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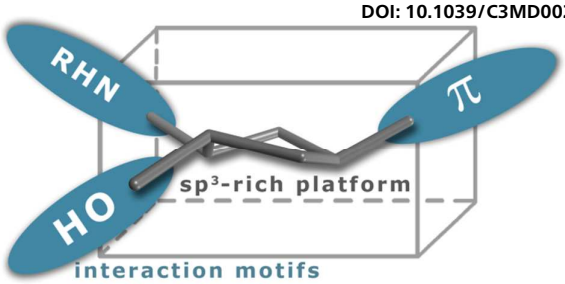
Stereochemically defined cyclopentanole derivatives were utilized as sp^3-rich platforms to prepare a screening library. Interaction motifs are displayed in a threedimensional manner to chart underexplored areas in chemical space.



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ARTICLE

4-Aminocyclopentane-1,3-diols as Platforms for Diversity: Synthesis of a Screening Library

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V. Zohrabi-Kalantari,[a] F. Wilde,[a] R. Grünert,[a] P. J. Bednarski[a] and A. Link[a]

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Trisubstituted cyclopentanes have a discrete shapely curvature. While the central ring of these compounds is devoid of rotatable bonds, the pseudo rotation of the cyclopentane ring leads to a desirable disruption of planarity. This is favorable for aqueous solubility and enables to address wide-ranging conformational space. The sp^3-rich framework of 4-aminocyclopentane-1,3-diols offers stereochemically defined attachment points for substituents and renders these fragment-like molecules good platforms for molecular diversity. By using an established N-selective polymer-assisted acylation protocol, these scaffolds with natural product-like properties were transformed into a screening library by attachment of substituents in defined positions. Here we describe the synthesis and characterization of these molecular platforms and the use as starting points for the construction of an 80-member library of 4-amidocyclopentane-1,3-diol monoethers. Five of the compounds displayed cytotoxicity in a tumor cell line assay with IC_{50} values in the low micromolar range.

Introduction

Introducing diversity into defined positions of nitrogen containing heterocycles such as quinolones, quinazolinones or pyrroles is a dominant concept for the generation of molecular diversity [1]. While existing combinatorial libraries of biologically active compounds based on this perception have proven the suitability of these core scaffolds, the chemical space addressable by the continuous use of these most commonly deployed heterocycles is limited [2]. Compared to the wealth of diversity of natural products, the coverage of conformational space is small and the planarity associated with aromaticity often leads to good crystallization properties and thus poor water solubility of library members [3]. According to Hert et al. nearly 80% of the ring scaffolds present in natural products are absent in commercially available screening compounds [4], most likely due to their limited synthetic accessibility. Moreover, a thorough analysis by Walters et al. revealed that the percentage of sp^3 carbons for molecules published in the Journal of Medicinal Chemistry steadily declined between 1995 and 2009 [5].

From this point of view, novel slim and shapely compounds with a high sp^3 to sp^2 ratio are looked-for starting points for the construction of libraries suitable to address new targets [6]. The use of such molecules enables to fill white patches in the chart of synthetically addressed molecular diversity that could hardly be explored using flat heterocyclic ring systems. This seems of considerable interest and has been explicated by Tsukamoto in a well-received commentary, recently [7]. Tsukamoto suggested the repeated selection of easily accessible but analogous compounds during the last decades as a possible reason for stagnation of success in medicinal chemistry per se and for the apparent non-druggability of many novel targets. It is conceivable that many putatively undruggable proteins could be turned into druggable targets by exploring more challenging chemical space [7]. In order to come up with shapely molecules we selected sp^3-rich cyclopentanes as the molecular platforms for a compound collection as we recently suggested [8, 9]. Thus, biologically underrepresented but clinically relevant space should be addressed [10]. While it is expensive and laborious to synthesize singletons for the screening in multi-step sequences, it is straightforward to prepare eight racemic trisubstituted cyclopentanoles, which were meant to display recognition motifs in a spatial arrangement after appropriate modifications via N-acylation using a polymer-assisted synthesis approach [11].

Results and Discussion

Synthesis

Key components for assessing structural diversity in diversity-oriented synthesis (DOS) were recognized by Spring et al. as (1) appendage diversity-variation in structural moieties, around a common core scaffold, (2) functional group diversity-variation in the functional groups introduced into the periphery, (3) stereochemical diversity-variation in the orientation of potential macromolecule-interacting elements and (4) skeletal (scaffold) diversity [12]. With the intention to generate a set of platforms for molecular diversity and subsequently ornament

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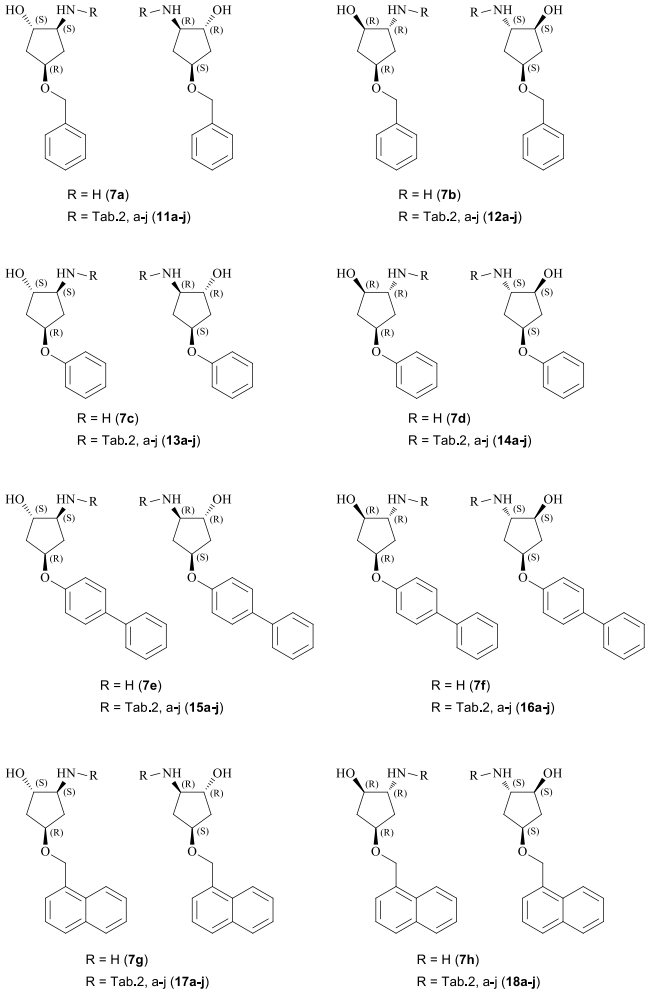
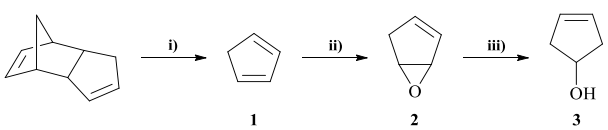
them with a limited set of interaction motifs inspired by these principles, we designed and synthesized eight trisubstituted cyclopentane monoethers, each of which were obtained as racemate (Tab.1).



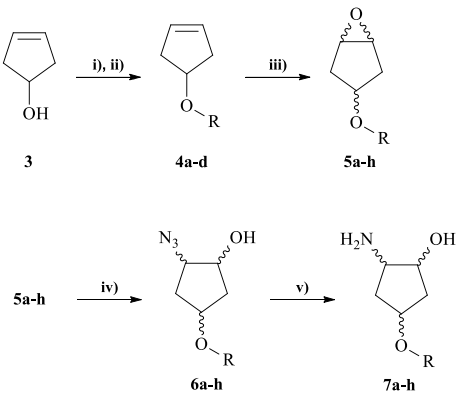
Tab.1: Eight racemic trisubstituted cyclopentanes (template **7a-h**) as building blocks for eighty 4-amidocyclopentane-1,3-diols (**11**–**18(a**–**j)**).

The starting point for the synthesis of the eight amino templates was achiral cyclopentadiene (**1**), which was freshly prepared from commercially available dicyclopentadiene by distillation, as reported [8]. An oxidation reaction with peracetic acid in dichloromethane generated the oxirane intermediate (**2**). It was directly reduced with lithium aluminum hydride to give cyclopent-3-en-1-ol (**3**), which is still achiral due to its internal mirror plane (Scheme 1).



Scheme 1: Synthesis of cyclopent-3-en-1-ol (**3**): **i)** ΔT (in situ distillation); **ii)** CH_2Cl_2, CH_3CO_3H, 19 h, yield: 56%; **iii)** Et_2O, $LiAlH_4$, 3 h, yield: 88%.

The alcohol **3** was reacted with sodium hydride and benzyl chloride to prepare the ether precursor (**4a**) of template **7a** and **7b** (Scheme 2). Because it was envisioned to introduce aryl ether groups to yield templates **7c**–**7f**, we prepared the corresponding cyclopentenol ethers **4b**–**4d** via a different route by the reaction of **3** with tosyl chloride and sodium hydride under reflux in tetrahydrofurane, following a previously reported procedure [13]. Ether **4d** could have been prepared by the same procedure as **4a** but the second procedure gave superior results. All products were purified by column chromatography before being further reacted with meta-chloroperoxybenzoic acid in dichloromethane to give the oxirane precursors (**5**) in moderate to good yields. Since this reaction step naturally forms diastereomers, a purification process via column chromatography was essential. The separated isomers were subsequently processed following a method published by Guan et al. [14]. The corresponding azides (**6**) were prepared in good to high yields by the addition of sodium azide and ammonium chloride in ethanol and water. This method further provided reaction conditions which ensured predomination of the desired S_N2 reaction mechanism. After the oxiranes´ ring opening, the three chirality centers formed resulted in racemic products and this stereoscopic arrangement was retained in the consecutive synthesis steps, which could be confirmed by chiral HPLC and an X-ray crystal structure (Fig.1) [9]. For the synthesis of the desired templates **7a**–**h**, a selective reduction of the introduced azido group to an amino function was aspired, without effecting the benzylic moiety present in **6a** and **6b**. This could be achieved with a method reported by Moreno-Vargas et al. [15] using lithium aluminum hydride as a mild reducing agent. The reaction proceeded nearly quantitatively within three hours. In-process control was realized by means of thin layer chromatography and IR spectroscopy, in which the fading absorption band of the azido group was detected.



Scheme 2: Synthesis of trisubstituted cyclopentane templates **7** as separated racemates with R = benzyl (**a**, **b**), phenyl (**c**, **d**), biphenyl (**e**, **f**) and 1-naphthylmethyl (**g**, **h**). **i)** synthesis of **4a**: NaH, BnCl, 10 h, yield: 83%; **ii)** synthesis of **4b**–**4d**: THF, appropriate phenol or alcohol (**b**: phenol, **c**: 4-phenylphenol **d**: 1-naphthylmethanol), 30 min reflux, NaH, 1 h reflux, cyclopent-3-en-1-yl 4-methylbenzenesulfonate, 28 h reflux, yields: 40–54%; **iii)** CH_2Cl_2, meta-chloroperoxybenzoic acid, 4 h rt, 2–17 h reflux, yields: 30–89%; **iv)** NaN_3, NH_4Cl, EtOH, 12 h reflux, yields: 67–98%; **v)** $LiAlH_4$, THF, : 75–96%.

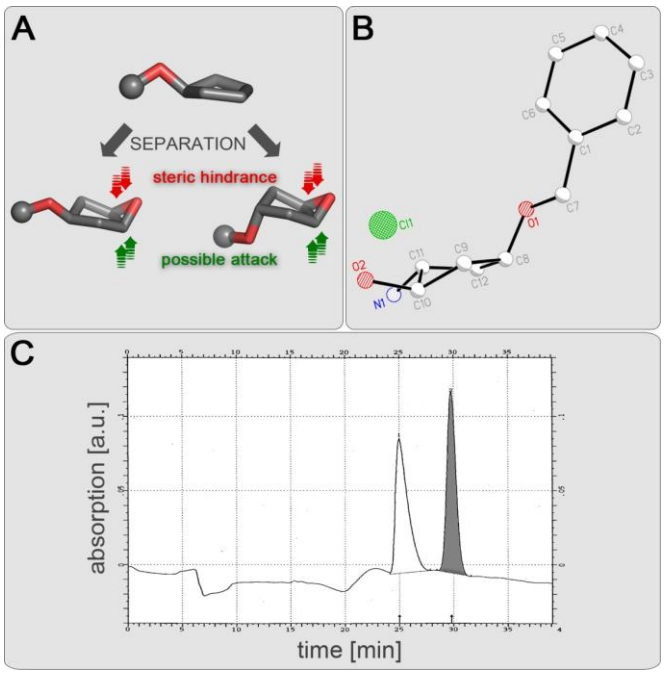
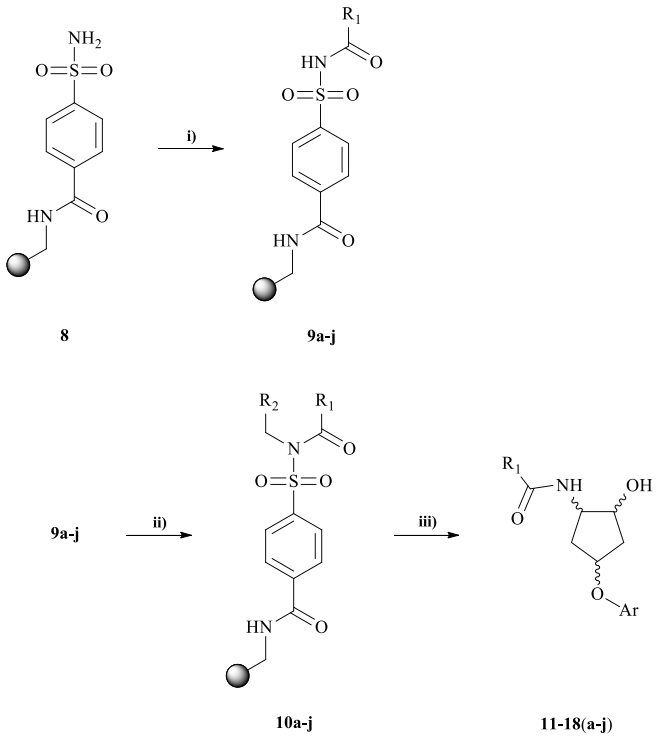


Fig.1: Assessment of the *trans*-substitution pattern between the hydroxyl- and amino group: **A)** separation of synthesized oxiranes leads to *cis*/*trans* isomers with only one possible side for attack by nucleophiles; **B)** X-ray crystal structure of compound **7b** as hydrochloride shows *trans*-positioning of N1 and O2; **C)** chiral HPLC of compound **14c**, (Chiracel® OD-H column), Area (%) = 50.327 (Peak 1, left and white)/ 49.673 (Peak 2, right and grey), separation due to complex stability (0-26.47 min 90:10 hexane/isopropanol-linear, in 10 min from 90:10 to 70:30-isocratically, 70:30 hexane/isopropanol).

Based on the eight racemic templates **7a**–**7h** we synthesized a 80-member library of 4-amido substituted cyclopentane-1,3-diol monoesters. To add potential macromolecule-interacting elements in a rapid manner, we applied a parallel synthetic approach using polymer-bound acylation reagents, based on Kenner's safety-catch linker [16]. Use and limitations of this linker in the related field of carbohydrate synthesis were recently explored by the group of Seeberger [17]. While the N-selective introduction of such diversity elements using this approach is straightforward, the functional group diversity achievable via this route is limited. Neither nucleophilic functions that could attack the activated linker construct nor functional groups that are prone to become alkylated during the linker activation step are compatible with this approach. Here we accepted these severe limitations in order to be able to synthesize a library of pure test candidates in a parallel fashion from a limited amount of valuable scaffold material. The advantage of this concept is the known N-selectivity that avoids formation of unwanted esters. Using this approach, complete transformation of the templae could be achieved. By-products with double acylation, O-acylation or unreacted starting material were not detected in the products and the excess of acylating reagent could easily be removed by filtration. Classical derivatization in solution would clearly offer a much broader array of possible functional groups in the periphery of the final compounds if the cyclopentanolamine templates **7a**–**h** would be available on a larger scale. The notoriously slow connection of a carboxylic acid functionality to the linker [17] was brought about by the use of *N*,*N*′-diisopropylcarbodiimid (DIC) (Scheme 3, Tab.2). The resulting polymer bound intermediates **9a**–**j** were activated with bromoacetonitrile or using *N*,*N*′-diisopropyl-*O*-2,3,4,5,6-pentafluorobenzyl-isourea, respectively. Due to the electron withdrawing cyanomethyl or pentafluorobenzyl moiety the nucleophilic attack on the anchor compound was facilitated and the acyl group was readily transferred to the amino function of **7a**–**h** N-selectively to give the target carboxamides **11**–**18**(**a**–**j**). Neither of these activating reagents is optimal. While the *O*-alkyl-isourea is easier to handle and cheaper, the reactivity of the *N*-acyl-*N*-alkylsulfonamides bearing a cyanomethyl residue is more pronounced [18]. All products were purified by medium pressure liquid chromatography (MPLC) on solid phase extraction (SEP) cartridges to remove particulates from the polymeric material because such impurities would be invisible in HPLC analyses but severely hamper biological evaluations. The subsequent analysis by HPLC revealed only two compounds with less than 80% purity and one compound with less than 85% purity. Therefore, the synthesized products were consistent with the quality standard for parallel synthetic compound libraries and were suitable for biological evaluation at this point already. To prevent decomposition processes of the amine group for the time of storage, we formulated the corresponding hydrochlorides of the final products, which usually and presumably here as well leads to a further purification by crystallization.



Scheme 3: Reaction of Kenner's safety-catch linker **i)** loading by *N*,*N*′-diisopropylcarbodiimid (DIC) activated carboxylic acids; for R_1 see table 2 **ii)** activation with bromoacetonitrile (R_2 = CN) or *N*,*N*′-diisopropyl-*O*-2,3,4,5,6-pentafluorobenzyl-isourea (R_2 = pentafluorophenyl); **iii)** nucleophilic attack by racemic amino templates **7a**–**h** gave target carboxamides **11**–**18**(**a**–**j**) as racemates.

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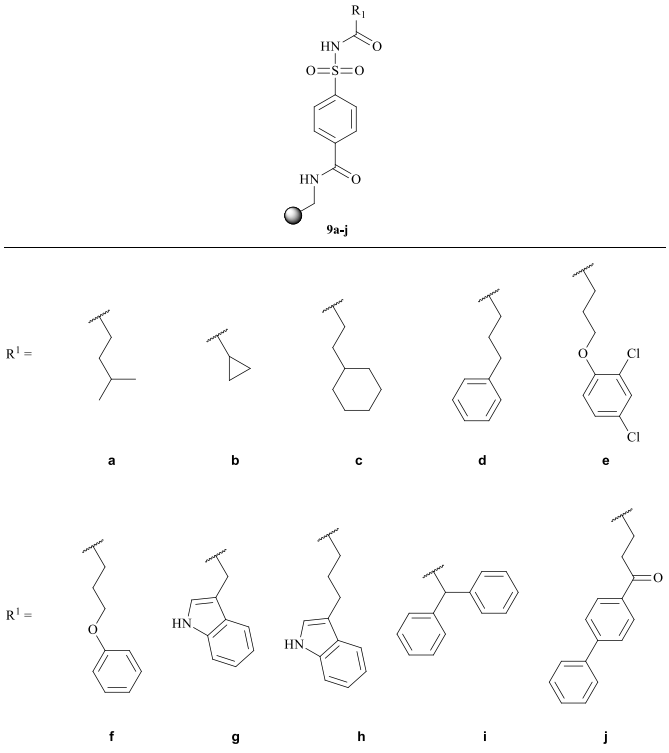

Tab.2: Compilation of carboxylic acid residues used to introduce structural and functional diversity in the 4-amidocyclopentane-1,3-diol products.

Biological evaluation

Compounds **11a-d**,**f**,**h**,**j**, **12a-j**, **13a-j**, **14a-c**,**f**,**g**,**i**,**j**, **15b-h**,**j**, **16d-i**, **17a**,**c**,**d**,**f-j**, **18a-c**,**e-j** were investigated as antiprotozoal drugs. None of them displayed noteworthy activity with respect to size and lipophilicity (lipophilic efficiency LiPE[19], data not shown). Thus, 15 representative compounds **11f**,**j**, **12f**,**j**, **13c**,**i**, **14c**,**h**,**i**, **15h**,**i**,**j**, **16i**, **18c**,**i** were tested for in vitro anti-tumor activity, only five of which showed marked antiproliferative activity and are listed in Table 3. The test system consisted of four human tumor cell lines derived from four kinds of cancer: urinary bladder carcinoma (5637), breast adenocarcinoma (MCF-7), pancreas carcinoma (DAN-G) and large cell lung carcinoma (LCLC-103H). The tumor cell lines were selected with a view to diverse tissue exposure and in-house availability. For each cell line the half maximal growth inhibitory concentration (IC_{50}) was determined. The results were compared to established anticancer drugs. Some of the synthesized products were found to be active in single digit micromolar range and thus even exceeded the potency of some of the reference substances (Table 3). Compound **15i** and **16i** as well as **11j** and **12j** are closely related stereo isomers with activities in the same order of magnitude. Together with **15h** the former compounds share a bulky biphenyl moiety. The replacement of the biphenyl ether with a benzyl ether in C4-position as well as the substitution at the carboxamide functionality with a moiety derived from the drug fenbufen (**15i**/**16i** → **11j**/**12j**) clearly results in a drop of activity. For more precise structure-activity information a broader set of compounds will need to be synthesized and investigated for cytotoxicity. Because the molecules presented here were prepared in an efficient and modular manner, analogous compounds can be obtained easily in larger amounts and focused libraries with a higher degree of functional diversity around the active structures can be generated expediently.

	5637 µM	MCF-7 µM	DAN-G µM	LCLC- µM
11j	>20	16.0±1.29	>20	>20
12j	20.4±3.52	14.2±3.02	>20	>20
15h	11.9±1.65	6.76±0.65	12.8±0.36	13.6±0.21
15i	12.2±1.65	8.91±1.23	13.0±0.57	12.3±1.26
16i	12.5[a]	10.3[a]	17.5[a]	13.1[a]
Chlo	6.55±3.46[b]	18.4±5.5[b]	27.8±5.0[b]	14.5±7.1[b]
Melp	1.32±0.14[b]	3.71±1.19	2.65±1.02[b]	4.00±0.42
Carb	4.34±1.70[b]	29.4±9.8[b]	12.79±6.81[b]	14.59±5.67

Table 3: IC_{50} values (µM ± SD) of antiproliferative activities of the most potent compounds compared to established anti-tumor drugs after a 96 h exposure; Chlo = Chlorambucil, Melp = Melphalan, Carb = Carboplatin; Values are averages of 3–4 independent experiments, a) n = 1; b) from reference [20].

Conclusions

Diversity-oriented synthesis strategies opposed to target oriented programs aim to generate molecular libraries with diversity based e.g. on sp^3-rich scaffolds and stereochemical complexity because biological macromolecules interact with each other in three-dimensional surroundings. The resulting high degree of structural and functional diversity is a prerequisite for cross-examination of previously 'un-tapped' regions of bioactive chemical space [21]. The new molecular entities of the small library of compounds presented in this study can thus serve as tools for the investigation of unresolved issues in various fields of molecular biology. Some of the novel compounds were found to have potent antiproliferative activities, demonstrating that the cyclopentane based spatial display of interaction motifs can lead to biologically active compounds. In addition, we performed the synthesis of the small, hydrophilic, and fragment-like new scaffolds, successfully. These scaffolds are devoid of rotatable bonds and offer stereochemically defined attachment points for diverse substituents. Thus, these platforms are suitable starting points for the diversity-oriented construction of combinatorial libraries of 4-amidocyclopentane-1,3-diols or for the synthesis of arrays of other cyclopentanoid natural products with high structural and functional diversity as could be illustrated by this study.

Experimental

General

Thin layer chromatography for reaction control was performed with ALUGRAM SIL G/UV254 silica gel plates from Macherey-Nagel (silica gel on aluminum sheets, layer thickness 0.20 mm). Melting points were recorded on a MEL-Temp Laboratory Device. The refractive index was measured on a Carl Zeiss Abbé refractometer at 20 °C. The yields of all parallel synthetic approaches were calculated via conversion rates, specifying the percentage of the product area to the total area of all peaks. All other yields correlate to the actual product quantity compared to the theoretical maximum. Silica gel 60, 0.05–0.1 mm, 270–140 mesh from Macherey-Nagel was used

for column chromatography. Medium pressure liquid chromatography was done with a Büchi pump device C-681, a Büchi UV/Vis-filter photometer at 254 nm and Merck Lobar-LiChroprep®-RP-18 columns (size A, B). The specified purities were determined by the 100% method of the DAD chromatogram at wavelengths as indicated. Nuclear magnetic resonance (NMR) spectra were recorded using a Jeol Eclipse + 500 (^{1}H: 500 MHz, ^{13}C: 126 MHz) at 25 °C with tetramethylsilane (TMS) as internal standard, using ppm scale. High resolution mass spectra (HRMS) were obtained after high performance liquid chromatography (HPLC) with a mass spectrometer AutoSpec M from Micromass, current loop probe supply, positive ionization, flow = 10 µl/min. Infrared (IR) spectra were recorded on a Nicolet 510P FT-IR spectrometer as KBr blanks or as a film on a NaCl window. Elemental analysis was determined using a CH-Analyzer according to Dr. Salzer from Labormatic/Wösthoff and a CHN-Autoanalyzer 185 from Hewlett-Packard.

Characterization of compounds

3,4-Epoxycyclopenten (2). A solution of 40 g (0.60 mol) cyclopentadiene and 258 g sodium carbonate in 666 ml dichloromethane was cooled. Then 112 g peracetic acid (40%) in sodium acetate were added drop wise. The reaction mixture was stirred at room temperature, in-process control was done by potassium iodide starch paper. A negative test (no violet coloring) indicated a quantitative reaction after 19 h. The reaction mixture was reduced in vacuo, washed with dichloromethane and residual solvent was removed by distillation (50 °C). A final vacuum distillation (13 mbar) gave the product as yellow oil. Yield: 56% (28.0 g); IR (cm^{-1}): 3047, 2909, 1749, 913, 828, 813; no further analysis, but instant reaction to form the appropriate stable product.

Cyclopent-3-en-1-ol (3). To an ice cooled suspension containing 7.0 g (0.18 mol) lithium aluminum hydride in dry ether 27.5 g (0.33 mol) 3,4-epoxycyclopentene were added drop wise and stirred for 3 h. Then careful addition of water inactivates the reaction mixture successively, which is dried over sodium sulfate and washed with ether. A final vacuum distillation (71 °C, 61 mbar) gave the product. Yield: 88% (24.8 g); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 5.64 (m, 2H), 4.56 (d, 1H), 4.34 (m, 1H), 2.48 (dd, 2H, *J* = 6.6/15.1 Hz), 2.14 (dd, 2H, *J* = 2.9/15.4 Hz); IR (cm^{-1}): 3334, 1430, 1047, 951; refractive index: 1.4431.

[(Cyclopent-3-en-1-yloxy)methyl]benzene (4a). In a three-necked flask 45 ml dry toluene and 12.0 g (0.28 mol) sodium hydride (60% suspension in oil) stirred under exclusion of moisture influences while cooling. After extensive flushing with nitrogen 18.0 g (0.21 mol) cyclopent-3-en-1-ol in toluene were added over a dropping funnel during 1 h. As no more gas evolved, a solution of 28.6 ml (0.25 mol) benzyl chloride in toluene was added drop wise and the reaction mixture refluxed over night, upon which the reaction mixture turned brownish. The excess of sodium hydride was inactivated by careful addition of methanol in toluene. The mixture was filtered, the organic phase (red color) washed with water, dried over sodium sulfate and evaporated in vacuo. A final vacuum distillation (160 °C, 11 mbar) gave the colorless, liquid product. Yield: 83% (30.0 g); IR (cm^{-1}): 1615, 1096, 1072, 734, 697.

Cyclopent-3-en-1-yl 4-methylbenzenesulfonate. To 8.0 g (96 mmol) cyclopent-3-en-1-ol (**3**) were added 100.0 ml pyridine and while cooling 22.4 g (0.11 mol) tosyl chloride The suspension turned green and after stirring for 2 h the reaction mixture was stored for 12 h at 8 °C, upon which it turned red. The suspension was poured onto 160 g ice and 48.0 ml concentrated hydrochloric acid and stirred for 30 min. The resulting residue was filtered and dried under reduced pressure. Yield: 89% (20.3 g); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 7.79 (d, 2H), 7.48 (d, 2H), 5.68 (s, 2H), 5.12 (m, 1H), 2.60 (dd, 2H, *J* = 6.2/17.2), 2.42 (s, 3H), 2.36 (d, 2H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 145.34, 134.16, 130.75, 128.26, 128.02, 82.77, 42.75, 21.01; IR (cm^{-1}): 1355, 1172, 934, 745, 679, 571; mp: 47-49 °C.

General procedure for the synthesis of cyclopentenyl ethers (procedure A) [13]. To a freshly dried solution of THF 21.0 mmol of the appropriate alcohol were added and then heated to reflux for 30 min. After cooling to room temperature 2.0 equivalents sodium hydride were added while cooling. As no more gas evolved, the mixture was heated to reflux for an additional hour, after which 5.0 g (21.0 mmol) cyclopent-3-en-1-yl 4-methylbenzenesulfonate were added. After 28 h, indicated by thin layer chromatography, the solvent was removed and dichloromethane and 2.0 mol/l sodium hydroxide solution were added. The organic phase was washed twice with 2.0 mol/l sodium hydroxide solution and saturated sodium hydroxide solution, then dried over sodium sulfate and concentrated in vacuo. The resulting residue was purified by column chromatography with hexane/ethyl acetate (7:3).

Cyclopent-3-enyloxy-benzene (4b) was prepared following the general procedure A using 1.97 g (21.0 mmol) phenol, 2.0 equivalents (1.01 g) sodium hydride and 5.0 g (21.0 mmol) cyclopent-3-en-1-yl 4-methylbenzenesulfonate. Product was obtained as oil. Yield: 54% (1.8 g); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 7.27 (m, 2H), 6.89 (m, 3H), 5.74 (s, 2H), 5.04 (s, 2H), 2.78 (dd, 2H, *J* = 6.6/16.3), 2.38 (m, 2H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 157.22, 129.91, 128.84, 120.67, 115.57, 76.11; IR (cm^{-1}): 1599, 1242, 753, 692; refractive index: 1.5438.

4-(Cyclopent-3-enyloxy)-biphenyl (4c) was prepared following the general procedure A using 3.59 g (21.0 mmol) 4-phenylphenol, 2.0 equivalents (1.01 g) sodium hydride and 5.0 g (21.0 mmol) cyclopent-3-en-1-yl 4-methylbenzene-sulfonate. Product was recrystallized from methanol/ethyl acetate to give a colorless solid. Yield: 40% (2.0 g); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 7.59 (m, 4H), 7.42 (m, 2H), 7.30 (m, 1H), 6.98 (m, 2H), 5.76 (s, 2H), 5.10 (m, 1H), 2.82 (dd, 2H, *J* = 6.6/16.3), 2.42 (d, 2H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 156.89, 139.78, 132.27, 128.77, 128.36, 127.71, 126.58, 126.06, 115.55, 75.90; IR (cm^{-1}): 2936, 1489, 1201, 832, 760; mp: 109-111 °C; no further analysis, but instant reaction to form the appropriate stable product.

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1-(Cyclopent-3-enyloxymethyl)-naphthalen (4d) was prepared following the general procedure A using 3.3 g (21.0 mmol) 1-naphthylmethanol, 2.0 equivalents (1.0 g) sodium hydride and 5.0 g (21.0 mmol) cyclopent-3-en-1-yl 4-methylbenzenesulfonate. Product was obtained as yellow oil. Yield: 48% (2.2 g); purity: 97% (254 nm); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 8.06 (d, 1H), 7.93 (m, 1H), 7.86 (d, 1H), 7.52 (m, 4H), 5.69 (s, 2H), 4.89 (s, 2H), 4.37 (m, 1H), 2.57 (m, 2H), 2.39 (m, 2H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 134.85, 133.82, 131.80, 128.97, 128.91, 128.62, 126.66, 126.58, 126.29, 125.86, 124.54, 78.91, 68.86, 39.53; IR (cm^{-1}): 2909, 1104, 1088, 791, 775; HRMS (ESI, *m/z*): [M+Na]$^+$ calc.: 247.1098, found: 247.1134; refractive index: 1.6012.

General procedure for the synthesis of cyclopentanyl oxiranes (procedure B). To an ice cold and nitrogen flushed solution of 0.17 mol of the appropriate cyclopentenyl ether in 85.0 ml dichloromethane were added drop wise 0.24 mol meta-chloroperoxybenzoic acid in 350 ml dichloromethane over a period of 2 h. The reaction mixture was stirred for 4 h at room temperature and then refluxed, while in-process control was accomplished by thin layer chromatography. After quantitative reaction was indicated, the resulting residue was washed twice with 150 ml sodium sulfite solution (10%) and sodium sulfate solution (10%). The organic phase was dried over sodium sulfate and concentrated under reduced pressure. The resulting mixture of diastereomers was purified by column chromatography over silica gel (5.5 × 54 cm) with hexane/ethyl acetate (7:3).

(1*R*,3*r*,5*S*)-3-(Benzyloxy)-6-oxabicyclo[3.1.0]hexane (5a) was prepared following the general procedure B using 30.0 g (0.17 mol) **4a** and 43.0 g (0.24 mol) meta-chloroperoxybenzoic acid, quantitative reaction was indicated after 120 min. Column chromatography gave trans isomer in the early fractions as colorless oil. Yield: overall 30% (10.0 g, thereof 6.0 g trans isomer); purity: 74% (254 nm); ^{1}H-NMR (500 MHz, [D6]-DMSO) = δ (ppm) 7.30 (m, 5H), 4.39 (s, 2H), 3.73 (m, 1H), 3.49 (m, 2H), 2.40-2.36 (dd, 2H, *J* = 7.1/14.2), 1.62-1.57(dd, 2H, *J* = 6.9/14.2); ^{13}C-NMR (126 MHz, [D6]-DMSO) = δ (ppm) 139.06, 128.74, 128.12, 127.94, 75.79, 71.32, 55.44, 34.44; IR (cm^{-1}): 1740, 1241, 1113, 836, 738; HRMS (ESI, *m/z*): [M+Na]$^+$ calc.: 213.0891, found: 213.0908; refractive index: 1.5258.

(1*R*,3*s*,5*S*)-3-(Benzyloxy)-6-oxabicyclo[3.1.0]hexane (5b) was prepared following the procedure for **5a**. The cis isomer came after the trans isomer and gave a colorless oil. Yield: overall 30% (10.0 g, thereof 4.0 g cis isomer), purity: 94% (254 nm); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 7.30 (m, 5H), 4.34 (s, 2H), 4.07 (m, 1H), 3.46 (m, 2H), 1.99 (s, 4H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 139.38, 128.68, 127.97, 127.73, 78.64, 70.39, 57.55, 35.15; IR (cm^{-1}): 1737, 1242, 1097, 839, 737; HRMS (ESI, *m/z*): [M+Na]$^+$ calc.: 213.0891, found: 213.0901; refractive index: 1.5360.

(1*R*,3*r*,5*S*)-3-Phenoxy-6-oxabicyclo[3.1.0]hexane (5c) was prepared following the general procedure B using 2.5 g (15 mmol) **4b** and 3.9 g (22 mmol) meta-chloroperoxybenzoic acid, quantitative reaction was indicated after 10 h. Column chromatography gave trans isomer in the early fractions as colorless solid. Yield: overall 68% (1.8 g, thereof 1.1 g trans isomer); purity: 99% (254 nm); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 7.26 (m, 2H), 6.89 (m, 3H), 4.49 (m, 1H), 3.59 (s, 2H), 2.62 (dd, 2H, *J* = 7.3/14.4), 1.74 (dd, 2H, *J* = 6.4/14.4); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 158.10, 130.09, 121.17, 115.74, 74.79, 55.74, 34.73; IR (cm^{-1}): 1493, 1243, 1083, 837, 751; HRMS (ESI, *m/z*): [M+Na]$^+$ calc.: 199.0734, found: 199.0734; mp: 33-34 °C.

(1*R*,3*s*,5*S*)-3-Phenoxy-6-oxabicyclo[3.1.0]hexane (5d) was prepared following the procedure for **5c**. The cis isomer came after the trans isomer and gave a yellow solid. Yield: overall 68% (1.8 g, thereof 0.7 g cis isomer); purity: 97% (254 nm); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 7.25 (m, 2H), 6.88 (m, 1H), 6.79 (m, 2H), 4.86 (m, 1H), 3.53 (s, 2H), 2.29 (d, 2H, *J* = 7.6 Hz), 2.01 (d, 2H, *J* = 15.6 Hz); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 157.97, 130.01, 120.67, 115.62, 76.43, 57.61, 35.46; IR (cm^{-1}): 1491, 1234, 1076, 840, 759; HRMS (ESI, *m/z*): [M+Na]$^+$ calc.: 199.0734, found: 199.0745; mp: 63-64 °C.

(1*R*,3*r*,5*S*)-3-([1,1′-Biphenyl]-4-yloxy)-6-oxabicyclo[3.1.0]hexane (5e) was prepared following the general procedure B using 2.0 g (8.0 mmol) **4c** and 2.2 g (12.0 mmol) meta-chloroperoxybenzoic acid, quantitative reaction was indicated after 13 h. Column chromatography gave trans isomer in the early fractions as colorless solid. Yield: overall 89% (1.9 g, thereof 1.3 g trans isomer); purity: 82% (254 nm); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 7.58 (m, 4H), 7.42 (m, 2H), 7.30 (m, 1H), 6.98 (m, 2H), 4.55 (m, 1H), 3.61 (s, 2H), 2.67-2.63 (dd, 2H, *J* = 7.3/14.4), 1.79-1.75(dd, 2H, *J* = 6.2/14.2); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 157.11, 139.71, 132.63, 128.78, 127.74, 126.65, 126.09, 115.57, 74.40, 55.13, 34.00; IR (cm^{-1}): 1488, 1201, 1117, 831, 684; Analysis calc.: C, 80.93; H, 6.39, found: C, 80.67; H, 6.32; mp: 144-145 °C.

(1*R*,3s,5*S*)-3-([1,1′-Biphenyl]-4-yloxy)-6-oxabicyclo[3.1.0]hexane (5f) was prepared following the procedure for **5e**. The cis isomer came after the trans isomer and gave a colorless solid. Yield: overall 89% (1.9 g, thereof 0.6 g trans isomer); purity: 80% (254 nm); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 7.58 (m, 4H), 7.42 (m, 2H), 7.29 (m, 1H), 6.89 (m, 2H), 4.92 (m, 1H), 3.56 (s, 2H), 2.30-2.25 (m, 2H), 2.05 (d, 2H, *J* = 15.6 Hz)); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 157.00, 139.77, 132.09, 128.77, 127.65, 126.57, 126.04, 115.44, 76.05, 56.99, 34.86; IR (cm^{-1}): 1491, 1249, 1077, 833, 764; Analysis calc.: C, 80.93; H, 6.39, found: C, 80.75; H, 6.29; mp: 164-165 °C.

(1*R*,3*r*,5*S*)-3-(Naphthalen-1-ylmethoxy)-6-oxabicyclo[3.1.0]hexane (5g) was prepared following the general procedure B using 2.3 g (10.0 mmol) **4d** and 2.5 g (14.0 mmol) meta-chloroperoxybenzoic acid, quantitative reaction was indicated after 17 h. Column chromatography gave trans isomer in the early fractions as oil. Yield: overall 75% (1.8 g, thereof 1.1 g trans isomer); purity: 89% (254 nm); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 8.05 (d, 1H, *J* =

8.3 Hz), 7.92 (m, 1H), 7.87 (d, 1H, *J* = 8.0 Hz), 7.54 (m, 3H), 7.46 (m, 1H), 4.84 (s, 2H), 3.84 (m, 1H), 3.49 (s, 2H), 2.42-2.38 (dd, 2H, *J* = 7.1/14.0), 1.63-1.59 (dd, 2H, *J* = 7.1/14.0); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 134.59, 133.80, 131.79, 128.91, 128.80, 126.81, 126.73, 126.35, 125.86, 124.57, 76.03, 69.84, 55.46, 34.43; IR (cm^{-1}): 1511, 1106, 832, 647; HRMS (ESI, *m/z*): [M+Na]$^+$ calc.: 263.1048, found: 263.1067.

(1*R*,3s,5*S*)-3-(Naphthalen-1-ylmethoxy)-6-oxabicyclo[3.1.0]hexane (5h) was prepared following the procedure for **5g**. The cis isomer came after the trans isomer and gave an oil. Yield: overall 75% (1.8 g, thereof 0.7 g cis isomer); purity: 97% (254 nm); NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 8.05 (m, 1H), 7.92 (m, 1H), 7.85 (d, 1H, *J* = 8.0 Hz), 7.53 (m, 4H), 4.78 (s, 2H), 4.18 (m, 1H), 3.47 (s, 2H), 2.03 (m, 4H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 134.21, 133.16, 131.15, 128.24, 127.94, 125.99, 125.68, 125.23, 124.05, 78.15, 68.35, 56.93, 34.50; IR (cm^{-1}): 1510, 1239, 1093, 841, 775; HRMS (ESI, *m/z*): [M+Na]$^+$ calc.: 263.1048, found: 263.1076; refractive index: 1.6050.

General procedure for the introduction of an azido group (procedure C) [14]. A solution of 20.0 mmol of the appropriate oxirane, 196 ml ethanol, 39.0 ml water, 4.1 g (60.0 mmol) sodium azide and 3.4 g ammonium chloride were heated to reflux for 12 h. After addition of water, the reaction mixture was extracted several times with ether, which was then washed with a saturated solution of sodium chloride, dried over soidum sulfate and concentrated under reduced pressure. The resiude was purified by column chromatography over silica gel (3.5 × 33.5 cm) with hexane/ethyl acetate (7:3).

(1*R*,2*R*,4*R*)-2-Azido-4-(benzyloxy)cyclopentanol (6a) was prepared following the general procedure C using 4.0 g (20.0 mmol) **5a**. The product was obtained as yellow oil. Yield: 77% (3.6 g); purity: 83% (254 nm); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 7.31 (m, 5H), 5.21 (d, 1H, *J* = 5.8 Hz), 4.40 (s, 2H), 4.02 (m, 2H), 3.64 (m, 1H), 2.37 (m, 1H), 1.93 (m, 1H), 1.74 (m, 1H), 1.56 (m, 1H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 139.13, 128.73, 128.10, 127.88, 75.49, 75.27, 70.44, 67.07, 39.64; IR (cm^{-1}): 3421, 2104, 698; refractive index: 1.5384.

(1*S*,2*S*,4*R*)-2-Azido-4-(benzyloxy)cyclopentanol (6b) was prepared following the general procedure C using 3.5 g (18.0 mmol) **5b**, 3.7 g (50.0 mmol) sodium azide and 3.1 g ammonium chloride. The product was obtained as yellow oil. Yield: 67% (2.8 g); purity: 95% (254 nm); ^{1}H-NMR 500 MHz, [D$_6$]-DMSO) = δ (ppm) 7.32 (m, 5H), 5.29 (d, 1H, *J* = 5.3 Hz), 4.40 (s, 2H), 3.93 (m, 1H), 3.86-3.76 (m, 2H), 2.32 (m, 1H), 2.04 (m, 1H), 1.71 (m, 1H), 1.54 (m, 1H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 139.13, 128.73, 128.10, 127.88, 75.49, 75.27, 70.44, 67.07, 39.64; IR (cm^{-1}): 3408, 2104, 699; refractive index: 1.5456.

(1*R*,2*R*,4*R*)-2-Azido-4-phenoxycyclopentanol (6c) was prepared following the general procedure C using 1.1 g (6.0 mmol) **5c**, 1.2 g (20.0 mmol) sodium azide and 1.0 g ammonium chloride. The product was obtained as yellow oil. Yield: 97% (1.3 g); purity: 100% (254 nm); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 7.27 (m, 2H), 6.88 (m, 3H), 5.32 (d, 1H, *J* = 4.8 Hz), 4.82 (m, 1H), 4.09 (m, 1H), 3.74 (m, 1H), 2.59 (m, 1H), 1.99 (m, 2H), 1.61 (m, 1H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 157.08, 129.45, 120.43, 115.20, 74.74, 74.16, 66.29, 35.33; IR (cm^{-1}): 3388, 2104, 755; HRMS (ESI, *m/z*): [M+H$_2$O]$^+$ calc.: 237.1113, found: 237.1116; refractive index: 1.5538.

(1*S*,2*S*,4*R*)-2-Azido-4-phenoxycyclopentanol (6d) was prepared following the general procedure C using 0.6 g (3.0 mmol) **5d**, 0.7 g (10.0 mmol) sodium azide and 0.6 g ammonium chloride. The product was obtained as yellow oil. Yield: 88% (0.7 g); purity: 93% (254 nm); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 7.26 (m, 2H), 6.89 (m, 3H), 5.35 (d, 1H, *J* = 5.3 Hz), 4.73 (m, 1H), 3.90 (m, 2H), 2.52 (m, 1H), 2.07 (m, 1H), 1.95 (m, 1H), 1.58 (m, 1H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 157.11, 129.44, 120.40, 115.16, 74.61, 73.27, 66.26, 35.12; IR (cm^{-1}): 3397, 2105, 755; HRMS (ESI, *m/z*): [M+Na]$^+$ calc.: 242.0905, found: 242.0847; refractive index: 1.5564.

(1*R*,2*R*,4*R*)-4-([1,1′-Biphenyl]-4-yloxy)-2-azidocyclopentanol (6e) was prepared following the general procedure C using 1.1 g (4.0 mmol) **5e**, 0.9 g (14.0 mmol) sodium azide and 0.7 g ammonium chloride. The product was obtained as colorless solid. Yield: 98% (1.3 g); purity: 83% (254 nm); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 7.59 (m, 4H), 7.42 (m, 2H), 7.30 (m, 1H), 6.95 (m, 2H), 5.34 (d, 1H, *J* = 5.0 Hz), 4.88 (m, 1H), 4.11 (m, 1H), 3.75 (m, 1H), 2.62 (m, 1H), 2.01 (m, 2H), 1.64 (m, 1H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 156.73, 139.72, 132.51, 128.76, 127.73, 126.62, 126.07, 115.65, 74.74, 74.44, 66.30, 35.35; IR (cm^{-1}): 3300, 2110, 766; Analysis calc.: C, 69.14; H, 5.80, found: C, 69.35; H, 5.99; mp: 99-100 °C.

(1*S*,2*S*,4*R*)-4-([1,1′-Biphenyl]-4-yloxy)-2-azidocyclopentanol (6f) was prepared following the general procedure C using 0.51 g (2.0 mmol) **5f**, 0.4 g (6.0 mmol) sodium azide and 0.3 g ammonium chloride. The product was obtained as colorless solid. Yield: 96% (0.6 g); purity: 100% (254 nm); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 7.59 (m, 4H), 7.43 (m, 2H), 7.30 (m, 1H), 6.96 (m, 2H), 5.37 (d, 1H, *J* = 5.3 Hz), 4.79 (m, 1H), 3.93 (m, 2H), 2.56 (m, 1H), 2.11 (m, 1H), 1.96 (m, 1H), 1.61 (m, 1H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 156.76, 139.72, 132.47, 128.76, 127.71, 126.62, 126.07, 115.63, 74.61, 73.44, 66.27, 35.45; IR (cm^{-1}): 3286, 2105, 761; HRMS (ESI, *m/z*): [M+Na]$^+$ calc.: 318.1218, found: 318.1238; mp: 94-95 °C.

(1*R*,2*R*,4*R*)-2-Azido-4-(naphthalen-1-ylmethoxy)cyclopentanol (6g) was prepared following the general procedure C using 1.0 g (4.0 mmol) **5g**, 0.8 g (12.0 mmol) sodium azide and 0.7 g ammonium chloride. The product was obtained as oil. Yield: 90% (1.1 g); purity: 94% (254 nm); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 8.07 (m, 1H), 7.94 (m, 1H), 7.87 (d, 1H, *J* = 8.3 Hz), 7.54 (m, 4H), 5.23 (d, 1H, *J* = 3.7 Hz), 4.87 (m, 2H), 4.13 (m, 1H), 4.03 (m, 1H), 3.66 (m, 1H), 2.40 (m, 1H), 1.99 (m, 1H), 1.77 (m, 1H), 1.61 (m, 1H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 138.18, 137.35, 135.31, 132.45, 132.24, 130.22, 129.88,

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129.42, 128.09, 80.13, 79.01, 72.58, 70.61, 39.50; IR (cm^{-1}): 3408, 2103, 776; HRMS (ESI, *m/z*): $[M+Na]^+$ calc.: 306.1218, found: 306.1213; refractive index: 1.6010.

(1*S*,2*S*,4*R*)-2-Azido-4-(naphthalen-1-ylmethoxy)cyclopentanol (6h) was prepared following the general procedure C using 0.7 g (3.0 mmol) **5h**, 0.6 g (8.0 mmol) sodium azide and 0.5 g ammonium chloride. The product was obtained as oil. Yield: 87% (0.7 g); purity: 89% (254 nm); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 8.08 (m, 1H), 7.94 (m, 1H), 7.87 (d, 1H, *J* = 8.3 Hz), 7.54 (m, 4H), 5.28 (d, 1H, *J* = 5.3 Hz), 4.87 (m, 2H), 4.05 (m, 1H), 3.81 (m, 2H), 2.35 (m, 1H), 2.08 (m, 1H), 1.74 (m, 1H), 1.56 (m, 1H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 134.64, 133.80, 131.78, 128.91, 128.71, 126.73, 126.70, 126.34, 125.88, 124.57, 75.76, 75.27, 68.96, 67.13, 39.64; IR (cm^{-1}): 3415, 2103, 776; HRMS (ESI, *m/z*): $[2M+Na]^+$ calc.: 589.2539, found: 589.2548; refractive index: 1.5999.

General procedure for the reduction of azido to amino group (procedure D) [15]. To a solution of 16.9 mmol lithium aluminum hydride in freshly over sodium/benzophenone dried THF was added drop wise 4.3 ml of the appropriate azido compound in 20.0 ml THF under nitrogen atmosphere. After complete addition the reaction was stirred for 2 h at room temperature, then diethyl ether and a solution of sodium sulfate was added until no more hydrogen was formed. The aqueous phase was cleared from the resulting residue and extracted several times with diethyl ether. The organic phases were combined, dried over sodium sulfate and concentrated under reduced pressure.

(1*R*,2*R*,4*R*)-2-Amino-4-(benzyloxy)cyclopentanol (7a) was prepared following the general procedure D using 1.0 g (4.3 mmol) **6a**. Product was obtained as colorless solid; Yield: calc. as hydrochloride; purity: 96% (254 nm); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 7.30 (m, 5H), 4.63 (bs, 1H), 4.38 (s, 2H), 3.96 (m, 1H), 3.66 (m, 1H), 2.78 (m, 1H), 2.19 (m, 1H), 1.92 (m, 1H), 1.66 (m, 1H), 1.51 (bs, 1H), 1.31 (m, 1H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 139.44, 128.73, 128.02, 127.78, 78.59, 76.99, 70.42, 59.34; IR (cm^{-1}): 3392, 2887, 1617, 1467, 1067, 749, 699; mp: 114-115 °C.

(1*R*,2*R*,4*R*)-4-(Benzyloxy)-2-hydroxycyclopentanaminium chloride (7a hydrochloride). 7a was dissolved in ether and cooled, then HCl gas was initiated, upon what immediately a colorless solid precipitated. Yield: 86% (0.9 g); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 8.31 (bs, 3H), 7.31 (m, 5H), 5.38 (s, 1H), 4.41 (s, 2H), 4.14 (m, 1H), 4.02 (m, 1H), 3.11 (m, 1H), 2.41 (m, 1H), 2.03 (m, 1H), 1.74 (m, 1H), 1.64 (m, 1H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 138.40, 128.13, 127.50, 127.30, 75.27, 72.57, 69.95, 56.44, 38.60, 34.86; IR (cm^{-1}): 3339, 3029, 1505, 1066, 735; Analysis calc.: C, 59.14; H, 7.44; N, 5.75; Cl, 14.55, found: C, 59.16; H, 7.14; N, 5.88; Cl, 14.39; mp: 156-157 °C.

(1*S*,2*S*,4*R*)-2-Amino-4-(benzyloxy)cyclopentanol (7b) was prepared following the general procedure D using 1.0 g (4.3 mmol) **6b**. Product was obtained as colorless solid; Yield: calc. as hydrochloride; purity: 97% (254 nm); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 7.30 (m, 5H), 5.67 (bs, 1H), 4.37 (s, 2H), 3.92 (m, 1H), 3.45 (m, 1H), 2.98 (m, 1H), 2.27 (m, 1H), 1.87 (m, 1H), 1.55 (s, 1H), 1.45 (m, 2H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 139.48, 128.71, 128.02, 127.76, 78.34, 76.41, 70.31, 58.64, 39.08; IR (cm^{-1}): 3390, 2887, 1617, 1359, 1063, 749, 698; mp: 88-89 °C.

(1*S*,2*S*,4*R*)-4-(Benzyloxy)-2-hydroxycyclopentanaminium chloride (7b hydrochloride). 7b was dissolved in ether and cooled, then HCl gas was initiated, upon what immediately a colorless solid precipitated. Yield: 81% (0.8 g); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 8.20 (bs, 3H), 7.32 (m, 5H), 5.36 (d, 1H, *J* = 5.0 Hz), 4.41 (s, 2H), 3.97 (m, 2H), 3.26 (m, 1H), 2.36 (m, 1H), 2.06 (m, 1H), 1.81 (m, 1H), 1.56 (m, 1H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 139.06, 128.79, 128.08, 127.94, 75.32, 73.46, 70.37, 57.05, 34.90; IR (cm^{-1}): 3325, 2891, 1510, 1068, 735; Analysis calc.: C, 59.14; H, 7.44; N, 5.75; Cl, 14.55, found: C, 59.20; H, 7.57; N, 5.90; Cl, 14.52; mp: 194-195 °C.

(1*R*,2*R*,4*R*)-2-Amino-4-phenoxycyclopentanol (7c) was prepared following the general procedure D using 0.4 g (10.7 mmol) lithium aluminum hydride and 0.6 g (2.7 mmol) **6c**. Product was obtained as colorless solid; Yield: calc. as hydrochloride; purity: 100% (254 nm); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 7.27 (m, 2H), 6.86 (m, 3H), 4.74 (m, 2H), 3.73 (m, 1H), 2.89 (m, 1H), 2.41 (m, 1H), 1.97 (m, 1H), 1.88 (m, 1H), 1.52 (bs, 2H), 1.38 (m, 1H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 157.47, 129.36, 120.07, 115.11, 77.70, 74.63, 58.61, 38.99; IR (cm^{-1}): 3400, 2927, 1600, 1489, 1239, 1074, 755, 694; Analysis calc.: C, 68.37; H, 7.82; N, 7.25, found: C, 67.99; H, 7.66; N, 7.55; mp: 104-106 °C.

(1*R*,2*R*,4*R*)-2-Hydroxy-4-phenoxycyclopentanaminium chloride (7c hydrochloride). 7c was dissolved in ether and cooled, then HCl gas was initiated, upon what immediately a colorless solid precipitated. Yield: 85% (0.5 g); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 8.32 (bs, 3H), 7.28 (m, 2H), 6.89 (m, 3H), 5.48 (d, 1H, *J* = 4.6 Hz), 4.83 (m, 1H), 4.22 (m, 1H), 3.20 (m, 1H), 2.64 (m, 1H), 2.07 (m, 1H), 1.95 (m, 1H), 1.71 (m, 1H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 156.98, 129.45, 120.55, 115.21, 73.45, 72.51, 56.24, 38.73, 34.70; IR (cm^{-1}): 3336, 3010, 1675, 1495, 1242, 751; mp: 185-186 °C.

(1*S*,2*S*,4*R*)-2-Amino-4-phenoxycyclopentanol (7d) was prepared following the general procedure D using 0.3 g (7.2 mmol) lithium aluminum hydride and 0.4 g (1.8 mmol) **6d**. Product was obtained as colorless solid; Yield: calc. as hydrochloride; purity: 91% (254 nm); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 7.25 (m, 2H), 6.86 (m, 3H), 4.76 (bs, 1H), 4.71 (m, 1H), 3.56 (m, 1H), 3.08 (m, 1H), 2.51 (m, 1H), 1.92 (m, 1H), 1.70 (m, 1H), 1.56 (bs, 2H), 1.52 (m, 1H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 158.16, 130.00, 120.67, 115.74, 78.16, 75.04, 58.64, 39.30; IR (cm^{-1}): 3200, 2927, 1600, 1489, 1242, 1091, 755, 693; mp: 81-82 °C.

(1*S*,2*S*,4*R*)-2-Hydroxy-4-phenoxycyclopentanaminium chloride (7d hydrochloride). 7d was dissolved in ether and cooled, then HCl gas was initiated, upon what immediately a colorless solid precipitated. Yield: 84% (0.4 g); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 8.35 (bs, 3H), 7.28 (m, 2H), 6.91 (m, 3H), 4.97 (m, 1H), 4.81 (m, 1H), 4.08 (m, 1H), 3.35 (m,

1H), 2.58 (m, 1H), 2.11 (m, 1H), 2.04 (m, 1H), 1.62 (m, 1H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 158.10, 130.01, 120.71, 115.72, 77.96, 74.95, 58.30, 39.10; IR (cm^{-1}): 3312, 2913, 1488, 1242, 754; Analysis calc.: C, 57.52; H, 7.02; N, 6.10, found: C, 57.59; H, 6.85; N, 6.17; mp: 199-201 °C.

(1*R*,2*R*,4*R*)-4-([1,1′-Biphenyl]-4-yloxy)-2-aminocyclopentanol (7e) was prepared following the general procedure D using 0.3 g (7.2 mmol) lithium aluminum hydride and 0.6 g (2.0 mmol) **6e**. Product was obtained as colorless solid; Yield: 78% (0.4 g); purity: 100% (254 nm); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 7.59 (m, 4H), 7.42 (m, 2H), 7.30 (m, 1H), 6.94 (m, 2H), 4.80 (m, 2H), 3.75 (m, 1H), 2.90 (m, 1H), 2.45 (m, 1H), 2.01 (m, 1H), 1.91 (m, 1H), 1.58 (bs, 2H), 1.41 (m, 1H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 157.80, 140.45, 132.81, 129.40, 128.31, 127.21, 126.69, 116.23, 78.35, 75.59, 59.27; IR (cm^{-1}): 3345, 2939, 1606, 1488, 1244, 1071, 829, 761, 688; Analysis calc.: C, 75.81; H, 7.11; N, 5.20, found: C, 75.85; H, 6.88; N, 5.31; mp: 163-164 °C.

(1*S*,2*S*,4*R*)-4-([1,1′-Biphenyl]-4-yloxy)-2-aminocyclopentanol (7f) was prepared following the general procedure D using 0.2 g (5.3 mmol) lithium aluminum hydride and 0.4 g (1.4 mmol) **6f**. Product was obtained as colorless solid; Yield: 75% (0.3 g); purity: 99% (254 nm); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 7.57 (m, 4H), 7.42 (m, 2H), 7.30 (m, 1H), 6.94 (m, 2H), 4.77 (m, 2H), 3.57 (m, 1H), 3.08 (m, 1H), 2.53 (m, 1H), 1.95 (m, 1H), 1.74 (m, 1H), 1.58 (bs, 2H), 1.52 (m, 1H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 157.21, 139.81, 132.09, 128.75, 127.64, 126.55, 126.03, 115.56, 77.63, 74.75, 58.06; IR (cm^{-1}): 3400, 2925, 1608, 1487, 1244, 762, 695; Analysis calc.: C, 75.81; H, 7.11; N, 5.20, found: C, 75.76; H, 6.83; N, 5.44; mp: 144-145 °C.

(1*R*,2*R*,4*R*)-2-Amino-4-(naphthalen-1-ylmethoxy)cyclopentanol (7g) was prepared following the general procedure D using 0.3 g (8.3 mmol) lithium aluminum hydride and 0.6 g (2.1 mmol) **6g**. Product was obtained as colorless solid; Yield: calc. as hydrochloride; purity: 98% (254 nm); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 8.07 (d, 1H, *J* = 8.0 Hz), 7.93 (d, 1H, *J* = 9.1 Hz), 7.86 (d, 1H, *J* = 8.2 Hz), 7.52 (m, 3H), 7.45 (m, 1H), 4.83 (s, 2H), 4.64 (bs, 1H), 4.07 (m, 1H), 3.66 (m, 1H), 2.80 (m, 1H), 2.24 (m, 1H), 1.97 (m, 1H), 1.70 (m, 1H), 1.46 (bs, 1H), 1.36 (m, 1H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 134.93, 133.80, 131.80, 128.90, 128.61, 126.66, 126.63, 126.31, 125.89, 124.57, 78.62, 77.30, 68.98, 59.35, 49.17; IR (cm^{-1}): 3346, 2900, 1617, 1100, 796, 770; mp: 88-89 °C.

(1*R*,2*R*,4*R*)-2-Hydroxy-4-(naphthalen-1-ylmethoxy)cyclopentanaminium chloride (7g hydrochloride). 7g was dissolved in ether and cooled, then HCl gas was initiated, upon what immediately a colorless solid precipitated. Yield: 80% (0.5 g); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 8.23 (bs, 3H), 8.07 (d, 1H, *J* = 8.3 Hz), 7.95 (m, 1H), 7.88 (d, 1H, *J* = 8.0 Hz), 7.55 (m, 3H), 7.47 (m, 1H), 5.36 (d, 1H, *J* = 4.6 Hz), 4.88 (m, 2H), 4.13 (m, 2H), 3.13 (m, 1H), 2.45 (m, 1H), 2.07 (m, 1H), 1.77 (m, 1H), 1.65 (m, 1H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 134.53, 133.81, 131.78, 128.94, 128.78, 126.79, 126.73, 126.37, 125.87, 124.55, 76.07, 73.25, 69.14, 57.03, 39.27; IR (cm^{-1}): 3325, 2931, 1508, 1064, 772; Analysis calc.: C, 65.41; H, 6.86; N, 4.77; Cl, 12.07, found: C, 65.68; H, 6.55; N, 5.16; Cl, 12.09; mp: 182-184 °C.

(1*S*,2*S*,4*R*)-2-Amino-4-(naphthalen-1-ylmethoxy)cyclopentanol (7h) was prepared following the general procedure D using 0.6 g (6.9 mmol) lithium aluminum hydride and 0.5 g (1.8 mmol) **6h**. Product was obtained as colorless solid; Yield: 96% (0.4 g); purity: 96% (254 nm); ^{1}H-NMR (500 MHz, [D$_6$]-DMSO) = δ (ppm) 8.07 (d, 1H, *J* = 8.2 Hz), 7.94 (m, 1H), 7.86 (d, 1H, *J* = 8.2 Hz), 7.54 (m, 3H), 7.46 (m, 1H), 4.83 (s, 2H), 4.68 (bs, 1H), 4.04 (m, 1H), 3.46 (m, 1H), 3.00 (m, 1H), 2.32 (m, 1H), 1.92 (m, 1H), 1.55-1.45 (m, 3H); ^{13}C-NMR (126 MHz, [D$_6$]-DMSO) = δ (ppm) 134.95, 133.80, 131.82, 128.89, 128.59, 126.65, 126.61, 126.30, 125.88, 124.59, 78.38, 76.73, 68.89, 58.70, 39.13; IR (cm^{-1}): 3346, 2890, 1617, 1331, 1105, 794, 768; Analysis calc.: C, 74.68; H, 7.44; N, 5.44, found: C, 74.32; H, 7.28; N, 5.32; mp: 74-75 °C.

Preparation of polymer-bound acylation reagents based on Kenner´s safety-catch linker

Coupling of carboxylic acids to the linker (resin 1). 1.0 g (1.2 mmol) of 4-sulfamoylbenzamidomethyl functionalized cross-linked polystyrene resin (prepared from very high load aminomethylated polystyrene, purchased from Novabiochem, Switzerland, batch number A20540) was dispersed in 12.5 ml THF, DMF or DCM, depending on the solubility of the appropriate carboxylic acid. To the suspension 290 µl DIPEA and 7.5 mg DMAP (dissolved in as less as possible DCM) were added and the reaction mixture was shaken for 5 h at room temperature. Meanwhile 4.6 mmol of the appropriate carboxylic acid was dissolved in as little as possible THF, DMF or DCM, depending on its solubility. To the solution 387 µl (2.3 mmol) DIC were added and the reaction mixture was shaken for 5 h at room temperature. When using THF or DCM the precipitating *N*,*N*'-diisopropylurea was filtered off. The solution of activated carboxylic acid was then poured into the resin suspension and shaken for at least 10 h at room temperature. Finally, the resin was filtered of, washed three times with DMF, DCM and MeOH and dried under reduced pressure.

Activation of the acylsulfamoyl functionality by means of alkylation with bromoacetonitrile (resin 2). 150 mg (ca. 0.2 mmol) of the appropriate 4-(*N*-acylsulfamoyl)-benzamide resin 1 was suspended in 1.5 ml dry NMP, then 128 µl DIPEA and 240 µl bromoacetonitrile were added and the reaction mixture was shaken for 10 h at room temperature. The resulting resin was filtered, washed five times with DMSO and three times with THF and the subsequent reaction was immediately performed.

Activation of the acylsulfamoyl functionality by means of alkylation with *N*,*N*′-diisopropyl-*O*-2,3,4,5,6-pentafluoro-benzyl-isourea (resin 3). 150 mg (ca. 0.2 mmol) of the appropriate 4-(*N*-acylsulfamoyl)-benzamide resin 1 was

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suspended in 1.5 ml dry NMP, then 128 µl DIPEA and 1.1 g (3.4 mmol) of *N*,*N*′-diisopropyl-*O*-2,3,4,5,6-pentafluorobenzyl-isourea were added and the reaction mixture was shaken for 24 h at 50 °C. The resulting resin was filtered, washed five times with DMSO and three times with THF and the subsequent reaction was immediately performed.

General transfer procedure of the acyl functionality to the amino template for the preparation of target carboxamide (procedure E). 150 mg of the appropriate activated resin 2 or 3 was suspended in 3.0 ml THF and 20.0 µmol of the appropriate amino template (dissolved in as less as possible THF) was added to shake the reaction mixture for 12 to 24 h at room temperature. In-process control was done by thin layer chromatography. After quantitative acylation of the amine, the resin was filtered and washed several times with THF, which was previously distilled over KOH. The solvent was evaporated under reduced pressure and the residue further dried in high vacuum. Finally, the residue was dissolved in MeOH/H_2O and purified by medium pressure column chromatography.

Antiproliferative compounds

***N*-[(1*R*,2*R*,4*S*)-4-(Benzyloxy)-2-hydroxycyclopentyl]-4-(1,1′-biphenyl-4-yl)-4-0xobutanamide (11j)** was prepared following the general procedure E using appropriate **resin 2** and 20.0 µmol **7a**. Yield: 93%; purity: 95% (254 nm); ^{1}H-NMR (500 MHz, [D_6]-DMSO) = δ (ppm) 8.05 (d, 2H, *J* = 8.5 Hz), 7.90 (d, 1H, *J* = 7.6 Hz), 7.83 (d, 2H, *J* = 8.5 Hz), 7.74 (m, 2H), 7.51 (m, 2H), 7.43 (m, 1H), 7.33 (m, 4H), 7.27 (m, 1H), 4.84 (m, 1H), 4.41 (s, 2H), 4.00 (m, 1H), 3.94 (m, 1H), 3.75 (m, 1H), 3.26 (m, 2H), 2.50 (m, 2H), 2.34 (m, 1H), 1.93 (m, 1H), 1.74 (m, 1H), 1.43 (m, 1H); HRMS (ESI, *m/z*): [M+Na]$^+$ calc.: 466.1994, found: 466.1972.

***N*-[(1*S*,2*S*,4*S*)-4-(Benzyloxy)-2-hydroxycyclopentyl]-4-(1,1′-biphenyl-4-yl)-4-oxobutanamide (12j)** was prepared following the general procedure E using appropriate **resin 2** and 20.0 µmol **7b**. Yield: 89%; purity: 96% (254 nm); ^{1}H-NMR (500 MHz, [D_6]-DMSO) = δ (ppm) 8.05 (d, 2H, *J* = 8.5 Hz), 7.88 (d, 1H, *J* = 7.1 Hz), 7.83 (d, 2H, *J* = 6.6 Hz), 7.75 (m, 2H), 7.51 (m, 2H), 7.43 (m, 1H), 7.32 (m, 4H), 7.26 (m, 1H), 4.85 (m, 1H), 4.40 (s, 2H), 3.93 (m, 2H), 3.79 (m, 1H), 3.26 (m, 2H), 2.50 (m, 2H), 2.28 (m, 1H), 1.99 (m, 1H), 1.61 (m, 1H), 1.51 (m, 1H); HRMS (ESI, *m/z*): [M+Na]$^+$ calc.: 466.1994, found: 466.2001.

***N*-[(1*R*,2*R*,4*S*)-4-(1,1′-Biphenyl-4-yloxy)-2-hydroxycyclopentyl]-2-(1*H*-Indol-3-yl)butanamide (15h)** was prepared following the general procedure E using appropriate **resin 2** and 20.0 µmol **7e**. Yield: 93%; purity: 96% (254 nm); ^{1}H-NMR (500 MHz, [D_6]-DMSO) = δ (ppm) 10.72 (s, 1H), 7.84 (d, 1H, *J* = 7.1 Hz), 7.56 (m, 4H), 7.48 (d, 1H, *J* = 7.8 Hz), 7.42 (m, 2H), 7.30 (m, 2H), 7.08 (m, 1H), 7.04 (m, 1H), 6.94 (m, 3H), 4.98 (d, 1H, *J* = 4.4 Hz), 4.85 (m, 1H), 4.04 (m, 1H), 3.87 (m, 1H), 2.66 (t, 2H, *J* = 7.4 Hz), 2.58 (m, 1H), 2.15 (t, 2H, *J* = 7.4 Hz), 2.02 (m, 1H), 1.96 (m, 1H), 1.86 (m, 2H), 1.53 (m, 1H); HRMS (ESI, *m/z*): [M+Na]$^+$ calc.: 477.2154, found: 477.2125.

***N*-[(1*R*,2*R*,4*S*)-4-(1,1′-Biphenyl-4-yloxy)-2-hydroxycyclopentyl]-2,2-diphenylacetamide (15i)** was prepared following the general procedure E using appropriate **resin 2** and 20.0 µmol **7e**. Yield: 96%; purity: 97% (254 nm); ^{1}H-NMR (500 MHz, [D_6]-DMSO) = δ (ppm) 8.33 (d, 1H, *J* = 7.1 Hz), 7.56 (m, 4H), 7.42 (m, 2H), 7.32-7.19 (m, 11H), 6.93 (m, 2H), 4.99 (d, 1H, *J* = 4.8 Hz), 4.97 (s, 1H), 4.85 (m, 1H), 4.07 (m, 1H), 3.89 (m, 1H), 2.59 (m, 1H), 2.03 (m, 1H), 1.97 (m, 1H), 1.52 (m, 1H); HRMS (ESI, *m/z*): [M+Na]$^+$ calc.: 486.2045, found: 486.2062.

***N*-[(1*S*,2*S*,4*S*)-4-(1,1′-Biphenyl-4-yloxy)-2-hydroxycyclopentyl]-2,2-diphenylacetamide (16i)** was prepared following the general procedure E using appropriate **resin 2** and 20.0 µmol **7f**. Yield: 95%; purity: 97% (254 nm); ^{1}H-NMR (500 MHz, [D_6]-DMSO) = δ (ppm) 8.37 (d, 1H, *J* = 7.3 Hz), 7.57 (m, 4H), 7.42 (m, 2H), 7.30 (m, 9H), 7.22 (m, 2H), 6.95 (m, 2H), 4.99 (d, 1H, *J* = 5.0 Hz), 4.93 (s, 1H), 4.79 (m, 1H), 4.02 (m, 1H), 3.90 (m, 1H), 2.53 (m, 1H), 2.09 (m, 1H), 1.79 (m, 1H), 1.60 (m, 1H); HRMS (ESI, *m/z*): [M+Na]$^+$ calc.: 486.2045, found: 486.2067.

Crystallographic data for compound 7b. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 766218. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). Mono-crystals were measured using a Rigaku-AFC7F diffractometer with Cu-Kα irradiation (α = 1,5418 Å).

Cytotoxicity assay. The antiproliferative activity of the tested compounds was determined by screening against four human tumor cell lines as previously described.[12] The cell lines were suspended in RPMI 1640 medium containing 10% fetal calf serum (FCS) and added to each well of the 96 well microplate (1000 cells per well). After 24 h incubation, five serial dilutions of the test compound in DMSO were added to the cultures at a 1000-fold dilution. A 1000-fold dilution of just DMSO served as the untreated control. The microtiter plates were then incubated for 96 h at 37 °C in 5% CO_2 atmosphere. Medium was removed and the cells were fixed with 1% glutaraldehyde. Cell staining was done with crystal violet (0.2‰ in water) for 30 min. After the dye was removed, the plates were washed to remove non-bound dye, 70% ethanol/water mixture was added to redissolve the cell-bound dye, and the optical density was measured at λ = 570 nm with an Anthos 2010 plate reader. The half maximal inhibitory concentrations (IC_{50}) were estimated by linear regression of the log dose to the T/C ratio [20].

Notes and references

[a] Institute of Pharmacy, Ernst-Moritz-Arndt-University, Friedrich-Ludwig-Jahn-Str. 17, 17487 Greifswald, Germany.

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