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Skeletal and appendage diversity as design elements in the synthesis of a discovery library of nonaromatic polycyclic 5-iminooxazolidin-2-ones, hydantoins, and acylureas

S. Werner*, D.M. Turner, P.G. Chambers, K.M. Brummond

Center for Chemical Methodologies and Library Development (UPCMLD), University of Pittsburgh, Pittsburgh, PA 15260, USA

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Abstract

Amino-acid derived cross-conjugated trienes were used as a starting point for the synthesis of a discovery library of over 200 polycyclic 5-iminooxazolidin-2-ones, hydantoins, and acylureas. The main feature of this library synthesis is a triple branching strategy, which provides efficient access to five skeletally diverse scaffolds. In addition, four sets of building blocks were applied in both a front end and a back end diversification strategy. Multiple fused rings were obtained by cyclization of diamides with phosgene and stereoselective Diels–Alder reactions with maleimides. The 5-iminooxazolidin-2-one scaffold was rearranged into the isomeric hydantoin scaffold through a sequence of ring-opening and ring-closing reactions.
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Keywords: Library design; Skeletal diversity; Appendage diversity; Polycycles; Diels–Alder reaction

1. Introduction

The search for new biological probes capable of modulating biological pathways has led to the rapid development of diversity oriented synthesis (DOS), a strategy used to access larger numbers of structurally unique compounds.[1–3] In addition to occupying new chemical space, these molecules need to bind to proteins, be of a defined molecular complexity,[4] be structurally rigid, and possess three-dimensionality.[5] Many DOS libraries are inspired by natural products because of their richness in stereochemical and three-dimensional structural diversity.[6,7] Although it is not easy to measure the diversity of a certain collection of compounds,[8,9] four diversity elements have been described: building block, stereochemical, appendage, and skeletal.[10] Recently, skeletal diversity has evolved as the most powerful element in the design of small molecule discovery libraries.[11] It can be generated through branching strategies[12] or through rearrangement and fragmentation processes[13] in the library design. Polymorphic scaffolds[14] and sigma-elements that contain appendages with pre-encoded skeletal information as defined by Schreiber[15] have been described as alternative strategies to obtain skeletal diversity.

Distributing compounds into chemical descriptor space can be achieved best by combining several diversity elements. For the discovery library of polycyclic nonaromatic 5-iminooxazolidin-2-ones, hydantoins, and acylureas presented here, a triple branching strategy (see Scheme 1) allowing for the combination of appendage and skeletal diversity elements was employed (Fig. 1).

The amino-acid derived δ-lactam **A** containing an electron deficient cross-conjugated triene system and diamide functionalities provides a densely functionalized key intermediate, which serves as a starting point in the skeletal diversity strategy for the generation of multiple scaffolds. The amide functionalities are cyclized with phosgene to form a sterically biased and electronically tuned 5-iminooxazolidin-2-one triene system. This second generation triene undergoes a single cycloaddition reaction with dienophiles followed by the newly

* Corresponding author.
E-mail address: werner-stefan@gmx.net (S. Werner).

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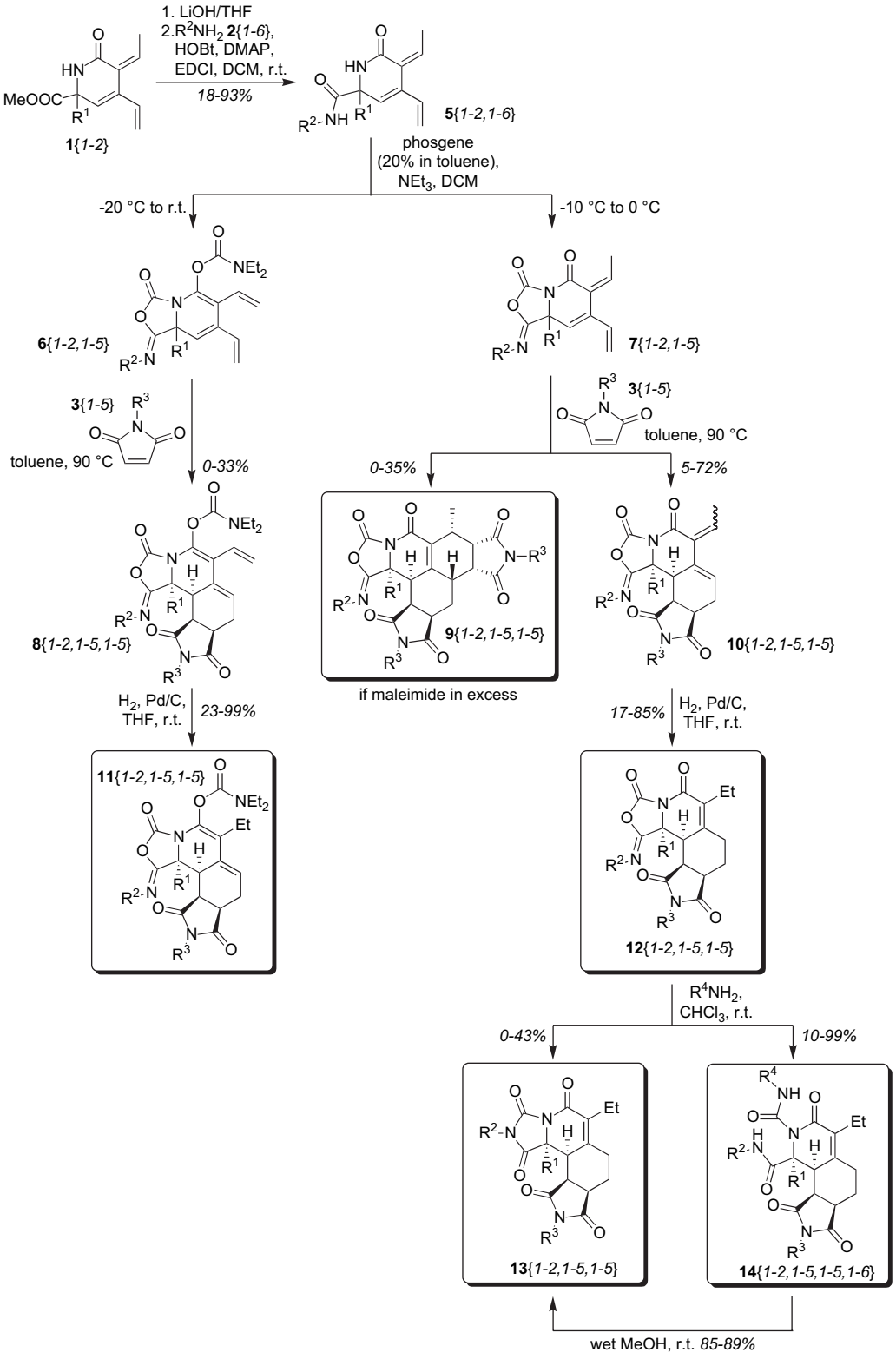

Scheme 1. Synthesis of polycyclic 5-iminooxazolidin-2-ones, hydantoins, and acylureas.

formed diene moiety reacting with another dienophile in a second Diels–Alder reaction or it can undergo a hetero-Diels–Alder reaction involving the carbonyl group.[16]

Further diversification of the 5-iminooxazolidin-2-one moiety can potentially be achieved by ring-opening reactions with amines and rearrangement into the isomeric hydantoin scaffold, an important pharmacophore.[17] Although 4-imino-oxazolidin-2-ones are of interest as fungicides,[18] little is known about the isomeric 5-iminooxazolidin-2-ones.[19] Therefore it was appealing to synthesize a discovery library based

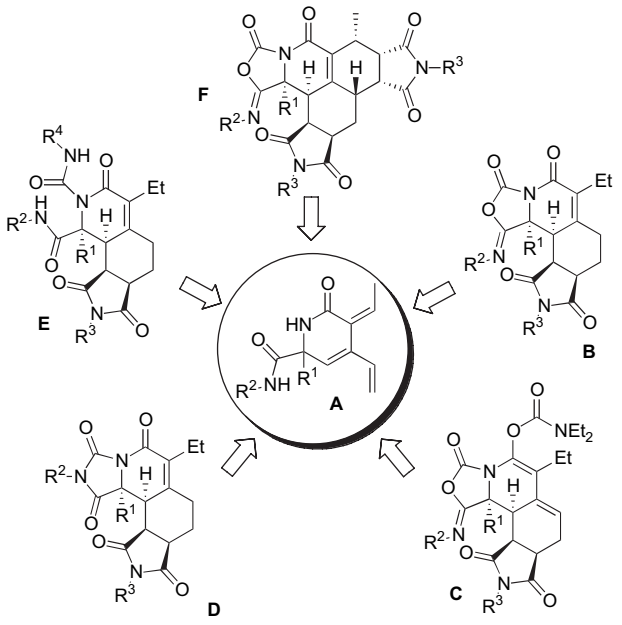

Figure 1. δ-Lactams **A** as key intermediates for a structurally diverse discovery library.

on this new motif. Furthermore, targeted scaffolds **B**–**F** are all nonaromatic and polycyclic in nature, a class of compounds of interest because of their natural product like character.[20]

2. Results and discussion

2.1. Library design

In addition to five highly functionalized scaffolds differing significantly in volume, flexibility, number of fused rings, and their ability to donate and accept hydrogen bonds, the library design involved four sets of building blocks. Two triene containing methyl esters **1**{*1*–*2*}[16] (Fig. 2) and a set of six amines **2**{*1*–*6*} (Fig. 3) were used for the essential conversion of **1**{*1*–*2*} to **5**{*1*–*2*,*1*–*6*} (Scheme 1). Cyclopropylmethylamine **2**{*1*} was chosen as a small lipophilic building block, methoxyethylamine **2**{*2*} and glycyl methyl ester **2**{*3*} as more polar substituents, benzylamine **2**{*4*} and 2-aminomethylpyridine **2**{*6*} to include aromatic and heteroaromatic systems, and tryptamine **2**{*5*} because of its hydrogen bond donor abilities. Five maleimides **3**{*1*–*5*} were applied as symmetric dienophiles in a Diels–Alder reaction in order to avoid the formation of regioisomers (Fig. 4). Maleimide itself **3**{*1*} was selected to include a second hydrogen bond donor, *N*-methyl and *N*-ethyl maleimide **3**{*2*} and **3**{*3*} because of

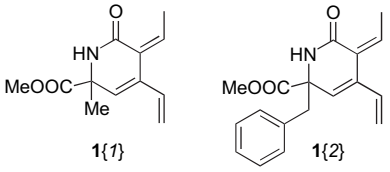

Figure 2. Building blocks **1**{*1*–*2*} used as starting points in the library synthesis.

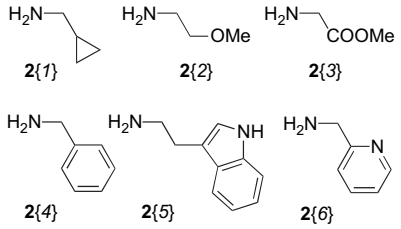

Figure 3. Building blocks **2**{*1*–*6*} used in the library synthesis.

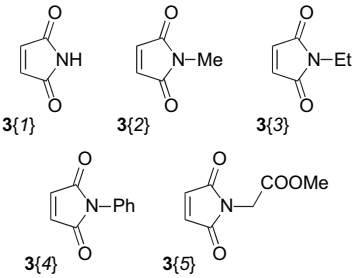

Figure 4. Building blocks **3**{*1*–*5*} used in the library synthesis.

their relatively small substituents, *N*-phenyl maleimide **3**{*4*} as an aromatic representative and methyl *N*-acetate maleimide **3**{*5*} because of its more polar character. The last set of building blocks consisted of six amines **4**{*1*–*6*} that were used to open the 5-iminooxazolidin-2-one moiety (Fig. 5). Again, the selection included small polar (**4**{*1*}, **4**{*6*}) and lipophilic (**4**{*4*}) aliphatic substituents as well as a polar (**4**{*2*}) and lipophilic (**4**{*5*}) aromatic representatives. *N*-(2-Aminoethyl)-morpholine **4**{*3*} was chosen because of its basic nitrogen and ethanolamine (**4**{*1*}) because of its ability to act as hydrogen bond donor.

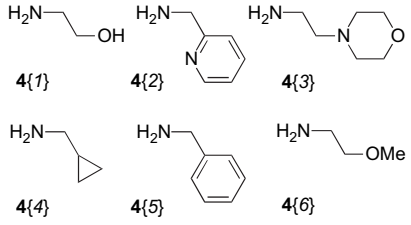

Figure 5. Building blocks **4**{*1*–*6*} used in the library synthesis.

2.2. Library synthesis

The cross-conjugated trienes **1**{*1*–*2*} were obtained via a Rh(I)-catalyzed Alder–ene reaction of propiolamides.[16,21] Saponification of the methyl esters **1**{*1*–*2*} with lithium hydroxide, followed by HOBt/DMAP/EDCI mediated amidation with amines **2**{*1*–*6*} provided amides **5**{*1*–*2*,*1*–*6*} in yields ranging from 18–93% (Scheme 1, Table 1) for the two steps.

The reaction conditions for the cyclization reaction with phosgene were optimized on small scale (0.1 mmol) with diamide **5**{*1*,*4*} prior to applying it on large scale to all diamides **5**{*1*–*2*,*1*–*6*}. Diamide **5**{*1*,*4*} was treated with 3 equiv of phosgene and triethylamine in dichloromethane at −10 °C

Table 1
Yields in % for the synthesis of amides **5**{*1–2,1–6*} from methyl esters **1**{*1–2*} and amines **2**{*1–6*}

5{*1–2,1–6*}	**2**{*1*}	**2**{*2*}	**2**{*3*}	**2**{*4*}	**2**{*5*}	**2**{*6*}
1{*1*}	68	18	65	75	93	—[a]
1{*2*}	55	51	83	30	79	55

[a] Not attempted as **5**{*2,6*} did not undergo a selective reaction with phosgene in the next step.

for 30 min. The reaction mixture was then warmed to 0 °C and quenched by adding a saturated ammonium chloride/brine (1/10) solution. 5-Iminooxazolidin-2-one **7**{*1,4*} was the only observed product. When the reaction was carried out on larger scale under otherwise identical conditions, the bicycle **7**{*1,4*} was immediately hydrolyzed back to **5**{*1,4*} while quenching with saturated ammonium chloride/brine (1/10) because of the large amount of HCl that was generated during the quenching process. This could be prevented by using 6 equiv of triethylamine and quenching the reaction mixture with a saturated sodium bicarbonate solution. All 5-iminooxazolidin-2-ones **7**{*1–2,1–5*} were highly acid sensitive and converted back into the starting material if a purification by chromatography on silica was attempted. Thus, they were not purified and instead used crude in the following Diels–Alder reaction. The pyridine containing diamide **5**{*2,6*} was the only diamide that did not undergo a cyclization reaction with phosgene. Upon addition of phosgene, the reaction mixture turned black and no product could be detected.

On large scale, it proved to be necessary to warm the reaction mixture from −10 °C to room temperature prior to quenching it with saturated sodium bicarbonate to obtain complete conversion. However, carbamate **6**{*1–2,1–5*} was now formed as a side product. Quenching the reaction at −10 °C or 0 °C led to incomplete reactions but prevented the carbamate formation (Table 2, footnotes b and c). Although a rather unusual reaction, the formation of *N*,*N*-diethyl carbamates from phosgene and triethylamine has been described.[22]

Assuming quantitative conversion in the cyclization step, 5-iminooxazolidin-2-ones **6**{*1–2,1–5*} and **7**{*1–2,1–5*} were taken on to the next reaction. Heating each in a Radley's Carousel for 2 h at 90 °C with 1.3 equiv of maleimide **3**{*1–5*} in toluene gave the Diels–Alder cycloadducts, which could be easily purified on an ISCO Optix 10 chromatography station. The carbamates **8**{*1–2,1–5,1–5*} were obtained in 0–33% while the adducts **10**{*1–2–1–5,1–5*} were isolated in 5–74% yield (Table 2). In several cases a second Diels–Alder reaction occurred providing adduct **9**{*1–2,1–5,1–5*} in 0–11% yield, which could also be separated by chromatography (Tables 2 and 3). It is thought that in those cases the cyclization reaction did not go to completion and thus the maleimide was present in excess. This hypothesis is supported by the cyclization reaction of **5**{*2,2*}, which was quenched at −10 °C, preventing completion of the reaction, and the crude reaction mixture was applied to the Diels–Alder reaction with **3**{*4*}. In this case, carbamate **6**{*2,2,4*} was not observed, but the double Diels–Alder adduct **9**{*2,2,4*} was obtained in 35% yield (Table 2, footnote b). An isomerization of the exocyclic double bond in **10**{*1–2,1–5,1–5*} was noticed[23] but the *E*/*Z*-isomers were not separated because the diene system was reduced in the following step.

Table 2
Yields in % for the synthesis of 5-iminooxazolidin-2-ones **8**{*1–2,1–5,1–5*}, **9**{*1–2,1–5,1–5*}, and **10**{*1–2,1–5,1–5*} from amides **5**{*1–2,1–5*} and maleimides **3**{*1–5*}[a]

8{*1–2,1–5,1–5*}/ **9**{*1–2,1–5,1–5*}/ **10**{*1–2,1–5,1–5*}	**3**{*1*}	**3**{*2*}	**3**{*3*}	**3**{*4*}	**3**{*5*}
5{*1,1*}	14/—/13	22/—/58	20/5/38	24/—/37	21/—/37
5{*1,2*}	13/—/13	12/3/17	13/—/18	10/—/17	17/—/13
5{*1,3*}	20/—/7	22/—/35	24/—/46	32/—/31	27/—/30
5{*1,4*}	27/—/33	28/8/42	28/—/47	25/—/53	27/—/32
5{*1,5*}	11/—/13	15/—/18	16/—/60	22/—/39	20/—/39
5{*2,1*}	18/—/5	25/—/43	27/—/53	28/—/42	22/—/37
5{*2,2*}	18/—/29	17/—/39	13/—/51	33/—/61 —/35/36[b]	12/7/29
5{*2,3*}	20/—/12	25/—/58	27/—/40	18/3/50	24/—/39
5{*2,4*}	—/—/32[c]	—/—/61[c]	—/—/74[c]	—/4/19[c]	—/—/68[c]
5{*2,5*}	17/11/42	24/—/57	19/—/72	13/2/61	9/—/70

[a] Yield in % for carbamate **8**{*1–2,1–5,1–5*}/double Diels–Alder adduct **9**{*1–2,1–5,1–5*}/Diels–Alder adduct **10**{*1–2,1–5,1–5*}.
[b] Phosgene reaction quenched at −10 °C.
[c] Phosgene reaction quenched at 0 °C.

Table 3
Purities in % for the double Diels–Alder adducts **9**{*1–2,1–5,1–5*}, purity detection by ELS

Compound	Purity
9{*1,1,3*}	>99
9{*1,2,2*}	64
9{*1,4,2*}	71
9{*2,2,4*}	90[a]
9{*2,2,5*}	>99
9{*2,3,4*}	99
9{*2,5,4*}	>99

[a] Purity estimated by ^{1}H NMR.

Because of concern for the reactivity[24] of the exocyclic double bond of the lactam, the diene in **8**{*1–2,1–5,1–5*} and **10**{*1–2,1–5,1–5*} was reduced by hydrogenation with Pd/C to give carbamates **11**{*1–2,1–5,1–5*} in 23–99% yield (Table 4) and lactams **12**{*1–2,1–5,1–5*} in 17–85% yield (Table 5). Most reactions were complete after 4 h, but the indole containing substrates required reaction times of 24 h.

The structure of the carbamates was confirmed by an X-ray structure analysis of **11**{*1,1,4*} (Fig. 6a). Both Diels–Alder reactions took place in a diastereoselective fashion. The initial Diels–Alder cycloaddition reaction occurred with *endo* selectivity from the opposite face of the R^1 substituent as seen in the X-ray structure analysis of **12**{*2,1,4*} (Fig. 6b). Based on comparison studies with a previously described double Diels–Alder adduct[16] the stereochemistry for **9**{*1–2,1–5,1–5*} has been tentatively assigned as resulting from an addition of the second dienophile from the less hindered convex face in *endo* mode.

Table 4
Yields (purities) in % for the hydrogenation of **8**{*1–2,1–5,1–5*}, purity detection by ELS

11{*1–2,1–5,1–5*}	**3**{*1*}	**3**{*2*}	**3**{*3*}	**3**{*4*}	**3**{*5*}
5{*1,1*}	92 (>99)	99 (>99)	85 (99)	70 (>99)	90 (96)
5{*1,2*}	85 (>99)	51 (97)	65 (93)	75 (70)	62 (>99)
5{*1,3*}	73 (98)	59 (95)	82 (93)	70 (87)	99 (90)
5{*1,4*}	70 (>99)	—	86 (99)	89 (>99)	78 (97)
5{*1,5*}	87 (>99)	70 (>99)	61 (96)	27 (86)	25 (>99)
5{*2,1*}	96 (98)	96 (99)	96 (98)	69 (>99)	78 (90)
5{*2,2*}	80 (>99)	81 (98)	86 (98)	86 (70)	67 (98)
5{*2,3*}	96 (97)	83 (96)	86 (86)	64 (98)	79 (96)
5{*2,4*}	—	—	—	—	—
5{*2,5*}	63 (94)	23 (>99)	38 (>99)	39 (90)[a]	41 (>99)

[a] Purity estimation by ^{1}H NMR.

Table 5
Yields (purities) in % for the hydrogenation of **10**{*1–2,1–5,1–5*}, purity detection by ELS

12{*1–2,1–5,1–5*}	**3**{*1*}	**3**{*2*}	**3**{*3*}	**3**{*4*}	**3**{*5*}
5{*1,1*}	51 (93)	48 (<50)	35 (82)	57 (>95)	50 (<50)
5{*1,2*}	23 (>99)	35 (57)	52 (<50)	43 (<50)	44 (<50)
5{*1,3*}	18 (91)	74 (97)	36 (93)	53 (94)	60 (98)
5{*1,4*}	25 (88)	58 (95)	32 (75)	36 (91)	46 (87)
5{*1,5*}	24 (93)	50 (77)	23 (90)[b]	17 (84)	43 (93)
5{*2,1*}	61 (99)	79 (94)	44 (>99)	46 (98)	73 (80)
5{*2,2*}	76 (78)	85 (97)	63 (99)	45 (95)	32 (95)
5{*2,3*}	25 (98)	83 (94)	83 (80)[a]	24 (80)	46 (84)[a]
5{*2,4*}	46 (90)	61 (77)[a]	37 (94)	34 (94)	53 (76)
5{*2,5*}	17 (<50)	42 (95)[b]	53 (85)	33 (98)	29 (94)

[a] Purity detection by UV 254 nm.
[b] Purity estimation by ^{1}H NMR.

Although the 5-iminooxazolidin-2-ones **12**{*1–2,1–5,1–5*} are very stable compounds, e.g., stirring in 1 M HCl/MeOH for 24 h did not result in any reaction or decomposition, the 5-iminooxazolidin-2-one ring system can be opened by reaction with an excess primary amine in chloroform at room temperature. This reaction tolerated a wide range of amines and 87 acylureas **14**{*1–2,1–5,1–5,1–6*} were prepared (Table 6). The structure of those tricycles was confirmed by an X-ray structure of **14**{*1,1,4,1*},[25] clearly showing the amide as well as the acylurea functionality. In several cases a less polar side product was observed, which could be easily separated by chromatography on silica and was identified as hydantoin **13**{*1–2,1–5,1–5*} based on a characteristic chemical shift change of a ^{13}C NMR resonance from 147 to 173 ppm. The structure was later confirmed by the X-ray structure analysis of **13**{*1,1,4*} (Fig. 6c). Alternatively, stirring the acylureas **14**{*1–2,1–5,1–5,1–6*} in wet methanol for 24 h resulted in a selective conversion into the corresponding hydantoins **13**{*1–2,1–5,1–5*} in 85–89% yield. In all cases, the substituent R^2 on the amide was preserved in the molecule while the substituent R^4 on the acylurea was cleaved off. The formation of hydantoins by an intramolecular nucleophilic attack of an amide hydrogen on an ureido carbonyl,[26] carbamoyl carbonyl[27] or benzotriazole carbonyl[28] has been reported previously, but in all cases a base was required. The intramolecular cyclization between the amide hydrogen and the acylurea carbonyl of **14**{*1–2,1–5,1–5,1–6*} took place under very mild conditions in wet methanol. As all library members will be stored in the UPCMLD compound collection as solution in DMSO at −78 °C, it was important to investigate the stability of the acylurea **14**{*1–2,1–5,1–5,1–6*} in DMSO-d_6 under those conditions. While **14**{*2,5,2,1*} had a half life time in DMSO-d_6 at room temperature of only 21 days and completely rearranged into **13**{*2,5,2,1*} after

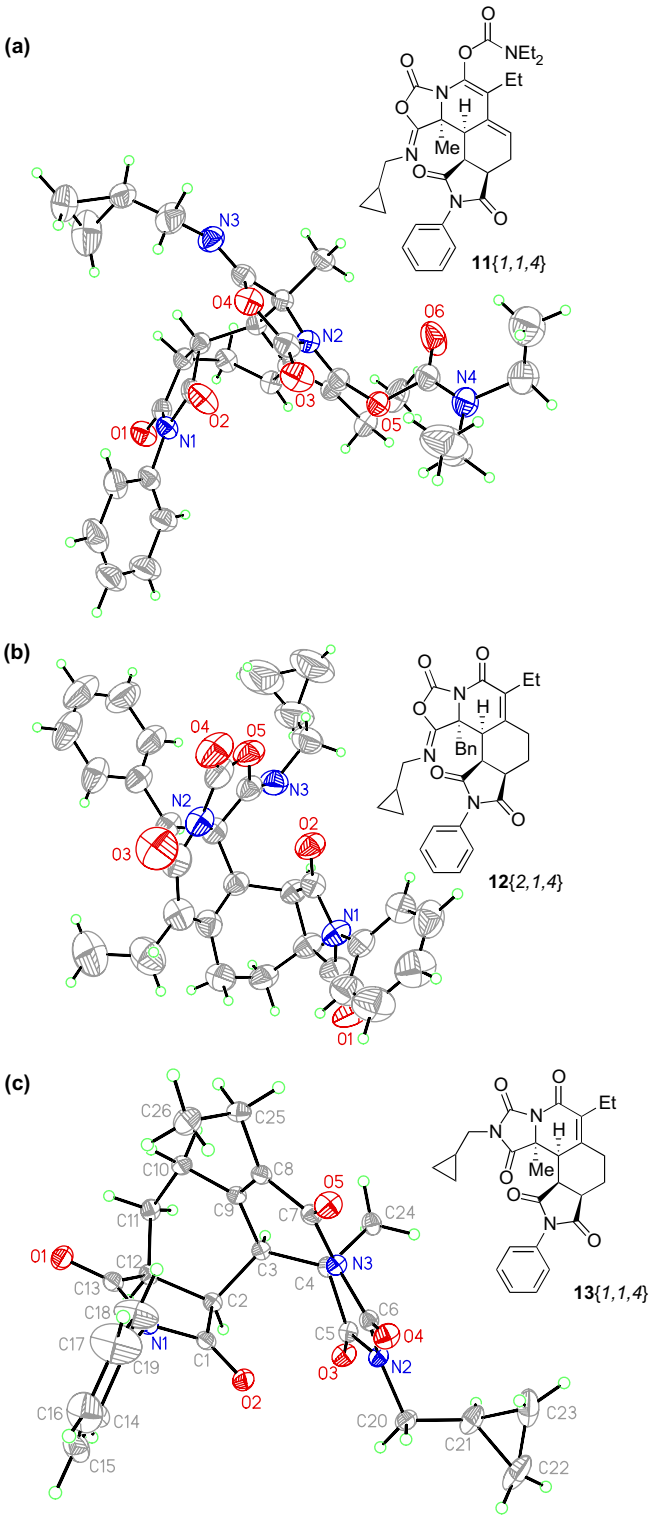

Figure 6. X-ray structures of **11**{*1,1,4*}, **12**{*2,1,4*}, and **13**{*1,1,4*}.[34]

Table 6
Yields (purities) in % for the formation of the hydantoins **13**{*1–2,1–5,1–5*} and acylureas **14**{*1–2,1–5,1–5,1–6*} from the Diels–Alder adducts **12**{*1–2,1–5,1–5*} and amines **4**{*1–6*}, purity detection by ELS[a]

13{*1–2,1–5,1–5*}/ **14**{*1–2,1–5,1–5,1–6*}	**4**{*1*}	**4**{*2*}	**4**{*3*}	**4**{*4*}	**4**{*5*}	**4**{*6*}
12{*1,1,1*}	43/22 (>99/>99)	—	—	—	—	—
12{*1,1,2*}	—/87 (—/83)	—/81 (—/84)	—	—/85 (—/82)	—	—
12{*1,1,3*}	—/94 (—/>99)	—/99 (—/>99)	—	—	—	—
12{*1,1,4*}	—/92 (—/>99)	—/94 (—/>99)	17/47 (>99/90[b])	—	—	—
12{*1,1,5*}	—[c]/58 (—[c]/98)	—/82 (—/95)		—	—	—
12{*1,3,2*}	16/56 (>99/>99)	—/73 (—/97)	—	—	—	—
12{*1,3,3*}	—/85 (—/97)	—/93 (—/98)	19/46 (93/90[b])	—	—	—
12{*1,3,4*}	6/38 (>99/71)	—/64 (—/96)	—	—	—	—
12{*1,3,5*}	—/67 (—/90[b])	—/65 (—/95[b])	—	—	—	—
12{*1,4,1*}	—/64 (—/>99)	—/80 (—/>99)	—	—	—	—
12{*1,4,2*}	—/96 (—/>99)	—/90 (—/>99)	—/67 (—/98)	—/80 (—/>99)	—/40 (—/>99)	—/42 (—/>99)
12{*1,4,4*}	—/52 (—/60)	—/52 (—/>99)	8/54 (91/95[b])	—/72 (—/>99)	—	—
12{*1,4,5*}	59/— (94/—)	—/70 (—/98)	—/7 (—/95[b])	—	—	—
12{*1,5,2*}	—/76 (—/>99)	—/88 (—/98)	—	—	—	—
12{*1,5,3*}	—/95 (—/88)	—/95 (—/>99)	—/56 (—/90[b])	—/79 (—/>99)	—	—
12{*1,5,4*}	—/63 (—/98)	—	—	—	—	—
12{*1,5,5*}	—/59 (—/90[b])	—/41 (—/90[b])	—	—	—	—
12{*2,1,1*}	—/63 (—/>99)	—	—	—	—	—
12{*2,1,2*}	—/61 (—/87)	—/52 (—/>99)	28/37 (95[b]/99)	—/61 (—/97)	—	—
12{*2,1,3*}	—[d]/70 (—[d]/>99)	—/66 (—/>99)	—/50 (—/95[b])	—/62 (—/99)	—	—
12{*2,1,4*}	—/73 (—/>99)	—/36 (—/>99)	—/16 (—/90[b])	—	—	—
12{*2,1,5*}	—/53 (—/99)	—/10 (—/>99)	—	—/37 (—/90)	—	—
12{*2,2,3*}	33/— (98/—)	—/54 (—/98)	9/— (99/—)	—/60 (—/99)	—	—
12{*2,2,4*}	—/51 (—/99)	—/86 (—/99)	—	—	—	—
12{*2,3,4*}	—/5 (—/>99)	16/62 (95/94)	—	—	—	—
12{*2,4,1*}	—	22/55 (95/90[b])	—	—	—	—
12{*2,4,2*}	—	—/45 (—/>99)	41/50 (<50/90[b])	—/54 (—/67[e])	—	—
12{*2,4,3*}	41/35 (95/95)	—	—	—	—	—
12{*2,4,4*}	44/36 (86/>99)	—/19 (—/>99)	—	—	—	—
12{*2,4,5*}	16/36 (81/97)	—/51 (—/92)	—/42 (—/90)	—	—	—
12{*2,5,2*}	—/89 (—/>99)	—/98 (—/99)	—/85 (—/95[b])	—/97 (—/>99)	—	—
12{*2,5,3*}	—/53 (—/90[b])	—/46 (—/77[e])	—	—/66 (—/93)	—/73 (—/>99)	—
12{*2,5,4*}	—	—/65 (—/>99)	—/63 (—/90[b])	—	—	—
12{*2,5,5*}	—/50 (—/99)	—/74 (—/79[e])	—/71 (—/95[b])	—	—	—

[a] Yield (purity) in % for hydantoin **13**{*1–2,1–5,1–5*}/acylurea **14**{*1–2,1–5,1–5,1–6*}.
[b] Purity estimated by ^{1}H NMR.
[c] Hydantoin **13**{*1,1,5*} was synthesized from pure acylurea **14**{*1,1,5,1*} by stirring in wet MeOH in 85% yield (purity >99%).
[d] Hydantoin **13**{*2,1,3*} was synthesized from pure acylurea **14**{*2,1,3,1*} by stirring in wet MeOH in 89% yield (purity 95%).
[e] Purity detected by UV 254 nm.

2 months, no rearrangement was observed if stored at −78 °C after 3 months.

In contrast to **12**{*1–2,1–5,1–5*}, carbamates **11**{*1–2,1–5,1–5*} did not undergo ring-opening with amines. Carbamate **11**{*2,1,4*} was irradiated in the microwave in chlorobenzene with benzylamine **4**{*5*} and after irradiation for 15 min at 180 °C no reaction was observed.

2.3. Purity analysis

Altogether 7 double Diels–Alder adducts **9**{*1–2,1–5,1–5*}, 44 carbamates **11**{*1–2,1–5,1–5*}, 50 Diels–Alder adducts **12**{*1–2,1–5,1–5*}, 18 hydantoins **13**{*1–2,1–5,1–5*}, and 87 acylureas **14**{*1–2,1–5,1–5,1–6*} were synthesized. All compounds were analyzed by LC–MS/ELSD (Tables 2–6). One hundred sixty-seven compounds (81% of all compounds) passed the purity criteria of 90% by ELSD for the UPCMLD compound collection. The average purity by ELSD of the accepted library members was 96.6% (Table 7). The Diels–Alder adducts **12**{*1–2,1–5,1–5*} contained the highest number of rejected compounds and the accepted compounds from this group had a slightly lower overall purity (94.6%)

Table 7
Number of compounds and purities in % for the five polycyclic scaffolds

Scaffold	Number of compounds in library	Number of compounds with purity ≥90%[a]	Average purity[a,b]
9{*1–2,1–5,1–5*}	7	5	97.8
11{*1–2,1–5,1–5*}	44	40	97.3
12{*1–2,1–5,1–5*}	50	30	94.6
13{*1–2,1–5,1–5*}	18	15	96.8
14{*1–2,1–5,1–5,1–6*}	87	77	97.0
Complete library	206	167	96.9

[a] Purity detected by ELS, for exceptions see Tables 2–6.
[b] Average purity for all compounds that were accepted into the UPCMLD compound collection (purity ≥90% by ELS).

because in several cases those compounds were contaminated with small amounts of the corresponding double Diels–Alder adducts.

2.4. Physicochemical profiling

3-D structures of all library members were built and minimized using the MM2 force field in Macro Model 8.6. The physicochemical profiling of the 206 library members was analyzed computationally using QikProp 2.1.[29] Besides slightly elevated molecular weights in case of the double Diels–Alder adducts **9**{*1–2,1–5,1–5*}, carbamates **11**{*1–2,1–5,1–5*}, and acylureas **14**{*1–2,1–5,1–5,1–6*}, all molecular descriptors show values well within the range that is considered tool-[30] and drug-like[31] (Table 8). Because of the combination of skeletal and appendage diversity, distinct differences in the physicochemical properties exist not only within the five compound classes but also among the scaffolds. A difference in the average molecular weight of around 160 Daltons can be observed between the double Diels–Alder adducts **9**{*1–2,1–5,1–5*}, the Diels–Alder adducts **12**{*1–2,1–5*}, and the hydantoins **13**{*1–2,1–5,1–5*}, which also have a clearly smaller solvent-accessible volume. While the acylureas **14**{*1–2,1–5,1–5,1–6*} attract attention because of their increased ability to act as hydrogen bond donors, the double Diels–Alder adducts **9**{*1–2,1–5,1–5*} are especially rich in the number of hydrogen bond acceptors. The average log P and log S values differ by almost an order of magnitude between the carbamates **11**{*1–2,1–5,1–5*} and the Diels–Alder adducts **12**{*1–2,1–5,1–5*}. The distinction is even more dramatic regarding the number of rotatable bonds with an average of 4.7 for the relatively rigid hydantoins **13**{*1–2,1–5,1–5*} and 9.0 for the more flexible carbamates **11**{*1–2,1–5,1–5*}. As expected due to their size, the double Diels–Alder adducts **9**{*1–2,1–5,1–5*} have a lower predicted permeability than all other scaffolds.

3. Conclusions

Two amino-acid derived cross-conjugated trienes were applied to the synthesis of a discovery library of nonaromatic polycyclic small molecules. Those key building blocks were converted into a sterically biased and electronically tuned 5-iminooxazolidin-2-one scaffold, which allowed excellent stereocontrol in the following Diels–Alder reactions. Although the 5-iminooxazolidin-2-ones are very stable compounds, a conversion into acylureas and hydantoins was accomplished. The combination of skeletal and appendage diversity led to a library of 206 tri- to hexacyclic 5-iminooxazolidin-2-ones, acylureas, and hydantoins. The physicochemical profiling of all compounds demonstrated a high degree of diversity within each compound class and among the five scaffolds. All compounds were analyzed by LC–MS and are currently being evaluated in several high-throughput-screening programs. Results on their biological activities can be accessed in PubChem (http://pubchem.ncbi.nlm.nih.gov).

4. Experimental section

4.1. General

All solvents or reagents were used without further purification. Reactions were monitored by TLC analysis (EM Science pre-coated silica gel 60 F_{254} plates, 250 μm layer thickness) and visualization was accomplished with a 254 nm UV light and by staining with Vaughn's reagent (4.8 g $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 0.2 g $Ce(SO_4)_2\cdot 4H_2O$ in 10 mL concd H_2SO_4 and 90 mL H_2O), $KMnO_4$ (1.0 g $KMnO_4$, 1.0 g K_2CO_3, 2 mL 5% aqueous NaOH, 100 mL H_2O), and *p*-anisaldehyde (2.5 mL *p*-anisaldehyde, 2 mL acetic acid, 3.5 mL concd H_2SO_4, 92 mL EtOH). NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 (298 K) at 300.1 MHz (^{1}H) or 75.5 MHz (^{13}C) using a Bruker Avance 300 with XWIN-NMR software. Chemical Shifts (δ) are reported in parts per million (ppm). Tetramethylsilane (^{1}H), chloroform-*d* (^{13}C), or DMSO-d_6 (^{13}C) were used as internal standards. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=dublet, t=triplet, q=quartet, m=multiplet, br s=broad singlet, app=apparent), integration and coupling constants. IR spectra were obtained on a Nicolet AVATAR 360 FTIR E.S.P. Spectrometer. Mass spectra were obtained on a Micromass Autospec double focusing instrument (EI) or a Waters Q-Tof mass spectrometer (ESI). Melting points were obtained using a heating rate of 2 °C/min on a MelTemp melting point apparatus with digital temperature reading and are reported uncorrected.

Table 8
Physicochemical profiling for the five scaffolds (average±standard deviation), calculated with QikProp 2.1[29]

Scaffolds	**9**{*1–2, 1–5,1–5*}	**11**{*1–2, 1–5,1–5*}	**12**{*1–2, 1–5,1–5*}	**13**{*1–2, 1–5,1–5*}	**14**{*1–2,1–5, 1–5,1–6*}
MW [g/mol]	648±114	586±60	489±60	490±52	591±68
Volume [Å^3]	1724±302	1676±156	1371±160	1371±138	1699±180
SASA [Å^2]	837±138	826±66	687±71	682±60	847±79
Fused rings	6	4	4	4	3
HBD	0.1±0.4	0.4±0.6	0.4±0.6	0.1±0.3	1.5±0.8
HBA	12.1±2.0	11.3±1.2	8.6±1.2	8.0±1.0	10.2±1.4
log P	3.9±2.4	4.4±1.4	3.5±1.5	3.9±1.4	3.8±1.4
log S	−5.2±2.4	−5.1±1.5	−4.2±1.4	−4.4±1.1	−4.0±1.4
Rotatable bonds	5.6±2.2	9.0±1.4	6.0±1.4	4.7±1.4	8.4±1.5
Caco-Perm [nm/s]	131±113	729±544	388±299	503±317	564±477

Compounds were analyzed by reverse-phase HPLC (Alltech Prevail C-18, 100×4.6 mm, 1 mL/min, 50–70% MeCN, 50–30% H_2O) with UV (210 and 254 nm), ELS (Nebulizer 45 °C, Evaporator 45 °C, N_2 flow 1.25 SLM) and MS detection using a Thermo Finnigan Surveyor LC and LCQ Advantage MS system (ESI positive mode).

4.1.1. General procedure for the formation of trienes 1{1–2} (protocol A)

A 1 L-three-necked round bottom flask equipped with a stir-bar and condenser was charged with allenyne (1.00 equiv, 10.90 mmol) and toluene (400 mL). Argon was bubbled through the solution for 5 min and $[Rh(CO)_2Cl]_2$ (0.05 equiv, 0.55 mmol) was added. The reaction was heated at 90 °C for 1 h, then a second portion of catalyst (0.025 equiv, 0.27 mmol) was added. After heating for additional 2.5 h at this temperature the reaction was complete by TLC. The reaction was allowed to cool to room temperature and the solution was loaded directly onto a silica gel column, eluting first with hexanes (200 mL) then 40% ethyl acetate/hexanes. The product-containing fractions were combined and concentrated to afford triene **1**{*1*} in 74% yield. The spectral data matched to that previously reported.[21]

4.1.2. General protocol for the saponification and amidation of esters 1{1–2} (protocol B)

The methyl ester **1**{*1–2*} (1.00 equiv, 5.0–10 mmol) was dissolved in THF (100–200 mL) and water (100–200 mL) was added slowly to maintain a homogeneous solution. Lithium hydroxide hydrate (2.00 equiv) was carefully added and the solution was stirred for 5 min. After complete hydrolysis a saturated solution of ammonium chloride was added (100 mL), the reaction mixture was acidified to pH=1 with 1 M-HCl, extracted with ethyl acetate (3×50 mL), and dried over sodium sulfate. Removal of all volatile components in vacuo gave the crude acid in quantitative yield, which was used in the following step without further purification.

The crude acid was dissolved in dry dichloromethane (150–300 mL) and treated with 1-hydroxybenzotriazole (HOBt, 1.00 equiv), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 1.00 equiv), and 4-dimethylaminopyridine (DMAP, 1.05 equiv). The selected amine **2**{*1–6*} (3.00 equiv of volatile **2**{*1*} or 1.50 equiv of non-volatile **2**{*2–6*}) was added over 10 min while stirring at room temperature. After 4 h the reaction mixture was extracted with water (100 mL) and saturated ammonium chloride (2× 100 mL). The combined aqueous fractions were re-extracted with dichloromethane (50 mL) and all organic fractions were combined and dried over magnesium sulfate. Removal of all volatile components in vacuo provided crude diamide **5**{*1–2,1–5*}, which was purified on an ISCO Companion chromatography station (40 g silica gel, hexane/ethyl acetate). Compounds **5**{*1–2,1–5*} were obtained in yields of 18–93% (Table 1).

4.1.2.1. (Z)-N-(Cyclopropylmethyl)-5-ethylidene-2-methyl-6-oxo-4-vinyl-1,2,5,6-tetrahydropyridine-2-carboxamide (5{1,1}).

IR (film) 2929, 1673, 1635, 1530, 1403, 1273 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.45–6.25 (m, 4H), 5.85 (s, 1H), 5.49 (dd, 1H, J=17.2, 1.5 Hz), 5.26 (dd, 1H, J=10.8, 1.5 Hz), 3.18–3.00 (m, 2H), 2.31 (d, 3H, J=7.5 Hz), 1.61 (s, 3H), 0.98–0.80 (m, 1H), 0.50–0.40 (m, 2H), 0.20–0.10 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 171.8, 165.7, 137.5, 135.3, 133.3, 125.2, 123.4, 117.4, 61.1, 43.7, 26.6, 15.5, 10.1, 2.7, 2.7; MS (ESI) *m/z* (rel intensity) 543 ($[2\,M+Na]^+$, 15), 283 ($[M+Na]^+$, 100); HRMS (EI) *m/z* calculated for $C_{15}H_{20}N_2O_2Na$ 283.1422, found 283.1419.

4.1.3. General protocol for 5-iminooxazolidin-2-one formation and Diels–Alder reaction of diamides 5{1–2,1–5} (protocol C)

Diamide **5**{*1–2,1–5*} (1.00 equiv, 2.5–7.5 mmol) was dissolved in dichloromethane (100–200 mL), cooled to −10 °C and treated with triethylamine (6.00 equiv). Phosgene (20% in toluene, 3.00 equiv) was slowly added while keeping the temperature at −10 °C. After stirring for another 30 min at −10 °C, the reaction mixture was allowed to warm up to room temperature and stirred for an additional 30 min. The reaction mixture was extracted with sodium bicarbonate (100 mL), water (100 mL), and brine (100 ml). The combined aqueous fractions were re-extracted with dichloromethane, and all organic fractions were combined and dried over sodium sulfate. Removal of all volatile components in vacuo provided a mixture of crude 5-iminooxazolidin-2-ones **6**{*1–2,1–5*} and **7**{*1–2,1–5*} in toluene, which was used immediately in the next step without further purification. Acidic workup or chromatography over silica gel led to the hydrolysis of the desired product to starting material **5**{*1–2,1–5*}. Quenching the reaction at −10 °C led to an incomplete reaction, but prevented the formation of the carbamate side product **6**{*1–2,1–5*}.

A mixture of crude 5-iminooxazolidin-2-ones **6**{*1–2,1–5*} and **7**{*1–2,1–5*} (1.00 equiv, 5.0–10 mmol assuming a quantitative conversion in the previous step) was dissolved in toluene (50–100 mL) and divided into five batches of equal volume. Using Radley's Carousel Reaction Station (6 Place or 12 Place) maleimide **3**{*1*}, *N*-methyl maleimide **3**{*2*}, *N*-ethyl maleimide **3**{*3*}, *N*-phenyl maleimide **3**{*4*}, and methyl 2-(*N*-maleimide)acetate **3**{*5*}[32] (1.30 equiv) were added at once to the five batches of 5-iminooxazolidin-2-one and the reaction mixture was heated to 90 °C for 1.5 h. After cooling to room temperature all volatile components were removed in vacuo and the residues were purified on an ISCO Optix 10 parallel chromatography station (12 g silica gel, hexane/ethyl acetate). In general, carbamates **8**{*1–2,1–5,1–5*} (first eluting), double Diels–Alder adducts **9**{*1–2,1–5,1–5*} (second eluting), and Diels–Alder adducts **10**{*1–2,1–5,1–5*} (third eluting, in most cases a mixture of *E*/*Z*-isomers[33]) could be separated (Table 2). In some cases, a second chromatography on an ISCO Companion chromatography station (12 g silica gel, hexane/ethyl acetate) was necessary to obtain pure material. If the reaction mixture was quenched at −10 °C during the formation of 5-iminooxazolidin-2-one **7**{*1–2,1–5*} (Table 2), no carbamate **6**{*1–2,1–5*} was obtained. The double

Diels–Alder adduct **9**{*1–2,1–5,1–5*} (Table 3) was especially observed if the formation of 5-iminooxazolidin-2-one **7**{*1–2,1–5*} was incomplete and the maleimides **3**{*1–5*} were therefore present in greater excess.

*4.1.3.1. rac-(8aR,11aS,11bR,11cS,Z)-1-(Cyclopropylmethylimino)-10-ethyl-11c-methyl-3,9,11-trioxo-6-vinyl-1,3,8,8a,9,10,11,11a,11b,11c-decahydrooxazolo[4,3-a]pyrrolo[3,4-h]isoquinoline-5-yl diethylcarbamate (**8**{1,1,3}).* IR (film) 2979, 2936, 1811, 1735, 1697, 1379, 1346, 1254, 1145, 995 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.18 (dd, 1H, J=17.7, 11.4 Hz), 6.00 (ddd, 1H, 6.9, 4.2, 1.9 Hz), 5.42 (dd, 1H, J=17.6, 1.7 Hz), 5.37 (dd, 1H, J=11.4, 1.8 Hz), 3.83 (dd, 1H, J=8.7, 4.6 Hz), 3.68–3.51 (m, 1H), 3.49–3.24 (m, 7H), 3.19 (app td, 1H, J=7.5, 0.9 Hz), 2.94–2.79 (m, 2H), 2.22 (dddd, 1H, J=15.2, 7.4, 4.3, 0.9 Hz), 1.78 (s, 3H), 1.23 (app t, 3H, J=7.1 Hz), 1.16 (app t, 3H, J=7.1 Hz), 1.38–1.08 (m, 1H), 1.00 (app t, 3H, J=7.2 Hz), 0.60–0.40 (m, 2H), 0.30–0.18 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 178.8, 176.6, 153.1, 151.6, 148.0, 133.2, 132.8, 126.7, 122.5, 120.0, 110.6, 62.4, 52.5, 44.5, 42.3, 42.0, 41.3, 41.1, 33.7, 27.8, 25.7, 13.9, 13.0, 12.9, 11.5, 3.4, 3.2; MS (EI) *m/z* (rel intensity) 510 (15), 466 (7), 385 (61), 286 (20), 160 (23), 100 (100), 72 (84); HRMS (EI) *m/z* calculated for $C_{27}H_{34}N_4O_6$ 510.2478, found 510.2485.

*4.1.3.2. rac-(3aS,3bR,3c^{1}R,8R,8aS,11aR,11bS,12aR,E)-4-(Cyclopropylmethylimino)-2,10-diethyl-3c^1,8-dimethyl-4,5,8,8a,11a,11b,12,12a-octahydro-5-oxa-2,6a,10-triazatricyclopenta[a,e,j]phenalene-1,3,6,7,9,11(2H,3aH,3bH,3c^{1}H,6aH,10H)-hexaone (**9**{1,1,3}).* IR (film) 2981, 2940, 1833, 1742, 1696, 1443, 1403, 1350, 1316, 1294, 1277, 1229 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.95 (dd, 1H, J=9.7, 5.5 Hz), 3.50–3.30 (m, 7H), 3.26 (dd, 1H, J=8.7, 6.6 Hz), 3.06 (dd, 1H, J=8.7, 5.7 Hz), 2.95 (app t, 1H, J=3.9 Hz), 2.71 (ddd, 1H, J=14.5, 13.0, 5.5 Hz), 2.63–2.57 (m, 1H), 2.53 (ddd, 1H, J=14.5, 4.9, 2.4 Hz), 2.28–2.20 (m, 1H), 1.89 (d, 3H, J=7.4 Hz), 1.56 (s, 3H), 1.10 (app t, 3H, J=7.2 Hz), 1.05–0.95 (m, 1H), 0.98 (app t, 3H, J=7.2 Hz), 0.53–0.42 (m, 2H), 0.28–0.15 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 177.9, 176.1, 175.7, 175.6, 155.9, 150.6, 150.0, 147.1, 131.9, 60.0, 52.6, 46.1, 42.6, 41.4, 39.4, 39.0, 35.4, 33.9, 33.9, 33.2, 29.8, 22.8, 15.4, 13.1, 12.9, 11.4, 3.4, 3.2; MS (ESI) *m/z* (rel intensity) 1095 ([2 M+Na]$^+$, 50), 1073 ([2 M+1]$^+$, 25), 975 (25), 559 ([M+Na]$^+$, 25), 537 ([M+1]$^+$, 100), 483 (55), 412 (35); HRMS (ESI) *m/z* calculated for $C_{28}H_{33}N_4O_7$ 537.2349, found 537.2341.

*4.1.3.3. rac-Methyl 2-((1Z,6Z,8aR,11aS,11bR,11cS)-11c-benzyl-1-(benzylimino)-6-ethylidene-3,5,9,11-tetraoxo-1,5,6,8a,9,11,11a,11c-octahydrooxazolo[4,3-a]pyrrolo[3,4-h]isoquinolin-10(3H,8H,11bH)-yl)acetate (**10**{2,4,5}).* IR (film) 2928, 1838, 1742, 1712, 1421, 1365, 1300, 1223 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–7.18 (m, 8H), 6.84–6.80 (m, 2H), 6.61 (q, 1H, J=7.4 Hz), 6.17–6.12 (m, 1H), 4.68 (d, 1H, J=14.1 Hz), 4.58 (d, 1H, J=14.1 Hz), 4.15 (d, 1H, J=17.2 Hz), 4.08 (d, 1H, J=17.2 Hz), 3.92 (dd, 1H, J=8.9, 5.3 Hz), 3.67 (s, 3H), 3.32–3.29 (m, 1H), 3.29 (d, 1H, J=13.5 Hz), 3.15 (d, 1H, J=13.5 Hz), 3.00–2.93 (m, 2H), 2.29 (d, 3H, J=7.5 Hz), 2.30–2.20 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 177.5, 175.8, 166.0, 159.3, 150.2, 146.7, 140.6, 137.8, 134.8, 132.1, 129.8, 129.5, 128.5, 128.3, 128.0, 127.8, 127.0, 123.5, 65.6, 52.3, 51.6, 47.9, 41.0, 40.5, 39.3, 39.2, 24.9, 15.5; MS (ESI) *m/z* (rel intensity) 1157 ([2 M+Na]$^+$, 10), 590 ([M+Na]$^+$, 100), 568 ([M+1]$^+$, 10), 413 (40); HRMS (ESI) *m/z* calculated for $C_{32}H_{29}N_3O_7Na$ 590.1903, found 590.1877.

*4.1.4. General protocol for the hydrogenation of Diels–Alder adducts **8**{1–2,1–5,1–5} and **10**{1–2,1–5,1–5} (protocol D)*

The Diels–Alder adducts **8**{*1–2,1–5,1–5*} or **10**{*1–2,1–5 1–5*} (1.00 equiv, 0.050–0.50 mmol), respectively, were dissolved in dry THF (10 mL) and treated with 20 wt % Pd/C (10%). Using a Radley's Carousel reaction station (12 Place) a single balloon filled with hydrogen was attached and the system was flushed five times with hydrogen. The reaction mixtures were stirred in parallel for 4 h, after which the Pd/C was removed through filtration over a plug of Celite, followed by washing with dichloromethane (3×20 mL). In the case of indole containing substrates **8**{*1–2,5,1–5*} or **10**{*1–2,5,1–5*} another 20 wt % Pd/C (10%) was added after 4 h, the system was flushed again five times with hydrogen and stirred for an additional 20 h. All volatile components were removed in vacuo and the residues were purified on an ISCO Optix 10 parallel chromatography station (12 g silica gel, hexane/ethyl acetate) to afford the reduced Diels–Alder adducts **11**{*1–2,1–5,1–5*} or **12**{*1–2,1–5,1–5*}, respectively (Tables 4 and 5).

*4.1.5. rac-(8aR,11aS,11bR,11cS,Z)-1-(Cyclopropylmethylimino)-6-ethyl-10,11c-dimethyl-3,9,11-trioxo-1,3,8,8a,9,10,11,11a,11b,11c-decahydrooxazolo[4,3-a]pyrrolo-[3,4-h]isoquinolin-5-yl diethylcarbamate (**11**{1,1,2})*

IR (film) 2973, 2935, 1810, 1734, 1699, 1431, 1383, 1255, 1140, 977 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.85 (ddd, 1H, J=7.0, 4.1, 2.2 Hz), 3.83 (dd, 1H, J=8.7, 4.5 Hz), 3.70–3.59 (m, 1H), 3.43–3.18 (m, 6H), 2.87 (ddd, 1H, J=15.4, 8.0, 1.3 Hz), 2.87 (s, 3H), 2.83–2.77 (m, 1H), 2.30–2.10 (m, 3H), 1.76 (s, 3H), 1.24 (app t, 3H, J=7.1 Hz), 1.17 (app t, 3H, J=7.1 Hz), 1.15–1.05 (m, 1H), 0.97 (app t, 3H, J=7.4 Hz), 0.53–0.40 (m, 2H), 0.27–0.20 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 179.1, 176.9, 153.3, 152.0, 147.9, 132.9, 132.3, 120.0, 113.0, 62.2, 52.4, 43.9, 42.3, 42.0, 41.4, 41.3, 27.7, 25.5, 24.9, 17.4, 13.9, 13.0, 11.4, 3.4, 3.2; MS (ESI) *m/z* (rel intensity) 1019 ([2 M+Na]$^+$, 25), 521 ([M+Na]$^+$, 100), 499 ([M+1]$^+$, 45); HRMS (ESI) *m/z* calculated for $C_{26}H_{34}N_4O_6Na$ 521.2376, found 521.2356.

4.1.5.1. rac-Methyl 2-((8aR,11aS,11bR,11cS,Z)-1-(benzylimino)-6-ethyl-11c-methyl-3,5,9,11-tetraoxo-1,7,8,8a,9,11,11a,11c-octahydrooxazolo[4,3-a]pyrrolo[3,4-h]isoquinolin-10(3H,5H,11bH)-yl)acetate (12{1,4,5}). IR (film) 2953, 1833, 1741, 1708, 1420, 1326, 1281, 1220, 975 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34–7.24 (m, 5H), 4.73 (d, 1H, J=14.6 Hz), 4.63 (d, 1H, J=14.6 Hz), 4.15 (d, 1H J=17.0 Hz), 4.05 (d, 1H,

J=17.0 Hz), 3.89 (dd, 1H, *J*=9.5, 5.5 Hz), 3.69 (s, 3H), 3.17 (ddd, 1H, *J*=9.6, 5.3, 2.4 Hz), 3.09 (d, 1H, *J*=5.4 Hz), 2.67–2.59 (m, 2H), 2.52–2.40 (m, 1H), 2.37–2.22 (m, 2H), 2.16–2.02 (m, 1H), 1.74 (s, 3H), 0.95 (app t, 3H, *J*= 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 177.3, 175.7, 166.3, 158.3, 152.0, 146.9, 145.1, 138.3, 133.5, 128.5, 127.8, 127.2, 60.4, 52.6, 51.8, 40.9, 40.7, 39.9, 39.3, 29.7, 25.9, 19.9, 19.0, 12.2; MS (ESI) *m/z* (rel intensity) 516 ([M+Na]$^+$, 20), 494 ([M+1]$^+$, 100), 333 (50); HRMS (ESI) *m/z* calculated for $C_{26}H_{28}N_3O_7$ 494.1927, found 494.1944.

4.1.6. General protocol for the formation of acylureas 14{1–2,1–5,1–5,1–6} (protocol E)

Using 16 mm test tubes, the reduced Diels–Alder adducts **12**{*1–2,1–5,1–5*} (1.0 equiv, 0.030–0.060 mmol) were dissolved in chloroform (1 mL), treated with amines **4**{*1–6*} (5.0 equiv) and stirred in parallel for 2 h at room temperature. All volatile components were removed in vacuo and the residues were purified on an ISCO Optix 10 parallel chromatography station (4 g silica gel, hexane/ethyl acetate) to afford amides **14**{*1–2,1–5,1–51–6*}. In several cases, hydantoins **13**{*1–2,1–5,1–5*} were observed as side product and could be easily separated as the first eluting component (Table 6).

*4.1.6.1. rac-(3aR,9S,9aR,9bS)-9-Benzyl-N^8,N^9-bis(cyclopropylmethyl)-6-ethyl-2-methyl-1,3,7-trioxo-3,3a,4,5,7,9,9a,9b-octahydro-1H-pyrrolo[3,4-h]isoquinoline-8,9(2H)-dicarboxamide (**14**{2,1,2,4}).*

IR (film) 3324, 2960, 1699, 1542, 1437, 1385, 1319, 1287, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.18 (app t, 1H, *J*=5.3 Hz), 7.93 (app t, 1H, *J*=5.1 Hz), 7.18–7.14 (m, 3H), 7.04–7.01 (m, 2H), 4.02 (d, 1H, *J*=14.4 Hz), 3.52 (d, 1H, *J*=14.3 Hz), 3.52 (dd, 1H, *J*=9.3, 3.6 Hz), 3.38–3.20 (m, 3H), 3.14–3.00 (m, 3H), 2.86 (s, 3H), 2.23–1.96 (m, 4H), 1.72–1.58 (m, 1H), 1.51–1.39 (m, 1H), 1.20–1.08 (m, 1H), 1.02–0.87 (m, 1H), 0.57 (app t, 3H, *J*=7.4 Hz), 0.60–0.51 (m, 2H), 0.48–0.42 (m, 2H), 0.34–0.28 (m, 2H), 0.21–0.16 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 178.5, 178.3, 170.3, 166.5, 154.6, 142.8, 138.4, 132.7, 129.8, 128.3, 126.8, 66.9, 45.5, 44.9, 44.7, 44.6, 42.2, 41.0, 25.0, 24.7, 20.5, 19.4, 12.5, 10.9, 10.2, 3.7, 3.6, 3.6, 3.2; MS (ESI) *m/z* (rel intensity) 569 ([M+Na]$^+$, 25), 547 ([M+1]$^+$, 25), 518 (15), 476 (100), 472 (60); HRMS (ESI) *m/z* calculated for $C_{31}H_{39}N_4O_5$ 547.2920, found 547.2883.

4.1.7. General protocol for the formation of hydantoins 13{1–2,1–5,1–5} (protocol F)

Acylurea **14**{*1–2,1–5,1–5,1–6*} (1.0 equiv, 0.030 mmol) was dissolved in methanol (1 mL) and stirred for 16 h. All volatile components were removed in vacuo and the residue was purified on an ISCO Companion chromatography station (4 g silica gel, hexane/ethyl acetate) to afford hydantoin **13**{*1–2, 1–5,1–5*} in 85–89% yield (Table 6, footnotes c and d).

*4.1.7.1. rac-Methyl 2-((8aR,11aS,11bR,11cS)-2-(cyclopropylmethyl)-6-ethyl-11c-methyl-1,3,5,9,11-pentaoxo-2,3,7,8,8a,9,11,11a-octahydro-1H-imidazo[5,1-a]pyrrolo[3,4-h]isoquinolin-10(5H,11bH,11cH)-yl)acetate (**13**{1,1,5}).*

IR (film) 2953, 1796, 1727, 1416, 1368, 1326, 1214 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.15 (d, 1H, *J*=17.1 Hz), 4.05 (d, 1H, *J*=17.0 Hz), 3.69 (s, 3H), 3.66 (dd, 1H, *J*=9.5, 5.1 Hz), 3.53 (dd, 1H, *J*=14.0, 6.8 Hz), 3.45 (dd, 1H, *J*=14.0, 7.4 Hz), 3.24 (ddd, 1H, *J*=9.5, 5.9, 3.1 Hz), 3.04 (d, 1H, *J*=5.1 Hz), 2.70–2.59 (m, 2H), 2.51–2.23 (m, 3H), 2.16–2.08 (m, 1H), 1,67 (s, 3H), 1.28–1.20 (m, 1H), 0.96 (app t, 3H, *J*=7.5 Hz), 0.52–0.46 (m, 2H), 0.39–0.35 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 177.5, 175.1, 173.5, 166.4, 158.3, 151.6, 143.4, 134.3, 60.6, 52.7, 43.8, 41.2, 40.2, 39.6, 39.4, 28.0, 25.7, 20.1, 19.2, 12.5, 9.5, 3.9, 3.7; MS (ESI) *m/z* (rel intensity) 480 ([M+Na]$^+$, 100), 458 ([M+1]$^+$, 10).

4.2. Stability study of acylureas 14{1–2,1–5,1–5,1–6} in DMSO

Acylurea **14**{*2,5,2,1*} (0.0050 mmol) was dissolved in DMSO-d_6 (0.7 mL, Cambridge Isotope Laboratories, Inc, D 99.9%) and stored in an NMR tube at room temperature for several weeks. The composition was determined regularly by ^{1}H NMR studies. Complete and selective conversion of acylurea **14**{*2,5,2,1*} to hydantoin **13**{*2,5,2*} was observed after 2 months. An identical sample was stored in a −78 °C freezer and no rearrangement was observed over 3 months.

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