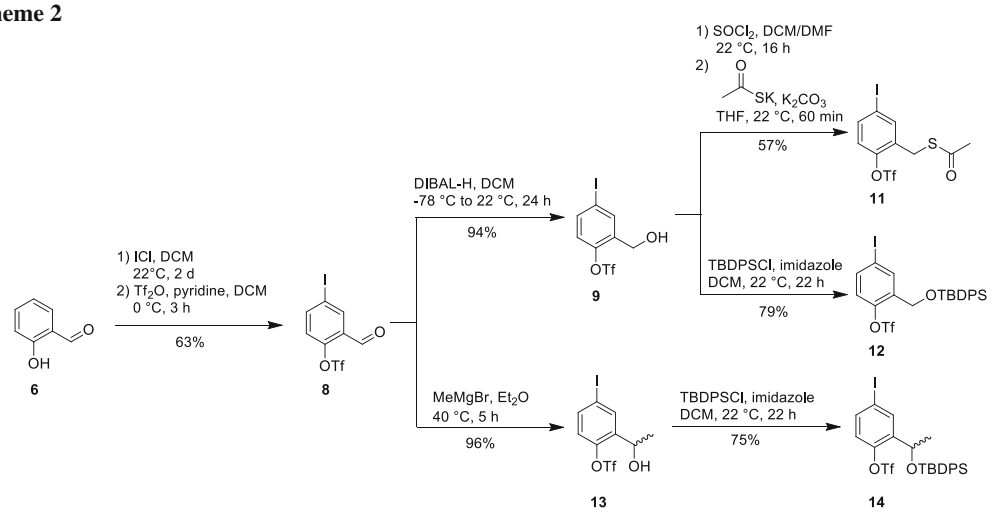
Reagent	Solvent	*T*/°C	Time	Conversion[a]/%
ICl	AcOH	22	3 days	45
ICl	AcOH	22	8 days	94[b]
ICl	AcOH	40	8 days	96
I_2, ICl	THF	22	48 h	32 %
I_2, ICl	THF	40	24 h	39
ICl	DCM	0–22	48 h	91 (68 % yield)[c]

[a] Conversion according to GC–MS

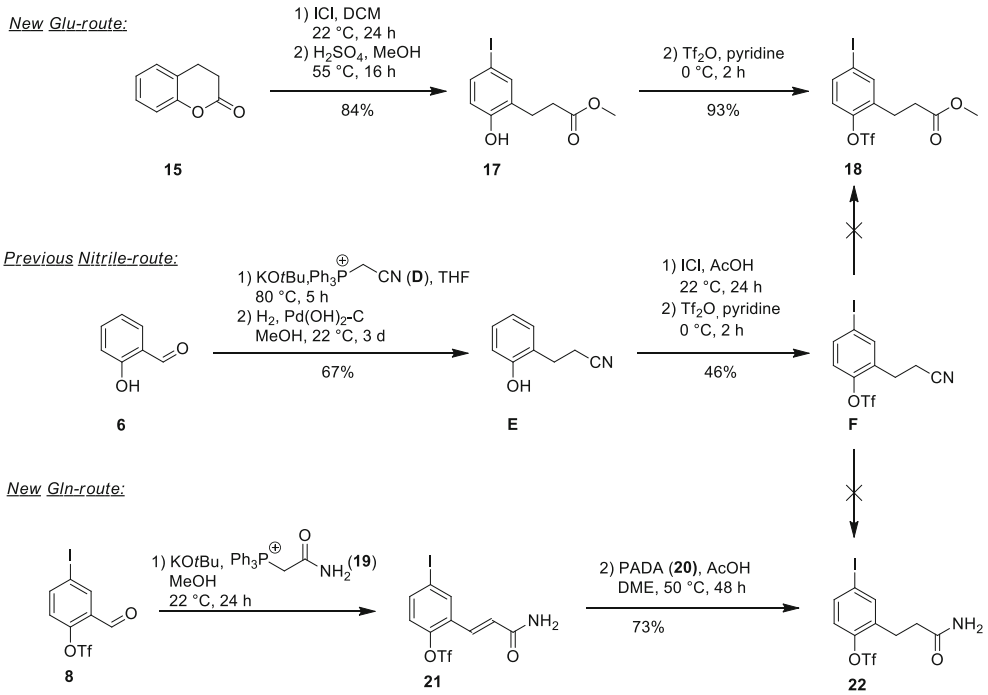
[b] Additional 0.5 eq ICl were added

[c] Isolated yield in parenthesis

Scheme 2



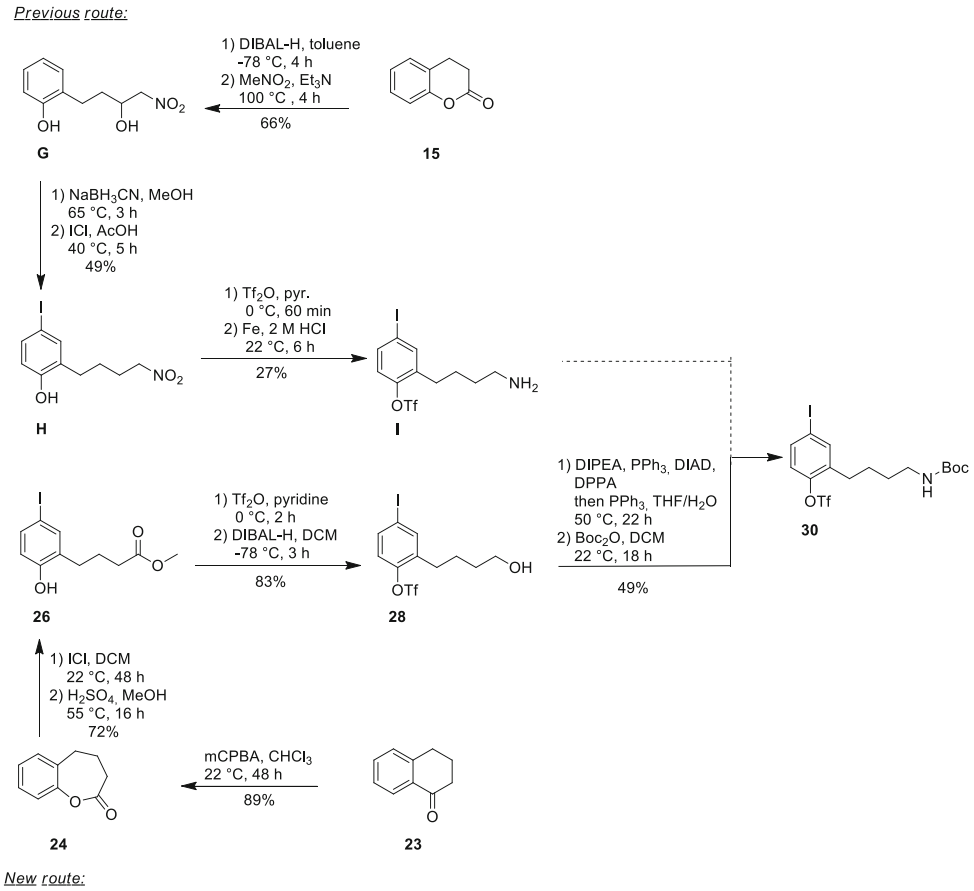
Scheme 3



facilitate teraryl assembly via Suzuki-coupling and purification.

Encouraged by the positive outcome of the successful transesterification sequence in the synthesis of the Glu-building block **18**, a similar strategy was used for the synthesis of the Lys-building block **30** starting from the 7-membered lactone **24** (Scheme 4). Lactone **24** was synthesized from α-tetralone (**23**) via Baeyer–Villiger oxidation, followed by introduction of the iodide and transesterification to methyl ester **26**. Triflation and reduction of the ester with DIBAL-H to the corresponding alcohol resulted in **28**, which was then converted to amine **29** via a Mitsunobu–Staudinger sequence using diphenylphosphorylazide (DPPA) as an azide donor [42]. In the final step, the amine was Boc-protected to yield Lys-core unit **30** in good 26 % overall yield (7 steps).

Scheme 4

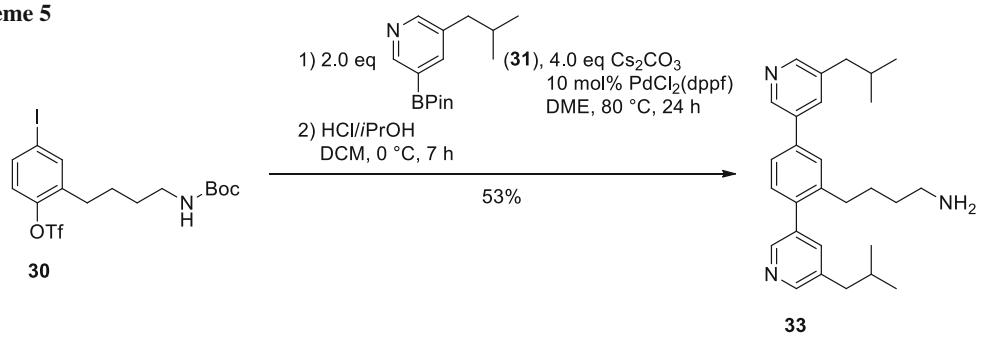


In order to exemplify an application of these new set of building blocks, we have used Lys-core unit fragment **30** for the assembly of the Leu-Lys-Leu teraryl **32** via Suzuki coupling [33]. Both leaving groups were coupled in one step since the pyridine building block **31** representing Leu should be attached twice. After simple acidic cleavage of the Boc-protecting group, the desired teraryl **32** was isolated in 53 % overall yield (Scheme 5).

Conclusion

In summary, we have reported second generation syntheses of 4-iodophenyltriflates serving as building blocks for the modular assembly of teraryl-based alpha-helix mimetics, which are scalable to gram quantities. Importantly, we have presented Ser-, Thr-, Gln-, Glu-, and Lys-building blocks in versions which are more suitable for long-term storage and

Scheme 5



offer advantages during teraryl assembly. At the moment, we use these routes to establish a comprehensive collection of building blocks allowing the synthesis of all permutations of teraryls containing all proteinogenic side chains relevant for protein–protein interactions.

Experimental

NMR spectra were recorded on a Bruker Avance III 300 MHz FT NMR spectrometer (300.36 MHz (^{1}H), 75.53 MHz (^{13}C)). Chemical shifts δ [ppm] are referenced to residual protonated solvent signals as internal standard DMSO-d_6: $\delta = 2.50$ ppm (^{1}H), 39.52 ppm (^{13}C) and $CDCl_3$: $\delta = 7.26$ ppm (^{1}H), 77.16 ppm (^{13}C). GC–MS measurements were performed on an Agilent Technologies 7890A (G3440A) GC system equipped with an Agilent Technologies J&W GC-column HP-5MS [(5 %-phenyl)-methylpolysiloxane; length 30 m; inner diameter 0.250 mm; film 0.25 µm] at a constant helium flow rate (He 5.0; Air Liquide; "Alphagaz"; 1.085 cm^3/min; average velocity 41.6 cm/s) in split mode 1/175 [inlet temperature 250 °C; injection volume 2.0 mm^3; sample concentration ~0.5 mg/cm^3 in ethyl acetate (EtOAc), methanol (MeOH), dichloromethane (DCM), or diethyl ether (Et_2O)]. The GC was coupled to a 5975C inert mass sensitive detector with triple-axis detector (MSD, EI, 70 eV; transfer line 300 °C; MS source 240 °C; MS quad 180 °C), with a solvent delay of 3.50 min. One general gradient MT_50_S (initial temperature 50 °C, 1.0 min; linear ramp 40 °C/min; final temperature 300 °C; final time 5.0 min; post run 1.0 min; detecting range 50.0–550.0 amu) was applied. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60-F_{254}, and spots were visualized by UV-light ($\lambda = 254$ and/or 366 nm), or by treatment with cerium ammonium molybdate solution (CAM) (CAM 2.0 g Ce(IV)SO_4, 50 g $(NH_4)_2MoO_4$, 50 cm^3 concentrated H_2SO_4 in 400 cm^3 water) or ninhydrin (1.5 g ninhydrin, 100 cm^3 *n*-butanol, 3.0 cm^3 acetic acid). Flash column chromatography was performed using silica gel 60 Å (35-70 µm particle size) from Acros Organics at an air pressure of ~1.5 bar. If the crude product was not well soluble in the eluent, the sample was dissolved in a proper solvent (DCM or EtOAc), and 2.5 fold amount of Celite® 545 (particle size 0.02-0.1 mm) was added, followed by removing the solvent using a rotary evaporator and drying in vacuo. High Resolution Mass Spectrometry (HRMS) was performed on an Agilent Technologies 7890A (G3440A) GC system equipped with an Agilent Technologies J&W GC-column DB-5MS (length 30 m; inner diameter 0.250 mm; film 0.25 µm) at a constant helium flow. The GC was coupled to a Waters GCT Premier Micromass. For Direct Inlet (DI-EI) only the Waters GCT Premier Micromass unit was used. Melting points were determined on a "Mel-Temp" melting-point apparatus (Electrothermal). Chemicals were purchased from Sigma-Aldrich, Fisher Scientific, Merck, or Alfa Aesar. All reagents were used without further purification unless otherwise noted. Tetrahydrofuran (THF) and Et_2O were distilled, to remove the stabilizer 2,6-di-*tert*-butyl-4-methyl-phenol (BHT) and stored over KOH to avoid peroxide formation. DCM was dried over CaH_2 and distilled under an argon atmosphere before use. When referring to "oil pump vacuum," the applied pressure is usually in the region of 10^{-2}-10^{-3} mbar by using a rotary vane pump. For reactions requiring cryogenic temperatures over several hours, a cryostat was used.

*2-(2-Methylallyl)phenol (**2**)*

A 15 cm^3 "Ace pressure tube®, back seal" (Aldrich Z181064) with a "Duro-Silicone O-ring" was charged with 4.0 cm^3 methallyl phenyl ether (**1**, 26.0 mmol) and 15 cm^3 *N*,*N*-dimethylacetamide. The flask was sealed, and the mixture was stirred at 190 °C for 5 days. When conversion stopped (~95 % according to GC–MS), the reaction was cooled to RT and 100 cm^3 *n*-pentane were added. The organic phase was extracted with 2 M NaOH (4 × 100 cm^3). The aqueous phase was acidified with 70 cm^3 conc. HCl (pH 2–3) and extracted with Et_2O (4 × 100 cm^3). The combined organic layers were washed with saturated NaCl-solution (1 × 200 cm^3), dried over Na_2SO_4 and filtered. The solvent was removed in vacuo, and 3.58 g (93 %) **2** was isolated as brown oil. The crude product was used in the next step without further purification. NMR data were found to agree with those described in Ref. [43].

*2-Isobutylphenol (**3**)*

Hydrogenation was performed utilizing an H-Cube™ at a pressure of 60 bar at 60 °C with a Raney-Ni powder cartridge (THS 01112). A solution of 3.50 g **2** (23.6 mmol) in 250 cm^3 MeOH (~0.1 M) was used in continuous flow mode of 1.0 cm^3/min. The hydrogenation was run in a loop until full conversion was detected by GC–MS (24 h). After removing the solvent under reduced pressure, 3.51 g (99 %) **3** was isolated as colorless oil. An analytical sample was purified by distillation. B.p. 45 °C/0.3 mbar (Ref. [44]; 45-50 °C/1.3 mbar); NMR data were found to agree with those described in Ref. [32].

*4-Iodo-2-isobutylphenol (**4**)*

The synthesis was performed in analogy to Ref. [45]. In a one-neck round-bottom flask, 1.50 g **3** (10.0 mmol) was

dissolved in 14 cm^3 acetic acid (~0.75 M) and 1.62 g iodine monochloride (ICl, 10.0 mmol) was added at RT. After 24 h, 648 mg ICl (3.99 mmol) was additionally added and quantitative conversion was detected after further 24 h. The reaction mixture was quenched by the addition of 100 cm^3 0.5 M $NaHCO_3$ solution and the aqueous phase was extracted with DCM (3 × 50 cm^3). The combined organic layers were washed with 1 M $Na_2S_2O_3$ solution (3 × 100 cm^3), followed by saturated NaCl solution (1 × 100 cm^3). After drying over $MgSO_4$ and filtering, the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (cyclohexane/EtOAc = 12/1, R_f = 0.20, UV and CAM) to yield 2.35 g (85 %) **4** as pale orange powder. M.p. 62–63 °C (Ref. [32]; 62–63 °C); NMR data were found to agree with those described in Ref. [32].

*4-Iodo-2-isobutylphenyl trifluoromethanesulfonate (**5**)*

The synthesis was performed in analogy to Ref. [32]. In a one-neck round-bottom flask, 2.20 g **4** (7.97 mmol) was dissolved in 9 cm^3 pyridine (~1 M). After cooling the solution to 0 °C 2.10 cm^3 trifluoromethanesulfonic anhydride (Tf_2O, 8.76 mmol) was added dropwise. After stirring 5 min at 0 °C, the solution was allowed to warm to RT and stirred until quantitative conversion was detected by TLC (2 h). Et_2O (60 cm^3) was added and the organic phase was washed with H_2O (3 × 30 cm^3), followed by extracting the combined aqueous layers with Et_2O (2 × 30 cm^3). The combined organic layers were washed with 1 M HCl (2 × 60 cm^3) and saturated NaCl solution (1 × 60 cm^3), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified via flash column chromatography (cyclohexane, R_f = 0.50, UV and CAM) and 2.97 g (91 %) **5** was isolated as pale yellow oil. NMR data were found to agree with those described in Ref. [32].

*6-Iodochroman-2-one (**16**)*

The synthesis was performed in analogy to Ref. [41]. In a flame dried and argon flushed 250 cm^3 two-neck round-bottom flask equipped with dropping funnel and argon-inlet 5.00 g dihydrocoumarin (**15**, 33.8 mmol) was dissolved in 35 cm^3 DCM. ICl (5.48 g, 33.8 mmol) dissolved in 35 cm^3 DCM was added through the dropping funnel within 15 min. After full conversion (20 h), the reaction mixture was diluted with 100 cm^3 DCM and washed with 0.1 M $Na_2S_2O_3$-solution (2 × 50 cm^3). The combined aqueous layers were re-extracted with DCM (2 × 50 cm^3). The combined organic layers were washed with saturated NaCl solution (1 × 200 cm^3), dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. Recrystallization from DCM/cyclohexane (1/4) afforded 8.28 g (90 %) **16** as colorless powder. M.p. 134–136 °C (Ref. [37]; 133–134 °C); NMR data were found to agree with those described in Ref. [41].

*Methyl 3-(2-hydroxy-5-iodophenyl)propanoate (**17**, $C_{10}H_{11}IO_3$)*

In a flame dried and argon flushed Schlenk flask 2.00 g 6-iodochroman-2-one (**16**, 7.30 mmol, 1.00 eq) was suspended in 140 cm^3 MeOH. H_2SO_4 (1.95 cm^3) was added to this colorless suspension. The suspension dissolved and the colorless solution was warmed to 55 °C and stirred overnight at this temperature. After full conversion (24 h) was detected by GC–MS, the brown solution was neutralized by addition of 50 cm^3 saturated $NaHCO_3$ solution and the solvent was removed in vacuo. The brown residue was diluted with 100 cm^3 H_2O, and extracted with DCM (3 × 100 cm^3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified via flash column chromatography (cyclohexane/EtOAc = 5/1, R_f = 0.18, UV and CAM) and 1.70 g (76 %) **17** were isolated as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.35 (m, 3H, H^{Ar}, OH), 6.65–6.62 (m, 1H, H^{Ar}), 3.66 (s, 3H, CH_3), 2.82 (t, J = 5.9 Hz, 2H, CH_2), 2.69 (t, J = 5.9 Hz, 2H, CH_2) ppm; ^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 176.2 (C_q, CO), 154.6 (C_q, C^{Ar}), 139.2 (C^{Ar}), 137.0 (C^{Ar}), 130.4 (C_q, C^{Ar}), 119.9 (C^{Ar}), 82.9 (C_q, C^{Ar}), 52.6 (CH_3), 35.0 (CH_2), 24.5 (CH_2) ppm; GC-MS (EI, 70 eV; MT_50_S): t_R = 6.92 -min; m/z (%) = 306 (17) [M^+], 274 (100) [M^+-OCH_3], 246 (64) [M^+-$C_2H_3O_2$], 91 (0.31) [M^+-$C_4H_7O_2I$]; TLC: R_f = 0.18 (cyclohexane/EtOAc = 5/1, UV and CAM); HRMS (EI): m/z calcd for [M^+] 305.9753, found 305.9766.

*Methyl 3-[5-iodo-2-[[(trifluoromethyl)sulfonyl]oxy]phenyl]propanoate (**18**, $C_{11}H_{10}F_3IO_5S$)*

In a one-neck round-bottom flask 800 mg **17** (2.61 mmol) was dissolved in 2.5 cm^3 pyridine (~1 M). After cooling the solution to 0 °C 700 mm^3 Tf_2O (2.90 mmol) was carefully added. After stirring 5 min at 0 °C, the solution was allowed to warm to RT and stirred until quantitative conversion was detected by TLC (2 h). Et_2O (100 cm^3) was added and the organic phase was washed with H_2O (3 × 50 cm^3), followed by extracting the combined aqueous layers with Et_2O (2 × 50 cm^3). The combined organic layers were washed with 1 M HCl (2 × 50 cm^3) and saturated NaCl solution (1 × 50 cm^3), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified via flash column chromatography (cyclohexane/EtOAc = 20/1, R_f = 0.26, UV and CAM) and 966 mg (84 %) **18** was isolated as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, J = 2.1 Hz, 1H, H^{Ar}), 7.62 (dd, J = 8.7 Hz, 2.1 Hz, 1H, H^{Ar}), 7.01 (d, J = 8.7 Hz, 1H, H^{Ar}), 3.69 (s, 3H, CH_3), 2.99 (t, J = 7.7 Hz, 2H, CH_2), 2.65 (t, J = 7.7 Hz, 2H, CH_2) ppm; ^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 172.3 (C_q, C^{Ar}), 147.9 (C_q, C^{Ar}), 140.3 (C^{Ar}), 137.6 (C^{Ar}), 135.8 (C_q, C^{Ar}), 123.4 (C^{Ar}), 118.7 (q, J = 318 Hz, CF_3), 93.4 (C_q, CN),

52.0 (CH_3), 33.7 (CH_2), 25.0 (CH_2) ppm; GC-MS (EI, 70 eV; MT_50_S): $t_R = 6.65$ min; m/z (%) = 438 (4) [M^+], 407 (11) [M^+-OCH_3], 289 (100) [M^+-CF_3O_3S] 91 (34) [M^+-$C_5H_3F_3IO_4S$]; TLC: $R_f = 0.26$ (cyclohexane/EtOAc = 20/1, UV and CAM); HRMS (EI): m/z calcd for [M^+] 437.9246, found 437.9276.

*(2-Amino-2-oxoethyl)triphenylphosphonium chloride (**19**)*

The synthesis was performed in analogy to Ref. [32]. In a flame dried Schlenk flask 7.86 g PPh_3 (30.0 mmol) and 2.67 g 2-chloroacetamide (28.6 mmol) were suspended in 30 cm^3 nitromethane. The mixture was stirred for 19 h at 105 °C. The pale brown solution was allowed to cool to RT, and the formed colorless precipitate was isolated by filtration, washed with EtOAc (2 × 10 cm^3), Et_2O (1 × 15 cm^3) and dried in vacuo. **19** (10.1 g, 99 %) was isolated as colorless powder. M.p. 219-221 °C (Ref. [29]; 215–218 °C); NMR data were found to agree with those described in Ref. [32].

*2-Hydroxy-5-iodobenzaldehyde (**7**)*

The synthesis was performed in analogy to Ref. [37]. In a one-neck round-bottom flask a solution of 16.1 g ICl (99.1 mmol) in 100 cm^3 DCM (~1 M) was cooled to 0 °C. Salicylaldehyde (**6**, 10.0 cm^3, 99.1 mmol) dissolved in 40 cm^3 DCM (~2.5 M) was added. The reaction was warmed to RT and stirred until full conversion was observed (24 h). The reaction mixture was diluted with 100 cm^3 DCM and washed with 1 M $Na_2S_2O_3$ solution (2 × 100 cm^3). The aqueous phase was extracted with DCM (3 × 50 cm^3) and the organic layer was then washed with saturated NaCl solution (1 × 200 cm^3). After drying over Na_2SO_4 and filtering, the solvent was removed in vacuo. Recrystallization from cyclohexane afforded 16.7 g (68 %) **7** as pale yellow powder. M.p. 97-99 °C (Ref. [32]; 97-99 °C); NMR data were found to agree with those described in Ref. [32].

*2-Formyl-4-iodophenyl trifluoromethanesulfonate (**8**)*

The synthesis was performed in analogy to Ref. [32]. In a flame dried and argon flushed two-neck round-bottom flask equipped with argon-inlet 13.5 g **7** (54.4 mmol) was dissolved in 110 cm^3 DCM and 6.60 cm^3 pyridine (81.7 mmol). The pale yellow solution was cooled to 0 °C and 18.3 cm^3 Tf_2O (109 mmol) was added. After 5 min, the orange suspension was allowed to warm to RT. When quantitative conversion was detected by GC–MS (4 h), the reaction mixture was washed with 200 cm^3 H_2O. The aqueous phase was extracted with DCM (6 × 100 cm^3) and the combined organic layers were washed with saturated NaCl solution (1 × 100 cm^3), dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The brown, oily crude product was purified via flash column chromatography (cyclohexane/EtOAc = 40/1, $R_f = 0.28$ UV and CAM) and 19.2 g (93 %) **8** were isolated as yellow oil. NMR data were found to agree with those described in Ref. [32].

*2-(3-Amino-3-oxoprop-1-en-1-yl)-4-iodophenyl trifluoromethanesulfonate (**21**, $C_{10}H_7F_3INO_4S$)*

In a flame dried and argon flushed Schlenk flask 983 mg phosphonium salt **19** (2.76 mmol) was suspended in 20 cm^3 absolute MeOH. After cooling the suspension to 0 °C, 310 mg KO*t*Bu (2.76 mmol) was added. The yellow reaction mixture was stirred at 0 °C for 10 min. **8** (1.00 g, 2.63 mmol) was added and the orange solution was stirred at RT until full conversion of the starting material was observed by TLC. After quantitative conversion (16 h), the solvent was removed under reduced pressure and the orange crude product was purified via flash column chromatography (cyclohexane/EtOAc = 1/1, $R_f = 0.21$, UV and CAM) to yield 616 mg (55 %) **21** as pale yellow crystals. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 8.16$ (bs, 1H, $CONH_2$), 7.91 (d, $J = 8.6$ Hz, 1H, H^{Ar}), 7.59 (bs, 1H, $CONH_2$), 7.44–7.31 (m, 3H, H^{Ar}, CH), 6.81 (d, $J = 15.7$ Hz, 1H, CH) ppm; ^{13}C NMR (76 MHz, DMSO-d_6, APT): $\delta = 165.3$ ($CONH_2$), 146.8 (C_q, C^{Ar}), 139.8 (CH), 136.5 (C^{Ar}), 130.4 (C_q, C^{Ar}), 128.8 (C^{Ar}), 128.4 (C^{Ar}), 124.2 (C^{Ar}), 118.0 (q, $J = 321$ Hz, CF_3), 95.3 (C_q, C^{Ar}) ppm; HPLC–MS (Poroshell, ESI$^+$, MT_general): $t_R = 3.67$ min; $m/z = 422$ [M+H$^+$], 444 [M+Na$^+$]; $\lambda_{max} = 239$ nm; TLC: $R_f = 0.21$ (cyclohexane/EtOAc = 1/1, UV and CAM); m.p. 115–117 °C; HRMS (EI): m/z calcd for [M^+] 420.9093, found 420.9094.

*Dipotassium azodicarboxylate (PADA) (**20**)*

The synthesis was performed in analogy to Ref. [39]. In a 100 cm^3 round-bottom flask, 18.3 cm^3 KOH solution (7 M) was cooled to −10 °C by a cryostat. Azodicarbonamide (5.84 g, 50.3 mmol) was added in small portions. The yellow-orange suspension was stirred at −10 °C for 60 min. Then the yellow precipitate was collected by filtration and washed with cold MeOH (3 × 50 cm^3). After drying in vacuo 9.34 g (96 %) **20** was collected as yellow powder. M.p 186 °C (decomposition).

*2-(3-Amino-3-oxopropyl)-4-iodophenyl trifluoromethanesulfonate (**22**, $C_{10}H_9F_3INO_4S$)*

In a 25 cm^3 round-bottom flask equipped with reflux condenser 280 mg **21** (665 µmol) was dissolved in 4.5 cm^3 1,2-DME. PADA (**20**, 387 mg, 1.99 mmol) was added. AcOH (114 mm^3, 1.99 mmol) was added to the yellow suspension and the reaction-mixture was heated to 50 °C. When full conversion (3 days) was achieved the reaction was cooled to RT and unreacted PADA was removed by filtration. The solution was concentrated in vacuo. The

brown, solid crude was purified via flash column chromatography (cyclohexane/EtOAc = 1/1, R_f = 0.23, CAM) and 258 mg (92 %) **22** was isolated as colorless powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.84 (s, 1H, H^{Ar}), 7.75 (dd, J = 8.6 Hz, 1.9 Hz, 1H, H^{Ar}), 7.34 (bs, 1H, $CONH_2$), 7.18 (d, J = 8.6 Hz, 1H, H^{Ar}), 6.85 (bs, 1H, $CONH_2$), 2.83 (t, J = 7.5 Hz, 2H, CH_2), 2.41 (t, J = 7.5 Hz, 2H, CH_2) ppm; ^{13}C NMR (76 MHz, DMSO-d_6, APT): δ = 172.4 ($CONH_2$), 147.4 (C_q, C^{Ar}), 139.7 (C^{Ar}), 137.2 (C^{Ar}), 136.4 (C_q, C^{Ar}), 123.3 (C^{Ar}), 118.0 (q, J = 320 Hz, CF_3), 94.8 (C_q, C^{Ar}), 34.1 (CH_2), 24.8 (CH_2) ppm; HPLC–MS (Poroshell, ESI$^+$, MT_general): t_R = 3.65 min; m/z = 424 [M+H$^+$], 446 [M+Na$^+$]; λ_{max} = 239 nm; TLC: R_f = 0.23 (cyclohexane/EtOAc = 1/1, UV and CAM); m.p. 115–118 °C; HRMS (EI): m/z calcd for [M$^+$] 422.9249, found 422.9258.

*2-(Hydroxymethyl)-4-iodophenyl trifluoromethanesulfonate (**9**)*

The synthesis was performed in analogy to Ref. [32]. In a flame dried and argon flushed Schlenk flask, 5.00 g **8** (13.2 mmol) was dissolved in 20 cm^3 absolute DCM. This solution was cooled to −78 °C and 26.3 cm^3 diiso-butylaluminum hydride (DIBALH, 1.0 M in toluene, 26.3 mmol) was slowly added via a dropping funnel. After stirring for 2 h at −78 °C the bright yellow solution was quenched by addition of 17 cm^3 MeOH and 60 cm^3 saturated Rochelle salt solution. A yellow emulsion was formed and stirred overnight until phase separation occurs. The phases were separated and the aqueous phase was extracted with DCM (3 × 100 cm^3). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The yellow, oily crude product was purified via flash column chromatography (cyclohexane/EtOAc = 5/1, R_f = 0.37, UV and CAM) and 4.19 g (83 %) **9** was isolated as pale yellow powder. M.p. 28–30 °C (Ref. [32]; 28–30 °C); NMR data were found to agree with those described in Ref. [32].

*2-[[(tert-Butyldiphenylsilyl)oxy]methyl]-4-iodophenyl trifluoromethanesulfonate (**12**, $C_{24}H_{24}F_3IO_4SSi$)*

A 500 cm^3 round-bottom flask with drying-tube was charged with 6.28 g **9** (16.4 mmol) dissolved in 75 cm^3 DCM. Imidazole (2.95 g, 43.4 mmol) and 6.5 cm^3 *tert*-butyldiphenylchlorsilane (TBDPSCl, 25.0 mmol) were added via syringe. When the whole amount of TBDPSCl was added a colorless solid started to precipitate. The reaction was stirred overnight (16 h) at RT. When quantitative conversion was detected by TLC, the reaction was quenched by the addition of 120 cm^3 3 M NaOH and transferred to a separation funnel. After phase separation, the aqueous phase was extracted with DCM (3 × 120 cm^3). The combined organic layers were washed with saturated NaCl solution (1 × 120 cm^3), dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The yellow, oily crude product was purified via flash column chromatography (cyclohexane/EtOAc = 100/1, R_f = 0.34, UV and CAM) and 8.07 g (79 %) **12** was isolated as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (m, 1H, H^{Ar}), 7.70–7.64 (m, 5H, H^{Ar}), 7.50–7.39 (m, 6H, H^{Ar}), 6.98 (d, J = 8.6 Hz, 1H, H^{Ar}), 4.79 (s, 2H, CH_2), 1.14 (s, 9H, 3 x CH_3) ppm; ^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 146.3 (C_q, C^{Ar}), 138.3 (C^{Ar}), 137.8 (C^{Ar}), 136.0 (C_q, C^{Ar}), 135.6 (C^{Ar}), 132.7 (C_q, C^{Ar}), 130.2 (C^{Ar}), 128.0 (C^{Ar}), 122.8 (C^{Ar}), 118.6 (q, J = 320 Hz, CF_3), 93.5 (C_q, C^{Ar}), 59.9 (CH_2), 27.0 (CH_3), 19.4 (C_q) ppm; TLC: R_f = 0.19 (cyclohexan, UV), 0.34 (cyclohexane/EtOAc 100/1 (v/v), UV); HRMS (EI): m/z calcd for [M$^+$-C_4H_9] 562.9457, found 562.9446.

*2-(1-Hydroxyethyl)-4-iodophenyl trifluoromethanesulfonate (**13**)*

The synthesis was performed in analogy to Ref. [32]. In a flame dried and argon flushed Schlenk flask 69.1 mg Mg turnings (2.84 mmol) was stirred for 20 min without solvent. Then the turnings were suspended in 5 cm^3 Et_2O and 180 mm^3 iodomethane (2.84 mmol) dissolved in 5 cm^3 Et_2O was added. The reaction mixture was heated to reflux until the complete amount of Mg was dissolved (30 min). The colorless suspension was added dropwise to a solution of 900 mg **8** (2.37 mmol) in 10 cm^3 Et_2O. The pale yellow suspension was stirred until quantitative conversion was detected by TLC (5 h). The reaction was diluted with 100 cm^3 Et_2O and washed with 1 M HCl (1 × 100 cm^3), saturated $NaHCO_3$ solution (1 × 100 cm^3) and saturated NaCl solution. The organic layer was dried over $MgSO_4$, filtered and the solvent was removed in vacuo. The yellow, oily crude product was purified via flash column chromatography (cyclohexane/EtOAc = 10/1, R_f = 0.21, CAM) and 882 mg (94 %) **13** was isolated as pale yellow powder. M.p. 37-40 °C (Ref. [32]; 37–40 °C); NMR data were found to agree with those described in Ref. [32].

*2-[1-[(tert-Butyldiphenylsilyl)oxy]ethyl]-4-iodophenyl trifluoromethanesulfonate (**14**, $C_{25}H_{26}F_3IO_4SSi$)*

In a 250 cm^3 round-bottom flask 8.24 g **13** (20.7 mmol) was dissolved in 95 cm^3 DCM and 3.52 g imidazole (51.8 mmol) was added. Then 5.4 cm^3 *tert*-butylchlorodiphenylsilane (20.8 mmol) was added to the yellow solution and a white precipitate was formed. After the reaction was stirred for 16 h at RT additional 540 mm^3 *tert*-butylchlorodiphenylsilane (2.1 mmol) was added because of incomplete conversion detected by TLC. After stirring the reaction for another 5 h the reaction was diluted with 20 cm^3 DCM and washed with 3 M NaOH (1 × 150 cm^3). The aqueous layer was re-extracted with DCM (1 × 150 cm^3) and the combined organic layers

were washed with saturated NaCl solution (1 × 200 cm^3). Then the organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give a yellow oil. The crude product was purified via flash column chromatography [cyclohexane to cyclohexane/EtOAc = 50/1, $R_f = 0.38$ (cyclohexane/EtOAc = 100/1, UV and CAM)] and 9.86 g (75 %) **14** was isolated as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.10$ (d, $J = 2.0$ Hz, 1H, H^{Ar}), 7.62 (d, $J = 6.3$ Hz, 2H, H^{Ar}), 7.53 (dd, $J = 8.6$ Hz, 2.2 Hz, 1H, H^{Ar}), 7.44 (d, $J = 6.6$ Hz, 2H, H^{Ar}), 7.35 (m, 4H, H^{Ar}), 7.23 (m, 2H, H^{Ar}), 6.79 (d, $J = 8.6$ Hz, 1H, H^{Ar}), 5.03 (m, 1H, CH), 1.32–1.30 (d, $J = 6.2$ Hz, 3H, CH_3), 1.04 (s, 9H, 3× CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, APT): $\delta = 145.0$ (C_q, C^{Ar}), 141.3 (C_q, C^{Ar}), 137.9 (C^{Ar}), 137.6 (C^{Ar}), 135.8 (C^{Ar}), 135.8 (C^{Ar}), 133.6 (C_q, C^{Ar}), 132.9 (C_q, C^{Ar}), 130.0 (C^{Ar}), 129.9 (C^{Ar}), 127.8 (C^{Ar}), 127.8 (C^{Ar}), 122.5 (C^{Ar}), 118.4 (q, $J = 320.2$ Hz, CF_3), 93.4 (C_q, C^{Ar}), 65.6 (CH), 27.1 (CH_3), 25.7 (CH_3), 19.5 (C_q) ppm; GC–MS (EI, 70 eV; MT_50_S): $t_R = 8.467$ min; m/z (%) = 485 (45) [M^+-CF_3O_3S]; TLC: $R_f = 0.38$ (cyclohexane/EtOAc = 100/1, UV and CAM); HRMS (EI): m/z calcd for [M^+-C_4H_9] 576.9614, found 576.9585.

*2-(Chloromethyl)-4-iodophenyl trifluoromethansulfonate (**10**, $C_8H_5ClF_3IO_3S$)*

A 50 cm^3 round bottom flask equipped with reflux condenser was charged with 2.12 g **9** (5.2 mmol) and 20 cm^3 thionylchloride. The pale yellow solution was heated to 95 °C for 24 h. When full conversion was detected by GC–MS the remaining thionylchloride was removed in vacuo. The brown, oily crude product was purified via flash column chromatography (cyclohexane, $R_f = 0.30$, UV and CAM) and 1.44 g (69 %) **10** was isolated as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.87$ (d, $J = 2.0$ Hz, 1H, H^{Ar}), 7,72 (dd, $J = 8.7$ Hz, 3.1 Hz, 1H, $H^{Ar)}$, 7.06 (d, $J = 8.7$ Hz, 1H, H^{Ar}), 4.43 (s, 2H, CH_2) ppm; ^{13}C NMR (76 MHz, $CDCl_3$): $\delta = 147.1$ (C_q, C^{Ar}), 141.1 (C^{Ar}), 139.6 (C^{Ar}), 133.1 (C_q, C^{Ar}), 132.6 (C^{Ar}), 120.8 (C^{Ar}), 118.6 (q, $J = 320$ Hz, CF_3), 93.3 (C_q, C^{Ar}), 24.5 (CH_2) ppm; GC-MS (EI, 70 eV; MT_50_S): $t_R = 6.08$; m/z (%) = 400 (75) [M^+], 267 (100) [M^+-CF_3O_2S], 365 (6) [M^+-Cl]; HRMS (EI): m/z calcd for [M^+] 399.8645, found 399.8626.

*S-5-Iodo-2-[[(trifluoromethyl)sulfonyl]oxy]benzyl ethanethioate (**11**)*

The synthesis was performed in analogy to Ref. [32]. In a flame dried and argon flushed Schlenk flask 300 mg **10** (674 µmol) was dissolved in 2 cm^3 absolute THF. K_2CO_3 (205 mg, 1.28 mmol) and 57.8 mm^3 thioacetic acid (809 µmol) were added. The colorless suspension was stirred at RT until full conversion was detected by GC-MS after 60 min. Then the reaction mixture was neutralized with 1 cm^3 1 M HCl and diluted with 20 cm^3 H_2O. The aqueous phase was extracted with DCM (3 × 20 cm^3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The oily crude product was purified via flash column chromatography (cyclohexane/EtOAc = 50/1, $R_f = 0.27$, UV and CAM) and 245 mg (82 %) **11** was isolated as colorless oil. NMR data were found to agree with those described in Ref. [32].

*4,5-Dihydrobenzo[b]oxepin-2(3H)-one (**24**)*

In a 250 cm^3 round-bottom flask 10.0 cm^3 1-tetralone (**23**, 75.3 mmol) was dissolved in 200 cm^3 $CHCl_3$. mCBPA (23.2 g, 94.1 mmol) was added to the resulting pale yellow solution. The yellow suspension was stirred until full conversion was detected by TLC (48 h). The reaction mixture was washed with 5 % $NaHCO_3$ solution (2 × 100 cm^3) and H_2O (1 × 100 cm^3). Then the organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (cyclohexane/EtOAc = 5/1, $R_f = 0.50$, UV and CAM) and 10.9 g (89 %) **24** was isolated as yellow oil. NMR data were found to agree with those described in Ref. [46].

*7-Iodo-4,5-dihydrobenzo[b]oxepin-2(3H)-one (**25**, $C_{10}H_9IO_2$)*

In a 100 cm^3 two-neck round-bottom flask equipped with dropping funnel and argon inlet, 1.5 g **24** (9.19 mmol) was dissolved in 10 cm^3 DCM. ICl (1.5 g, 9.19 mmol) dissolved in 10 cm^3 DCM was added dropwise. After full conversion (20 h) the reaction was diluted with 100 cm^3 DCM and washed with 1 M $Na_2S_2O_3$ solution (2 × 50 cm^3). The combined aqueous layers were re-extracted with DCM (2 × 50 cm^3). The combined organic layers were washed with saturated NaCl solution (1 × 200 cm^3), dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The brown, oily crude product was purified via flash column chromatography (cyclohexane/EtOAc = 10/1, $R_f = 0.33$, UV and CAM) and 2.20 g (83 %) **25** was isolated as yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.58$ (dd, $J = 8.4$ Hz, 2.0 Hz, 1H, H^{Ar}), 7.54 (d, $J = 1.8$ Hz, 1H, H^{Ar}), 6.84 (d, $J = 8.4$ Hz, 1H, H^{Ar}), 2.84 (t, $J = 7.2$ Hz, 2H, CH_2), 2.48 (t, $J = 7.2$ Hz, 2H, CH_2), 2.23 (q, $J = 7.1$ Hz, 2H, CH_2) ppm; ^{13}C NMR (76 MHz, $CDCl_3$, APT): $\delta = 170.9$ (C_q, CO), 151.9 (C_q, C^{Ar}), 138.5 (C^{Ar}), 137.8 (C^{Ar}), 132.8 (C_q, C^{Ar}), 121.6 (C^{Ar}), 89.6 (C_q, C^{Ar}), 31.1 (CH_2), 28.1 (CH_2), 26.4 (CH_2) ppm; GC-MS (EI, 70 eV; MT_50_S): $t_R = 6.86$ min; m/z (%) = 288 (100) [M^+], 233 (64) [M^+-C_2H_4O], 161 (14) [M^+-I]; TLC: $R_f = 0.33$ (cyclohexane/EtOAc = 10/1, UV and CAM); m.p. 75–78 °C; HRMS (EI): m/z calcd for [M^+] 287.9647, found 287.9660.

*Methyl 4-(2-hydroxy-5-iodophenyl)butanoate (**26**, $C_{11}H_{13}IO_3$)*

In a Schlenk flask 4.10 cm^3 conc. H_2SO_4 was added to a colorless suspension of 2.20 g **25** (7.64 mmol) in 30 cm^3 MeOH. The solid dissolved and the pale yellow solution was warmed to 55 °C and stirred overnight at this temperature. After full conversion (24 h) was detected by TLC, the brown solution was neutralized with 50 cm^3 saturated $NaHCO_3$ solution and the phases were separated. The aqueous phase was extracted with DCM (3 × 100 cm^3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified via flash column chromatography (cyclohexane/EtOAc = 5/1, R_f = 0.16, UV and CAM) and 2.42 g (99 %) **26** was isolated as light brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.36 (m, 2H, H^{Ar}), 6.75 (bs, 0.8H, OH), 6.63 (d, J = 9.0 Hz, 1H, H^{Ar}), 3.73 (s, 3H, CH_3) 2.58 (t, J = 7.7 Hz, 2H, CH_2), 2.40 (t, J = 6.6 Hz, 2H, CH_2), 1.86 (q, J = 7.1 Hz, 2H, CH_2) ppm; ^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 175.7 (C_q, CO), 154.7 (C_q, C^{Ar}), 138.7 (C^{Ar}), 136.6 (C^{Ar}), 130.1 (C_q, C^{Ar}), 118.5 (C_q, C^{Ar}), 82.2 (C_q, C^{Ar}), 52.2 (CH_3), 32.6 (CH_2), 29.2 (CH_2), 24.9 (CH_2) ppm; GC-MS (EI, 70 eV; MT_50_S): t_R = 7.22 min; m/z (%) = 320 (48) [M^+], 288 (100) [M^+-CH_3O], 260 (20) [M^+-$C_2H_3O_2$], 233 (66) [M^+-$C_4H_7O_2$]; TLC: R_f = 0.16 (cyclohexane/EtOAc = 5/1, UV and CAM); HRMS (EI): m/z calcd for [M^+] 319.9909, found 319.9914.

*Methyl 4-[5-iodo-2-[[(trifluoromethyl)sulfonyl]oxy]phenyl]-butanoate (**27**, $C_{12}H_{12}F_3IO_5S$)*

In a one-neck round-bottom flask 2.40 g **26** (7.84 mmol) was dissolved in 8 cm^3 pyridine (~1 M). After cooling the solution to 0 °C, 2.10 cm^3 Tf_2O (8.62 mmol) was carefully added. After stirring 5 min at 0 °C, the solution was allowed to warm to RT and stirred until quantitative conversion was detected by TLC (2 h). Et_2O (60 cm^3) was added and the organic phase was washed with H_2O (3 × 30 cm^3), followed by extracting the combined aqueous layers with Et_2O (2 × 30 cm^3). The combined organic layers were washed with 1 M HCl (2 × 60 cm^3) and saturated NaCl solution (1 × 60 cm^3), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified via flash column chromatography (cyclohexane/EtOAc = 20/1, R_f = 0.28, UV and CAM) and 2.68 g (78 %) **27** were isolated as pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, J = 1.9 Hz, 1H, H^{Ar}), 7.59 (dd, J = 8.6 Hz, 2.1 Hz, 1H, H^{Ar}), 6.99 (d, J = 8.6 Hz, 1H, H^{Ar}), 3.67 (s, 3H, CH_3), 2.69 (t, J = 7.8 Hz, 2H, CH_2), 2.37 (t, J = 7.3 Hz, 2H, CH_2), 1.94 (q, J = 7.5 Hz, 2H, CH_2) ppm; ^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 173.3 (C_q, CO), 147.9 (C_q,C^{Ar}), 140.2 (C^{Ar}), 137.3 (C^{Ar}), 136.7 (C_q, C^{Ar}), 118.6 (q, J = 320.2 Hz, CF_3), 123.3 (C^{Ar}), 93.5 (C_q, C^{Ar}), 51.8 (CH_3), 33.3 (CH_2), 29.0 (CH_2), 25.0 (CH_2) ppm; GC-MS (EI, 70 eV; MT_50_S): t_R = 6.94 min; m/z (%) = 425 (27) [M^+], 421 (26) [M^+-CH_3O], 378 (25) [M^+-$C_3H_5O_2$], 319 (31) [M^+-CF_3O_2S]; TLC: R_f = 0.28 (cyclohexane/EtOAc = 20/1, UV and CAM); HRMS (EI): m/z calcd for [M^+] 451.9402, found 451.9423.

*2-(4-Hydroxybutyl)-4-iodophenyl trifluoromethanesulfonate (**28**, $C_{11}H_{12}F_3IO_4S$)*

In a flame dried and argon flushed Schlenk flask 2.60 g **27** (5.75 mmol, 1.0 eq) was dissolved in 8.0 cm^3 absolute DCM. This solution was cooled to −78 °C and 11.5 cm^3 diiso-butyl-aluminum hydride (DIBALH, 1.0 M in DCM, 11.5 mmol) was carefully added via syringe. The colorless solution was warmed to RT. After quantitative conversion was detected by TLC (2 h), the solution was cooled again to −78 °C and quenched by the addition of 8 cm^3 MeOH. Saturated Rochelle-salt solution (20 cm^3) was added and the emulsion was stirred until phase separation occurred (24 h). The phases were separated and the aqueous phase was extracted with DCM (3 × 50 cm^3). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. **28** (2.26 g, 93 %) was isolated as colorless oil and used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, J = 1.9 Hz, 1H, H^{Ar}), 7.59 (dd, J = 8.6 Hz, 2.1 Hz, 1H, H^{Ar}), 6.98 (d, J = 8.6 Hz, 1H, H^{Ar}), 3.69 (t, J = 6.1 Hz, 2H, CH_2), 2.69 (t, J = 7.6 Hz, 2H, CH_2), 1.73-1.61 (m, 4H, 2× CH_2) ppm; ^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 148.0 (C_q, C^{Ar}), 140.2 (C^{Ar}), 137.6 (CH_2), 137.0 (C^{Ar}), 123.3 (C^{Ar}), 118.7 (d, J = 320.2 Hz, CF_3), 93.5 (C_q, C^{Ar}), 62.5 (CH_2), 32.3 (CH_2), 29.5 (CH_2) ppm; GC-MS (EI, 70 eV; MT_50_S): t_R = 6.90 - min; m/z (%) = 424 (31) [M^+], 378 (92) [M^+-C_2H_5O]; TLC: R_f = 0.23 (cyclohexane/EtOAc = 5/1, UV and CAM); HRMS (EI): m/z calcd for [M^+] 423.9453, found 451.9423.

*2-[4-[(tert-Butoxycarbonyl)amino]butyl]-4-iodophenyl trifluoromethanesulfonate (**30**, $C_{16}H_{21}F_3INO_5S$)*

In a 50 cm^3 round-bottom flask, 2.20 g **28** (5.20 mmol) was dissolved in 20 cm^3 THF. The colorless solution was cooled to 0 °C and 930 mm^3 DIPEA (5.20 mmol), 1.63 mg PPh_3 (6.23 mmol), 1.24 cm^3 DIAD (6.23 mmol), and 1.34 cm^3 DPPA (6.23 mmol) was added. The pale yellow suspension was stirred for 4 h at RT. When quantitative conversion of alcohol **28** was detected by TLC, 1.77 g PPh_3 (6.48 mmol) dissolved in 4.0 cm^3 THF was added and the reaction was stirred overnight at RT. After adding 2.0 cm^3 H_2O, the reaction was warmed to 50 °C and stirred until full conversion of the azide intermediate was detected by GC–MS. The solvent was removed under reduced pressure and the oily residue (amine intermediate **29**) was

dissolved in 50 cm^3 DCM. Boc_2O (1.13 g, 5.20 mmol) was added to this pale yellow solution. The reaction was stirred at RT overnight. When quantitative conversion of amine **29** was detected by TLC the reaction was dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The pale yellow, oily crude product was purified via flash column chromatography (cyclohexane/EtOAc = 15/1, $R_f = 0.26$, UV and ninhydrin) and 1.32 g (49 %) **30** was isolated as pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.66$ (d, $J = 1.9$ Hz, 1H, H^{Ar}), 7.58 (dd, $J = 8.6$ Hz, 2.0 Hz, 1H, H^{Ar}), 6.58 (d, $J = 8.6$ Hz, 1H, H^{Ar}), 4.54 (bs, 1H, NH), 3.15 (d, $J = 5.4$ Hz, 2H, CH_2), 2.69–2.63 (m, 2H, CH_2), 1.67–1.51 (m, 4H, 2× CH_2), 1.44 (s, 9H, 3× CH_3) ppm; ^{13}C NMR (76 MHz, $CDCl_3$, APT): $\delta = 156.5$ (C_q, CO), 147.5 (C_q, C^{Ar}), 141.1 (C^{Ar}), 137.4 (C_q, C^{Ar}), 136.9 (C^{Ar}), 125.1 (C_q, C^{Ar}), 119.0 (d, $J = 320$ Hz, CF_3), 93.3 (C_q, C^{Ar}), 79.2 (C_q), 40.1 (CH_2), 29.5 (CH_2), 29.1 (CH_2), 28.1 (3× CH_3), 27.0 (CH_2) ppm; TLC: $R_f = 0.44$ (cyclohexane/EtOAc = 5/1, UV and ninhydrin); HRMS (EI): *m/z* calcd for [M^+] 523.0137, found 523.0171.

*tert-Butyl [4-[2,5-bis(5-isobutylpyridin-3-yl)phenyl]butyl]-carbamate (**32**, $C_{33}H_{45}N_3O_2$)*

The synthesis was performed in analogy to Ref. [30]. A flame dried Schlenk flask was charged with 270 mg pyridine boronic acid ester **31** (1.03 mmol), 672 mg Cs_2CO_3 (2.06 mmol), and 42.1 mg $PdCl_2$(dppf) (10 mol %). After drying in vacuo, a solution of 270 mg core unit fragment **30** (516 µmol) in 5 cm^3 absolute, degassed 1,2-DME (~0.2 M) was added. The reaction mixture was stirred at 80 °C overnight. The resulting black suspension was filtered through a pad of SiO_2 (3 × 2 cm, eluent 100 cm^3 MeOH) and after concentrating to dryness, the crude product was purified via flash column chromatography (15 g SiO_2, 1.5 × 20 cm, eluent: cyclohexane/EtOAc = 2/1, $R_f = 0.30$, UV and CAM). To obtain pure substrate, the product was purified via semi-preparative HPLC and 142 mg teraryl **32** (53 %) was isolated as pale yellow, highly viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.64$ (bs, 1H, H^{Ar}), 8.36 (bs, 3H, (H^{Ar}), 7.63 (bs, 1H, H^{Ar}), 7.41 (d, $J = 11.2$ Hz, 3H, H^{Ar}), 7.24–7.20 (m, 1H, H^{Ar}), 4.43 (bs, 1H, NH), 2.96–2.94 (m, 2H, CH_2), 2.61–2.55 (m, 2H, CH_2), 2.52–2.48 (m, 4H, CH_2), 1.95–1.79 (m, 2H, CH_2), 1.50–1.40 (m, 2H, CH_2), 1.34 (s, 9H, CH_3), 0.91–0.88 (m, 12H, CH_3) ppm; ^{13}C NMR (76 MHz, $CDCl_3$): $\delta = 145.1$ (C_q, $C^{Carbonyl}$), 149.1 (C^{Ar}), 148.9 (C^{Ar}), 147.0 (C^{Ar}), 144.5 (C^{Ar}), 141.0 (C_q, C^{Ar}), 137.9 (C_q, C^{Ar}), 137.9 (C_q, C^{Ar}), 137.5 (C^{Ar}), 137.1 (C_q, C^{Ar}), 136.5 (C_q, C^{Ar}), 136.0 (C_q, C^{Ar}), 135.3 (C^{Ar}), 131.1 (C^{Ar}), 128.4 (C^{Ar}), 125.0 (C^{Ar}), 89.2 (C_q), 42.5 (CH_2), 42.3 (CH_2), 40.3 (CH_2), 33.0 (CH_2), 30.2 (CH), 30.1 (CH_2), 28.7 (CH_2), 28.5 (CH_3), 22.4 (CH_3), 22.3 (CH_3) ppm; HPLC–MS (Poroshell, ESI^+, MT_60 to 100): $t_R = 4.06$ min; $m/z = 526$ [$M+H^+$], 539 [$M+Na^+$]; $\lambda_{max} = 269$ nm; TLC: $R_i = 0.30$ (cyclohexane/EtOAc = 2/1, UV and CAM); HRMS (DI-EI): *m/z* calcd for [M^+] 515.3512, found 515.3525.

*4-[2,5-Bis(5-isobutylpyridin-3-yl)phenyl]butan-1-amine hydrochloride (**33**, $C_{28}H_{38}ClN_3$)*

Compound **32** (100 mg, 194 µmol) was dissolved in 4 cm^3 DCM in a 10 cm^3 round-bottom flask. The colorless solution was cooled to 0 °C and 390 mm^3 HCl (5 M in *i*PrOH, 1.94 mmol) was added. The colorless solution was stirred at RT until full conversion of the starting material was detected by HPLC–MS (7 h). The solvent was removed in a N_2-flow and the product was dried in vacuum. **33** (81.0 mg, quant.) was isolated as colorless powder. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 9.28$ (s, 1H, H^{Ar}), 8.92–8.80 (m, 4H, H^{Ar}), 8.45 (s, 1H, H^{Ar}), 8.20 (bs, 3H, NH_3), 8.09 (s, 1H, H^{Ar}), 7.93 (d, $J = 7.8$ Hz, 1H, H^{Ar}), 7.54 (d, $J = 7.9$ Hz, 1H, H^{Ar}), 3.80–3.72 (m, 1H, CH), 2.77–2.67 (m, 8H, CH_2), 2.07-1.96 (m, 2H, CH_2), 1.61–1.50 (m, 4H, CH_2), 0.92 (d, $J = 6.1$ Hz, 12H, CH_3) ppm; ^{13}C NMR (76 MHz, DMSO-d_6): $\delta = 145.3$ (C^{Ar}), 143.1 (C^{Ar}), 141.1 (C_q, C^{Ar}), 140.9 (C_q, C^{Ar}), 140.5 (C^{Ar}), 140.4 (C_q, C^{Ar}), 139.6 (C^{Ar}), 138.3 (C_q, C^{Ar}), 137.8 (C^{Ar}), 137.7 (C^{Ar}), 137.5 (C_q, C^{Ar}), 136.1 (C_q, C^{Ar}), 134.6 (C_q, C^{Ar}), 131.3 (C^{Ar}), 128.7 (C^{Ar}), 125.2 (C^{Ar}), 40.5 (CH_2), 38.3 (CH_2), 31.6 (CH_2), 27.1 (CH_2), 26.6 (CH_2), 25.5 (CH), 21.8 (CH_3), 21.7 (CH_3) ppm; HPLC–MS (Poroshell, ESI^+, MT_general): $t_R = 4.55$ min; $m/z = 416$ [$M+H^+$]; $\lambda_{max} = 269$ nm; HRMS (DI-EI): *m/z* calcd for [M^+-HCl] 415.2987, found 415.2995.

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References

1. Stumpf MPH, Thorne T, de Silva E, Stewart R, An HJ, Lappe M, Wiuf C (2008) Proc Natl Acad Sci USA 105:6959
2. Stelzl U, Worm U, Lalowski M, Haenig C, Brembeck FH, Goehler H, Stroedicke M, Zenkner M, Schoenherr A, Koeppen S, Timm J, Mintzlaff S, Abraham C, Bock N, Kietzmann S, Goedde A, Toksöz E, Droege A, Krobitsch S, Korn B, Birchmeier W, Lehrach H, Wanker EE (2005) Cell 122:957
3. http://ppi.fli-leibniz.de/. Accessed 3 Nov 2015
4. Jochim AL, Arora PS (2010) ACS Chem Biol 5:919
5. Jochim AL, Arora PS (2009) Mol BioSyst 5:924
6. Berg T (2003) Angew Chem Int Ed Engl 42:2462

7. Pelay-Gimeno M, Glas A, Koch O, Grossmann TN (2015) Angew Chem Int Ed 54:8896
8. Kim YW, Grossmann TN, Verdine GL (2011) Nat Protocols 6:761
9. Johnson LM, Mortenson DE, Yun HG, Horne WS, Ketas TJ, Lu M, Moore JP, Gellman SH (2012) J Am Chem Soc 134:7317
10. Kritzer JA, Lear JD, Hodsdon ME, Schepartz A (2004) J Am Chem Soc 126:9468
11. Robinson J (2008) Acc Chem Res 41:278
12. Azzarito V, Prabhakaran P, Bartlett AI, Murphy NS, Hardie MJ, Kilner CA, Edwards TA, Warriner SL, Wilson AJ (2012) Org Biomol Chem 10:6469
13. Sopkova-de Oliveira Santos J, Voisin-Chiret AS, Burzicki G, Sebaoun L, Sebban M, Lohier JF, Legay R, Oulyadi H, Bureau R, Rault S (2012) J Chem Inf Model 52:429
14. Gomes CP, Metz A, Bats JW, Gohlke H, Göbel MW (2012) Eur J Org Chem 3270
15. Williams AB, Hanson RN (2012) Tetrahedron 68:5406
16. Thompson S, Vallinayagam R, Adler MJ, Scott RTW, Hamilton AD (2012) Tetrahedron 68:4501
17. Reuter C, Huy P, Neudoerfl JM, Kuehne R, Schmalz HG (2011) Chem Eur J 17:12037
18. Ehlers I, Maity P, Aubé J, König B (2011) Eur J Org Chem 2474
19. Lee TK, Ahn JM (2011) ACS Comb Sci 13:107
20. Lee JH, Zhang Q, Jo S, Chai SC, Oh M, Im W, Lu H, Lim HS (2011) J Am Chem Soc 133:676
21. Restorp P, Rebek J Jr (2008) Bioorg Med Chem Lett 18:5909
22. Moisan L, Odermatt S, Gombosuren N, Carella A, Rebek Jr J (2008) Eur J Org Chem 1673
23. Che Y, Brooks BR, Marshall GR (2007) Biopolymers 86:288
24. Oguri H, Tanabe S, Oomura A, Umetsu M, Hirama M (2006) Tetrahedron Lett 47:5801
25. Antuch W, Menon S, Chen QZ, Lu Y, Sakamuri S, Beck B, Schauer-Vukasinovic V, Agarwal S, Hess S, Dömling A (2006) Bioorg Med Chem Lett 16:1740
26. Jacoby E (2002) Bioorg Med Chem Lett 12:891
27. Horwell DC, Howson W, Ratcliffe GS, Willems HMG (1996) Bioorg Med Chem 4:33
28. Moon H, Lim H (2015) Curr Opin Chem Biol 24:38
29. Jayatunga MDP, Thompson S, Hamilton AD (2014) Bioorg Med Chem Lett 24:717
30. Azzarito V, Long K, Murphy NS, Wilson AJ (2013) Nat Chem 5:161
31. Cummings CG, Hamilton AD (2010) Curr Opin Chem Biol 14:341
32. Peters M, Trobe M, Tan H, Kleinweischede R, Breinbauer R (2013) Chem Eur J 19:2442
33. Peters M, Trobe M, Breinbauer R (2013) Chem Eur J 19:2450
34. Trobe M, Peters M, Grimm SH, Breinbauer R (2014) Synlett 25:1202
35. Toumi M, Couty F, Evano G (2007) Angew Chem Int Ed 46:572
36. Djukic B, Poddutoori PK, Dube PA, Seda T, Jenkins HA, Lemaire MT (2009) Inorg Chem 48:6109
37. Martínez RF, Ávalos M, Babiano R, Cintas P, Jiménez JL, Light ME, Palacios JC (2011) Eur J Org Chem 3137
38. Subhas Bose D, Jayalakshmi B (1999) Synthesis 64
39. Beruben D, Marek I, Normant JF, Platzer N (1995) J Org Chem 60:2488
40. Peng W, Blagg BSJ (2006) Org Lett 8:975
41. Davies SG, Pyatt D, Thomson C (1990) J Organomet Chem 387:381
42. Scott JP, Alam M, Bremeyer N, Goodyear A, Lam T, Wilson RD, Zhou G (2011) Org Process Res Dev 15:1116
43. Nicolai S, Erard S, González DF, Waser J (2010) Org Lett 12:384
44. Azzena U, Dettori G, Pireddu R, Pisano L (2004) Tetrahedron 60:1617
45. Rodriguez JM, Ross NT, Katt WP, Deepali D, Lee G, Hamilton AD (2009) ChemMedChem 4:649
46. Nicolaou KC, Yu R, Shi L, Cai Q, Lu M, Heretsch P (2013) Org Lett 15:1994