Synthesis of Perhydroindenes and Perhydroisoindoles via One-Pot Enyne Metathesis/Diels–Alder Reaction; Remarkable Stability of Grubbs Catalyst under Lewis Acidic Conditions

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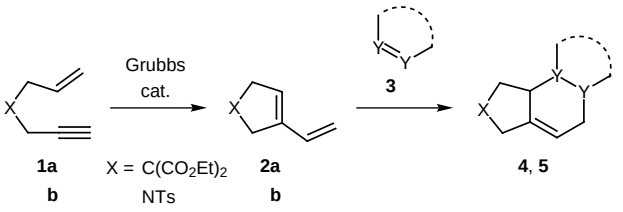
Dedicated to Prof. Bernd Giese on the occasion of his 60th birthday.

Abstract: Perhydroindenes **4a–c** and perhydroisoindoles **5a–c** were obtained by one-pot enyne metathesis and subsequent Diels–Alder reaction starting from diethyl 4-allyl-4-prop-2-ynyl malonate (**1a**) or *N*-allyl-*N*-prop-2-ynyl *p*-toluenesulfonamide (**1b**) and different dienophiles **3a–c** in the presence of Grubbs catalyst. The one-pot reactions proceeded with higher yields as compared to the stepwise sequence. Due to the surprising stability of Grubbs catalyst against Lewis acids such as BCl_3 and $AlCl_3$, it was also possible to perform one-pot enyne methathesis/Diels–Alder reactions with ethyl acrylate (**10**) as dienophile giving the perhydroisoindole **11** in good yield.

Key words: metathesis, Diels–Alder reaction, tandem reactions, Lewis acids

Tandem or domino reactions are of considerable interest for the synthetic chemist due to the convenient experimental procedures, which do not require the isolation and purification of intermediates. An additional advantage is the minimization of solvents.[1] The application of transition metal-mediated transformations in such tandem sequences is also well established. In particular Pd-catalyzed cross-couplings have been successfully utilized for this purpose.[2] Combinations of cross-couplings, either multi Heck-type,[3] multi cycloisomerizations (Pd-zipper reaction),[4] Suzuki–Heck,[5] or Stille–Heck reactions[6] were reported. The major advantage of Pd chemistry is the high tolerance against different reaction conditions and substitution patterns. Thus, Pd cross-couplings were also combined with other reaction types, such as Diels–Alder reactions,[7] Michael additions,[8] 6π electrocyclizations,[9] ene reactions,[10] and anion-capture processes.[11] In contrast, ring closing metathesis and olefin cross metathesis, which have been elaborated into powerful synthetic tools,[12] were only rarely used in tandem with other reaction types. Grigg for example reported a sequential metathesis-Heck reaction.[13]

With respect to the broad applications of Diels–Alder reactions,[14] we anticipated that it might be useful to combine an enyne metathesis[15,16] of **1** yielding functionalized dienes **2** with a subsequent Diels–Alder reaction (Scheme 1). Mori demonstrated that *N*-tosyl-3-vinyl-1,2,5,6-tetrahydropyridines, which were obtained by enynes metathesis, could be used as dienes in thermal [4+2] cycloadditions.[16] A similar approach was used by Heerding for the solid phase synthesis of isoindolines.[17] Very recently, Hoye reported a stepwise enyne metathesis/[4+2] dimerization route to the perhydroisobenzofuranone *rac*-differolide,[18] a natural product isolated from cultures of *Streptomyces aurantiogriseus.*[19] However, all of the above mentioned metathesis/cycloaddition sequences were carried out stepwise. This was also true for the synthesis of pseudooligosaccharide by Blechert,[20] in which the Diels–Alder reaction required either Lewis acid activation or high pressure conditions. We thus attempted to perform the sequence starting from **1** in a one-pot fashion. Depending on the type of dienophile **3** perhydroindenes, perhydroisoindoles and other anellated derivatives **4** with potential biological and pharmaceutical activity should be available. For example, perhydroisoindol-4-ones are potent non-peptidic substance P inhibitors, which are selective for NK_1 receptors.[21] The corresponding pyridazine derivatives of **4** are useful precursors for the synthesis of herbicides.[22] We were particularly interested to test whether the metathesis proceeds in the presence of Lewis acids, because this would allow the use of dienophiles which are too unreactive for thermal Diels–Alder reactions. Furthermore, this would broaden the scope of the enyne metathesis/[4+2] cycloaddition sequence. The results towards this end are reported below.



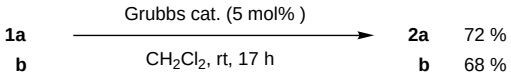
3	Y–Y	4, 5	X
3a	$(CO)_2O$	**4a**	$C(CO_2Et)_2$
3b	$(N–CO_2Et)_2$	**4b**	$C(CO_2Et)_2$
3c	$(N–CO)_2NPh$	**4c**	$C(CO_2Et)_2$
3a	$(CO)_2O$	**5a**	NTs
3b	$(N–CO_2Et)_2$	**5b**	NTs
3c	$(N–CO)_2NPh$	**5c**	NTs

Grubbs cat. = $(Cy_3P)_2Cl_2Ru$=CHPh

Scheme 1

For comparison, metathesis and cycloaddition were first performed in separate steps. As shown in Scheme 2,

enynes **1a**,**b** underwent clean cross metathesis in dichloromethane at room temperature in the presence of 5 mol% of Grubbs catalyst $(PCy_3)_2Cl_2Ru{=}CHPh$[23] to give vinylcyclopentene **2a** and *N*-tosyl-1-vinyldihydropyrrole (**2b**) in 72% and 68% yield, respectively.[24]

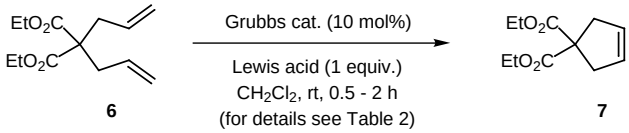


Scheme 2

Then dienes **2a**,**b** were submitted to cycloaddition with either maleic anhydride (**3a**), diethyldiazodicarboxylate (**3b**), or *N*-phenyl-1,2,4-triazol-3,5-dione (**3c**) in dichloromethane at room temperature.[25] After 50 hours, the cycloadducts **4**, **5** were isolated in good yields (Method A, Table 1, entries 1, 3, 5, 7, 9, 11). Next the enynes **1a**,**b** were directly treated with 5 mol% of ruthenium catalyst and 1 equivalent of dienophile **3** in dichloromethane at room temperature. We were pleased to find that the desired cycloadducts **4**, **5** were formed in most cases in higher yields (Method B, Table 1, entries 4, 8, 12) as compared to the overall yields of the stepwise reaction.

The relative configuration of cycloadduct **4a** derived from maleic anhydride (**3a**) was established via NOE experiments. A similar *all-cis* configuration was concluded for **5a** based on analogous NMR spectra.[26]

In order to investigate the tolerance of Grubbs catalyst against Lewis acidic conditions, we examined the ring closing metathesis of **6**.[27] As shown in Scheme 3, diethyl diallylmalonate (**6**) was treated with 10 mol% of Grubbs catalyst and 1 equivalent of Lewis acid in dichloromethane at room temperature. The conversion to the desired cyclopentene **7** was monitored by capillary GC. The results (Table 2) reveal that the formation of the metathesis product **7** is not affected by strong Lewis acids such as BCl_3 and $AlCl_3$ (entries 2, 3). In both cases complete conversion was achieved after 30 min. Weaker Lewis acids such as $V(acac)_2$, $FeCl_3$, $ZnCl_2$, $ZnBr_2$ and $ZnEt_2$ resulted in slightly decreased conversions (entries 6–10). $EtAlCl_2$ required longer reaction times. In contrast, $TiCl_4$ and $SnCl_4$ led to a pronounced decrease of the conversion, which could not be improved by prolonged reaction times. However, even with these Lewis acids the overall conversion was still more than 50%. It should be mentioned that Fürstner observed during the synthesis of the macrolide (−)-gloeosporone decomposition of the Grubbs catalyst when he attempted the ring closing metathesis in the presence of strong Lewis acids.[28] However, the yield of the desired macrolide was increased by using catalytic amounts of $Ti(OiPr)_4$ together with the Grubbs catalyst.[29,30]



Scheme 3

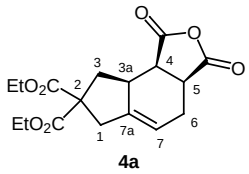
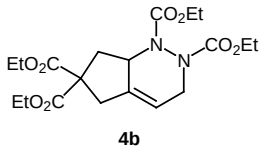
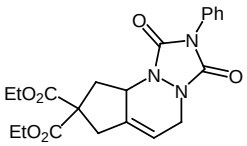
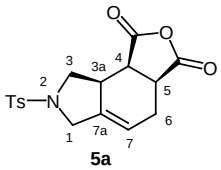
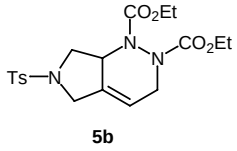
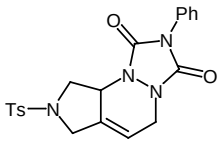
After these exploratory studies, we turned our attention to the Lewis acid-catalyzed Diels–Alder reaction. We antic-

Biographical Sketches

Dagmar Bentz was born in Flensburg in 1967. After working as a technician in the Biochemistry Department, University in Kiel, she studied chemistry in Kiel and finished her diploma in 1997 under the guidance of Prof. Tochtermann. She then moved to the Technical University of Braunschweig where she is currently working on her Ph.D. thesis under the supervision of Prof. Laschat. Her research interests deal with catalytic organometallic reactions.

Sabine Laschat was born in Darmstadt in 1963. She received her diploma in 1987 at the University of Würzburg under the direction of Prof. Jäger and a Ph.D. in 1990 from the University of Mainz under the supervision of Prof. Kunz. After postdoctoral studies with Prof. Overman at the University of California in Irvine, she worked at the University of Münster with Prof. Erker to obtain her habilitation. In 1997, she joined the faculty of the Chemistry Department at the Technical University in Braunschweig, where she is now Associate Professor of Organic Chemistry. Her research interests deal with stereoselective synthesis of biologically active compounds, development of organometallic reagents and catalysts for organic synthesis, and liquid crystal chemistry.

Table 1 Diels–Alder Reaction of Dienes **2a**,**b** and One-Pot Metathesis/Diels–Alder Reaction of Enynes **1** with Different Dienophiles **3a–c** [a,b]

Entry	Enyne	X	Diene	Dienophile	Method	Yield of **4**, **5** (%)	Product
1	**1a**	$C(CO_2Et)_2$	**2a**	**3a**	**A**	38 (53)	 **4a**
2	**1a**	$C(CO_2Et)_2$	**2a**	**3a**	**B**	66	
3	**1a**	$C(CO_2Et)_2$	**2a**	**3b**	**A**	42 (58)	 **4b**
4	**1a**	$C(CO_2Et)_2$	**2a**	**3b**	**B**	57	
5	**1a**	$C(CO_2Et)_2$	**2a**	**3c**	**A**	46 (64)	 **4c**
6	**1a**	$C(CO_2Et)_2$	**2a**	**3c**	**B**	44	
7	**1b**	NTs	**2b**	**3a**	**A**	49 (72)	 **5a**
8	**1b**	NTs	**2b**	**3a**	**B**	75	
9	**1b**	NTs	**2b**	**3b**	**A**	56 (82)	 **5b**
10	**1b**	NTs	**2b**	**3b**	**B**	78	
11	**1b**	NTs	**2c**	**3c**	**A**	58 (85)	 **5c**
12	**1b**	NTs	**2c**	**3c**	**B**	68	

[a] Reaction conditions: Method A (Diels–Alder reaction of isolated diene **2**): CH_2Cl_2, r.t., 50 h. Method B (one pot metathesis/Diels–Alder reaction): 5 mol % of $(PCy_3)_2Cl_2Ru$=CHPh, 1 equiv. of **1**, 1 equiv. of **3**, CH_2Cl_2, r.t., 50 h.
[b] Yields refer to isolated overall yields starting from **1**. Yields in parentheses refer to Diels–Alder reaction of isolated dienes **2**.

ipated that dihydropyrrol **9** (Scheme 4) should be sufficiently activated in order to undergo cycloadditions with dienophiles which are less reactive than **3a**–**c**.[31] Compound **9** was obtained via cross metathesis of **8** in 68% isolated yield (Scheme 4). Then dihydropyrrole **9** was treated with ethyl acrylate (**10**) under various conditions to yield the 4-acyl-7-phenyl-hexahydroisoindole **11**.[32] The results are summarized in Table 3. Preliminary studies showed that no cycloaddition took place, when the amount of Lewis acid was kept below 2.5 equivalents. Higher conversions were obtained with BCl_3 in dichloromethane and particularly in toluene (entries 1, 3) as compared to $AlCl_3$ (entries 2, 4). On a preparative scale, treatment of acrylate **10** with 2.5 equivalents of BCl_3 in toluene for 9 hours at room temperature, and subsequent hydrolysis with bicarbonate, followed by aqueous workup and chromatography yielded 65% of the desired cycloadduct **11**.

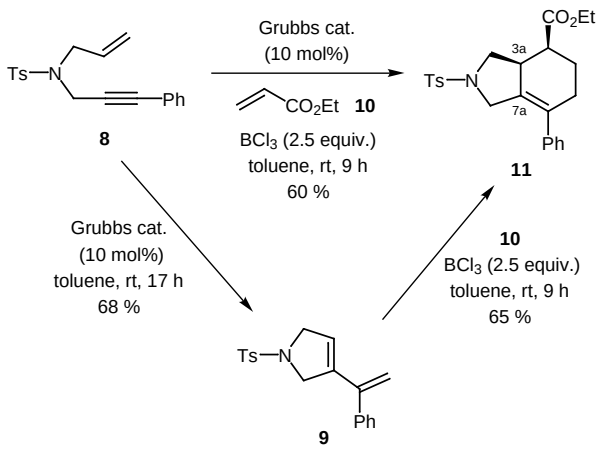
Next, the behavior of BCl_3 in the one pot cross metathesis/Diels–Alder reaction was investigated. As shown in Scheme 4, enyne **8** was treated simultaneously with 10 mol% of Grubbs catalyst and 2.5 equivalents of BCl_3 in toluene at room temperature. The reaction progress was monitored by capillary GC. After 1.5 hours, conversion had reached 87.4% and the reaction was almost complete

Table 2 Ring-closing Metathesis of Diethyl 2,2-diallylmalonate **6** with Grubbs Catalyst in the Presence of Various Lewis Acids [a,b]

Entry	Lewis acid	Conversion [%]
1	–	> 99.0
2	BCl_3	> 99.0
3	$AlCl_3$	> 99.0
4	$EtAlCl_2$	82.0 [c]
5	$TiCl_4$	63.0 [d]
6	$V(acac)_2$	97.0 [d]
7	$FeCl_3$	97.0 [d]
8	$ZnCl_2$	96.0 [d]
9	$ZnBr_2$	98.4 [d]
10	$ZnEt_2$	79.8 [d]
11	$SnCl_4$	55.0 [d]

[a] Reaction conditions: 10 mol % of $(PCy_3)_2Cl_2Ru$=CHPh, 1 equiv. of Lewis acid, CH_2Cl_2, r.t., 30 min.
[b] Conversions were determined by capillary GC.
[c] Complete conversion (> 99.0 %) was observed after 2 h.
[d] No further conversion was detected after 2 h.

after 5 hours (93.5% conversion). Compound **11** was isolated in 60% yield. To verify that the Lewis acid does not interfere with the ruthenium catalyst, the reaction was performed in a sequential fashion. That is, enyne **8** was stirred with Grubbs catalyst for 1.5 hours at room temperature in toluene and then the Lewis acid was added. After 5 hours, 91.4% conversion to the desired cycloadduct **9** was obtained.



Scheme 4

In conclusion, a sequence of Ru-catalyzed enyne metathesis followed by intermolecular Diels–Alder reaction has been elaborated, which allows the convenient preparation of perhydroindenes and perhydroisoindoles in a one-pot fashion at ambient temperature. Grubbs catalyst turned out to be remarkably stable even in the presence of stoichiometric amounts of strong Lewis acids, thus allowing the use of less activated dienophiles such as ethyl acrylate. Possible applications of Grubbs catalyst in other Lewis acid-catalyzed reactions are currently under investigation in our laboratory.

Table 3 Lewis Acid-Catalyzed Diels–Alder Reaction of Diene **9** with Ethyl Acrylate **10** to Hexahydroisoindole **11** under Various Conditions [a,b]

Entry	Solvent	Lewis acid	Conversion [%]
1	CH_2Cl_2	BCl_3	96.0
2	CH_2Cl_2	$AlCl_3$	83.6
3	toluene	BCl_3	98.0
4	toluene	$AlCl_3$	28.6

[a] Reaction conditions: 2.5 equiv. of Lewis acid, r.t., 5 h. When the amount of Lewis acid was kept below 2.5 equiv. no conversion was observed.
[b] Conversions were determined by capillary GC. For isolated yields of **11** see Scheme 4.

All reactions were carried out under N_2 using standard Schlenk techniques. Solvents were dried and deoxygenated by standard procedures. Analytical TLC was performed on precoated Merck Si 254 F plates (0.25 mm thickness) and the products were visualized by spraying with a solution of phosphomolybdic acid in EtOH (5%, v/v) or I_2. Flash chromatography[33] was carried out with Merck silica gel 60 (230–400 mesh). NMR spectra: Bruker AC 200 P [^{1}H (200 MHz), ^{13}C (50 MHz)], Bruker AM 400 [^{1}H (400 MHz), ^{13}C (100 MHz)]. Multiplets in ^{13}C NMR spectra were assigned with the aid of DEPT experiments. Mps were determined by differential scanning calorimetry with a Rheometric Scientific DSC SP, heating and cooling rate: 10 K min^{-1}. IR: Nicolet 5DXC FT-IR spectrometer. GC: Hewlett-Packard HP 6890, HP5-fused silica capillary column (ID 0.32 mm, length 30 m). Temperature program: 80 °C with 8 °C min^{-1} up to 280 °C, then isothermal for 20 min. MS: Finnigan Model MAT 8430 (EI, 70 eV). Diethyl 4-allyl-4-prop-2-inylmalonate (**1a**),[34] diethyl 1-vinylcyclopenten-3,3-dicarboxylate (**2a**),[35] *N*-allyl-*N*-prop-2-inyl-*p*-toluenesulfonamide (**1b**),[16] *N*-tosyl-1-vinyl-2,4-dihydro-2*H*-pyrrole (**2b**)[16] and *N*-allyl-*p*-toluenesulfonamide,[16] were prepared according to literature procedures. Diethyl 2,2-diallylmalonate was commercially available.

Enyne Metathesis; General Procedure

To a solution of $(Cy_3P)_2Cl_2Ru$=CHPh (41 mg, 0.05 mmol) in CH_2Cl_2 (10 mL) was added dropwise a solution of enyne **1** (5.00 mmol) in CH_2Cl_2 (2 mL) and the resulting mixture was stirred for 17 h at r.t. Then the solvent was evaporated and the crude product was purified by flash chromatography on SiO_2.

Diels–Alder Reaction of Dienes 2;General Procedure

To a solution of diene **2** (1.00 mmol) in CH_2Cl_2 (1 mL) was added dropwise a solution of dienophile **3** (1.10 mmol) in CH_2Cl_2 and the mixture was stirred for 50 h at r.t. Then the solvent was evaporated and the crude product was purified by recrystallization or flash chromatography on SiO_2 (Method A, Table 1) .

One-pot Metathesis/Diels−Alder Reaction; General Procedure
To a solution of $(Cy_3P)_2Cl_2Ru$=CHPh (41 mg, 0.05 mmol) in CH_2Cl_2 (5 mL) was added dropwise a solution of enyne **1** (1.00 mmol) and dienophile **3** (1.10 mmol) in CH_2Cl_2 (2 mL) and the mixture was stirred for 50 h at r.t. Then the solvent was evaporated and the crude product was purified by recrystallization or flash chromatography on SiO_2 (Method B, Table 1).

Diethyl 1,3,3a,3b,8,8a-Hexahydrocyclopenta[c]isobenzofuran-1,3-dione-5,5-dicarboxylate (4a)
After evaporation of the solvent, the excess of maleic anhydride was removed by sublimation under high vacuum to yield 178 mg (0.53 mmol, 53%) of a colorless oil.

IR (film): ν = 2984, 2939, 1733, 1447, 1390, 1297, 1256, 1162, 1098, 1073, 1017, 953, 862, 755, 697 cm^{-1}.

UV/VIS (CH_3CN): λ_{max} (lg ε) = 206 (5.98), 216 (5.64) nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.78 (dddd, 1H, *J* = 7.3, 5.1, 5.1, 2.5 Hz, 7-H), 4.19 (q, 4H, *J* = 7.1 Hz, OC*H*$_2$CH$_3$), 3.43 (ddd, 1H, *J* = 9.8, 9.8, 7.6 Hz, 4-H), 3.36 (ddd, 1H, *J* = 9.8, 6.7, 1.5 Hz, 5-H), 2.93 (dd, 2H, *J* = 13.5, 1.5 Hz, 1-H), 2.80−2.71 (m, 3H, 6-H$_a$, 3a-H, 3-H$_a$), 2.58 (dd, 1H, *J* = 12.6, 10.5 Hz, 3-H$_b$), 2.19 (dddd, 1H, *J* = 13.4, 6.7, 3.5, 3.0 Hz, 6-H$_b$), 1.25 (t, 3H, *J* = 7.1 Hz, OCH$_2$C*H*$_3$), 1.25 (t, 3H, *J* = 7.1 Hz, OCH$_2$C*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4 (COOEt), 170.4 (CO), 143.5 (C-7a), 117.9 (C-7), 61.7 (O*C*H$_2$CH$_3$), 59.8 (C-2), 42.6 (C-4), 41.7 (C-5), 38.3 (C-1), 37.9 (C-3a), 34.7 (C-3), 24.7 (C-6), 14.0 (OCH$_2$*C*H$_3$).

GC-MS (EI): *m/z* (%) = 336 (M^+, 3), 291 (23), 263 (61), 234 (15), 216 (88), 189 (43), 161 (25), 143 (50), 117 (100), 105 (6), 91 (30), 77 (6), 65 (5).

HRMS (EI): *m/z* calcd. for $C_{17}H_{20}O_7$: 336.1203. Found: 336.1209.

Anal. calcd. for $C_{17}H_{20}O_7$: C, 60.71; H, 5.99. Found: C, 60.53; H, 6.05.

Tetraethyl 1,2,2a,7-Tetrahydrocyclopenta[*c*]pyridazin-1,2,6,6-tetracarboxylate (4b)
Flash chromatography (Et_2O/*n*-pentane, 1: 1) yielded 238 mg (0.60 mmol, 58%) of a colorless oil.

IR (film): ν = 2985, 1731, 1656, 1467, 1446, 1411, 1378, 1336, 1313, 1299, 1256, 1239, 1176, 1095, 1075, 1049, 1024 cm^{-1}.

UV/VIS (CH_3CN): λ_{max} (lg ε) = 192 (2.87) nm.

^{1}H NMR (360 MHz, DMSO-d_6, 382 K): δ = 5.86 (br s, 1H, 7-H), 4.27−4.20 (m, 1H, 3a-H), 4.19 (q, 8H, *J* = 7.0 Hz, OC*H*$_2$CH$_3$), 2.94 (br s, 2H, 6-H), 2.92 (m, 2H,1-H) 2.15 (m, 2H, 3-H), 1.27 (t, 6H, *J* = 7.0 Hz, OCH$_2$C*H*$_3$), 1.24 (t, 6H, *J* = 7.0 Hz, OCH$_2$C*H*$_3$).

^{13}C NMR (90 MHz, DMSO-d_6, 303 K): δ = 172.1 [(C-2) *C*OOEt], 171.4 [(C-2) *C*OOEt], 156.5 (N-COOEt), 156.1 (N-COOEt), 138.1 (C-7a), 117.2 (C-7), 62.7 (O*C*H$_2$CH$_3$), 56.6 (C-3a), 55.5 (C-2), 44.4 (C-6), 39.2 (C-3), 35.9 (C-1), 14.7 (OCH$_2$*C*H$_3$).

MS (EI): *m/z* (%) = 412 (M^+, 39), 366 (57), 339 (100), 323 (21), 310 (9), 292 (42), 267 (21), 265 (25), 249 (69), 237 (11), 221 (20), 193 (39), 176 (22), 165 (22), 147 (13), 119 (24), 104 (22), 91 (26), 73 (16).

HRMS (EI): *m/z* calcd. for $C_{19}H_{28}N_2O_8$: 412.1846. Found: 412.1838.

Anal. calcd. for $C_{19}H_{28}N_2O_8$: C, 55.33; H, 6.84; N, 6.79. Found: C, 55.13; H, 6.95; N, 6.51.

Diethyl *N*-Phenyl-4,4a,5,6,7,8,9,10-octahydro-2-cyclopenta[*c*]-pyridazino[1,2-*a*]-2,4,10-triazoline-1,3-dione 6,6-dicarboxylate (4c)
Flash chromatography (*n*-pentane/EtOAc, 1: 1) gave 260 mg (0.64 mmol, 64%) of a colorless solid; mp: 130 °C.

IR (KBr): ν = 2983, 2939, 2867, 1776, 1723, 1502, 1417, 1364, 1305, 1288, 1235, 1193, 1140, 1074, 1053, 1016, 769, 710, 690 cm^{-1}.

UV/VIS (CH_3CN): λ_{max} (lg ε) = 194 (2.66), 220 (2.22) nm.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.58−7.43 (m, 5H, Ph), 5.81 (br s, 1H, 7-H), 4.38 (dddd, 1H, *J* = 9.5, 7.5, 2.8, 2.6 Hz, 3a-H), 4.30 (br d, 1H, *J* = 16.2 Hz, 6-H$_a$), 4.22 (q, 2H, *J* = 7.1 Hz, OC*H*$_2$CH$_3$), 4.20 (q, 2H, *J* = 7.1 Hz, OC*H*$_2$CH$_3$), 4.00 (br d, 1H, *J* = 16.2 Hz, 6-H$_b$), 3.07 (m, 2H, 1-H), 3.06 (dd, 1H, *J* = 13.3, 7.5 Hz, 3-H$_a$), 2.23 (dd, 1H, *J* = 13.3, 9.5 Hz, 3-H$_b$), 1.23 (t, 3H, *J* = 7.1 Hz, OCH$_2$C*H*$_3$), 1.22 (t, 3H, *J* = 7.1 Hz, OCH$_2$C*H*$_3$).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.8 (COO), 171.2 (COO), 154.5 (CO), 152.1 (CO), 136.6 (C-7a), 132.3 (C-*i*), 129.79 (C-*m*), 129.0 (C-*p*), 127.2 (C-*o*), 114.6 (C-7), 62.7 (O*C*H$_2$CH$_3$), 62.6 (O*C*H$_2$CH$_3$), 57.6 (C-2), 57.1 (C-3a), 43.3 (C-6), 38.8 (C-3), 36.1 (C-1), 14.7 (OCH$_2$*C*H$_3$).

MS (EI): *m/z* (%) = 413 (M^+ 100), 368 (24), 340 (37), 339 (41), 310 (26), 294 (18), 266 (78), 241 (5), 221 (8), 191 (12), 175 (6), 164 (7), 147 (18), 119 (23), 104 (9), 91 (34), 77 (11).

HRMS (EI): *m/z* calcd. for $C_{21}H_{23}N_3O_6$: 413.1587. Found: 413.1581.

Anal. calcd. for $C_{21}H_{23}N_3O_6$: C, 61.01; H, 5.61; N, 10.06. Found: C, 61.02; H, 5.63; N, 10.07.

***N*-Tosyl-2,2a,2b,3,5,7,7a,8-dodecahydroisoindolo[5,6-*c*]furan-2,8-dione (5a)**
Recrystallization of the crude product from acetone gave 250 mg (0.72 mmol, 72%) of a colorless solid; mp: 191 °C (dec.).

IR (KBr): ν = 3065, 2971, 2956, 2921, 2909, 2853, 1839, 1774, 1598, 1471, 1344, 1304, 1223, 1161, 1123, 1099, 1093, 1028, 967, 831, 819, 794 cm^{-1}.

UV/VIS (CH_3CN): λ_{max} (lg ε) = 230 (2.78), 196 (3.27) nm.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.70 (d, 2H, *J* = 8.1 Hz, *o*-H), 7.49 (d, 2H, *J* = 8.1 Hz, *m*-H), 5.86 (ddd, 1H, *J* = 7.4, 2.0, 2.0 Hz, 7-H), 3.73-3.65 (m, 4H, 4-H, 5-H, 1-H), 3.59 (dd, 1H, *J* = 9.1, 1.7 Hz, 3-H$_a$), 3.45 (dd, 1H, *J* = 10.1, 9.1 Hz, 3-H$_b$), 2.83 (br s, 1H, 3a-H), 2.55 (ddd, 1H, *J* = 13.9, 7.4, 1.5 Hz, 6-H$_a$), 2.44 (s, 3H, CH_3), 2.14 (ddd, 1H, *J* = 13.9, 6.4, 2.0 Hz, 6-H$_b$).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.0 (CO), 173.1 (CO), 144.8 (C-*i*), 140.9 (C-*p*), 132.3 (C-7a), 130.8 (C-*m*), 128.8 (C-*o*), 118.8 (C-7), 51.6 (C-1), 49.6 (C-9), 42.6 (C-4), 41.5 (C-5), 37.3 (C-3a), 25.2 (C-6), 21.9 (CH_3).

MS (EI): *m/z* (%) = 347 (M^+, 1), 319 (1), 274 (1), 192 (100), 164 (10), 155 (14), 146 (5), 139 (2), 118 (11), 91 (59), 77 (4), 65 (15).

HRMS (EI): *m/z* calcd. for $C_{17}H_{17}NO_5S$: 347.0827. Found: 347.0823.

Anal. calcd. for $C_{17}H_{17}NO_5S$: C, 58.78; H, 4.93; N, 4.03; S, 9.23. Found: C, 58.68; H, 5.00; N, 3.94; S, 9.41.

Diethyl *N*-Tosyl-1,2,2a,3,4,5,7-octahydropyrrolo[3,4-*c*]pyridazin-1,2-dicarboxylate (5b)
After evaporation of the solvent, the crude product was washed with CH_2Cl_2 and dried to give 347 mg (0.82 mmol, 82%) of a colorless solid; mp: 223 °C.

IR (KBr): ν = 2964, 2935, 2929, 2872, 1718, 1598, 1494, 1467, 1436, 1412, 1379, 1347, 1306, 1280, 1224, 1163, 1095, 1066, 1028, 1018, 818 cm^{-1}.

UV/VIS (CH_3CN): λ_{max} (lg ε) = 248 (6.52), 194 (7.66) nm.

^1H NMR (200 MHz, DMSO-d_6, 313 K): δ = 7.75 (d, 2H, *J* = 8.4 Hz, *o*-H), 7.46 (d, 2H, *J* = 8.6 Hz, *m*-H), 5.95 (br s, 1H, 7-H), 4.20 (q, 2H, *J* = 7.0 Hz, OCH_2CH_3), 4.14 (q, 2H, *J* = 7.0 Hz, OCH_2CH_3), 4.09−3.93 (m, 4H, 1-H, 3-H), 3.76 (dd, 1H, *J* = 10.0, 1.0 Hz, 6-H_a), 2.94 (dd, 1H, *J* = 9.8, 1.0 Hz, 3a-H), 2.78 (dd, 1H, *J* = 10.0, 1.0 Hz, 6-H_b), 2.43 (s, 3H, CH_3), 1.22 (t, 3H, *J* = 7.0 Hz, OCH_2CH_3), 2.10 (t, 3H, *J* = 7.0 Hz, OCH_2CH_3).

^{13}C NMR (50 MHz, DMSO-d_6, 413 K): δ = 155.4 (COO), 154.7 (COO), 143.6 (C-*i*), 135.3 (C-*p*), 133.8 (C-7a), 129.8 (C-*o*), 127.1 (C-*m*), 118.9 (C-7), 62.3 (OCH_2CH_3), 62.0 (OCH_2CH_3), 54.4 (C-3a), 50.9 (C-6), 48.8 (C-3), 43.8 (C-1), 20.7 (CH_3), 13.9 (OCH_2CH_3), 13.8 (OCH_2CH_3).

MS (EI): *m/z* (%) = 423 (M^+, 7), 378 (5), 351 (18), 334 (2), 321 (1), 268 (76), 247 (86), 240 (5), 224 (15), 196 (100), 179 (18), 168 (44), 155 (30), 150 (11), 139 (12), 122 (34), 107 (14), 94 (45), 91 (70), 80 (15), 65 (21).

HRMS (EI): *m/z* calcd. for $C_{19}H_{25}N_3O_6S$: 423.1464. Found: 423.1464.

Anal. calcd. for $C_{19}H_{25}N_3O_6S$: C, 53.89; H, 5.95; N, 9.92; S, 7.57. Found: C, 53.73; H, 6.00; N, 9.64; S, 7.59.

2-*N*-Phenyl-6-*N*-tosyl-4,4a,5,6,7,9,10-octahydropyrrolo[3,4-*c*]-pyridazino[1,2-*a*][2,4,10]triazoline-1,3-dione (5c)

Recrystallization from $CHCl_3$ yielded 360 mg (0.85 mmol, 85%) of a colorless solid; mp: 249 °C.

IR (KBr): ν = 3070, 2880, 1767, 1714, 1598, 1506, 1494, 1442, 1410, 1369, 1343, 1305, 1284, 1199, 1185, 1160, 1091, 1067, 1016, 823, 764, 709 cm^{-1}.

UV/VIS (CH_3CN): λ_{max} (lg ε) = 224 (4.35), 196 (4.80) nm.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.76 [d, 2H, *J* = 8.1 Hz, *o*-H (N-Ts)], 7.48−7.38 (m, 5H, Ph), 7.36 [d, 2H, *J* = 7.9 Hz, *m*-H (N-Ts)], 5.81 (br s, 1H, 7-H), 4.41 (dd, 1H, *J* = 10.0, 7.3 Hz, 3-H_a), 4.39 (ddd, 1H, *J* = 9.9, 3.5, 3.5 Hz, 6-H_a), 4.14 (br d, 2 H, *J* = 13.3 Hz, 1-H), 4.00−3.92 (m, 2H, 6-H_b, 3a-H), 3.16 (dd, 1H, *J* = 10.2, 9.9 Hz, 3-H_b), 2.45 (s, 3H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.6 (COO), 151.4 (COO), 144.1 [C-*i* (N-Ts)], 133.3 [C-*p* (N-Ts)], 133.0 (C-7a), 130.7 [C-*i* (N-Ph)], 130.0 [C-*m* (N-Ts)], 129.2 [C-*o* (N-Ts)], 128.3 [C-*p* (N-Ph)], 127.6 [C-*m* (N-Ph)], 125.3 [C-*o* (N-Ph)], 114.7 (C-7), 55.2 (C-3a), 51.6 (C-6), 48.9 (C-3), 42.6 (C-1), 21.5 (CH_3).

MS (EI): *m/z* (%) = 424 (M^+, 37), 270 (18), 269 (100), 268 (44), 248 (28), 247 (62), 241 (70), 155 (13), 150 (9), 139 (3), 121 (61), 119 (25), 94 (30), 91 (70), 80 (19).

HRMS (EI): *m/z* calcd. for $C_{21}H_{20}N_4O_4S$: 424.1205. Found: 424.1200.

Anal. calcd. for $C_{21}H_{20}N_4O_4S$: C, 59.42; H, 4.75; N, 13.20; S, 7.55. Found: C, 59.48; H, 4.73; N, 12.99; S, 7.30.

Ring-closing Metathesis of 6; General Procedure

To a solution of (20 mg, 0.08 mmol) diethyl 2,2-diallylmalonate (**6**) in CH_2Cl_2 (2 mL) were added Grubbs catalyst (6.6 mg, 0.008 mmol) and Lewis acid (see also Table 2) and the resulting mixture was stirred at r.t. Aliquots were taken after 30 min and 2 h, respectively, and analyzed via capillary GC. For analytic and spectroscopic data of product **7,** see ref.[27]

***N*-Allyl-*N*-3-phenylprop-2-inyl-*p*-toluenesulfonamide (8)**

A solution of *N*-allyl-*p*-toluenesulfonamide (1.11 g, 5.00 mmol) in THF (10 mL) was added dropwise at 0 °C to a suspension of NaH (0.14 g, 6.00 mmol) in THF (80 mL) and the resulting mixture was stirred for 30 min at 0 °C. Then a solution of phenylproparyl bromide (0.98 g, 5.00 mmol) in THF (10 mL) was added dropwise and the mixture was refluxed for 90 min. After cooling to r.t., the reaction mixture was poured onto ice (100 mL), the organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on SiO_2 (Et_2O/*n*-pentane, 1: 5) to give 1.10 g (3.40 mmol, 68%) of a colorless solid; mp: 93−94 °C.

IR (KBr): ν = 3202, 3106, 3039, 3025, 2935, 2881, 2805, 1788, 1630, 1335, 1138, 954, 930, 727, 650, 515 cm^{-1}.

UV/VIS (CH_3CN): λ_{max} (lg ε) = 252 (7.35), 232 (7.17), 196 (7.35) nm.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.82 [d, 2H, *J* = 8.5 Hz, *o*-H (Ts)], 7.34−7.09 (m, 5H, Ph), 7.29 [d, 2H, *J* = 10.1 Hz, *m*-H (Ts)], 5.84 (dddd, 1H, *J* = 16.7, 9.9, 6.3, 6.3 Hz, = CH), 5.38 (dddd, 1H, *J* = 16.7, 1.5, 1.5, 1.5 Hz, = CH_2), 5.31 (dddd, 1H, *J* = 10.1, 1.3, 1.3, 1.3 Hz, = CH_2), 4.35 (s, 2H, 1-H), 3.94 (dd, 2H, *J* = 7.6, 1.3 Hz, $CH_2CH = CH_2$), 2.37 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.4 (C-*i*, Ts), 135.8 (C-*p*, Ts), 132.0 (C-*o*, Ph), 131.4 (= CH), 129.5 (C-*m*, Ph), 128.3 (C-*p*, Ph), 128.0 (C-*m*, Ts), 127.7 (C-*o*, Ts), 122.1 (C-*i*, Ph), 119.9 (= CH_2), 85.6 (C-3), 81.5 (C-2), 49.2 (C-1), 36.6 ($CH_2CH = CH_2$), 21.3 (CH_3).

MS (EI): *m/z* (%) = 325 (M^+, 3), 298 (2), 260 (4), 248 (1), 222 (6), 192 (6), 170 (67), 169 (26), 155 (12), 142 (58), 139 (8), 128 (19), 115 (100), 102 (7), 91 (68), 89 (17), 77 (6).

HRMS (EI): *m/z* calcd. for $C_{19}H_{19}NO_2S$: 325.1132. Found: 325.1136.

***N*-Tosyl-1-(1-phenylvinyl)-2,4-dihydro-2*H*-pyrrole (9)**

To a solution of Grubbs catalyst (206 mg, 0.25 mmol) in toluene (10 mL) was added dropwise a solution of enyne **8** (1.63 g, 5.00 mmol) in toluene (2 mL) and the resulting mixture was stirred for 17 h at r.t. Then the solvent was removed in vacuo and the crude product was purified by flash chromatography on SiO_2 (pentane/Et_2O 70:30) to give 1.10 g (3.40 mmol, 68%) of a colorless amorphous solid.

IR (KBr): ν = 3001, 2942, 2877, 1610, 1320, 1178, 1081, 866, 826, 654, 582, 560
cm^{-1}.

UV/VIS (CH_3CN): λ_{max} (lg ε) = 232 (7.38), 194 (7.40) nm.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.74 [d, 2H, *J* = 8.3 Hz, *o*-H (Ts)], 7.33 [d, 2H, *J* = 8.1 Hz, *m*-H (Ts)], 7.30−7.17 (m, 5H, Ph), 5.45 (dd, 1H, *J* = 3.8, 2.0 Hz, 4-H), 5.15 (s, 1H, = CH_2), 5.05 (s, 1H, = CH_2), 4.33 (ddd, 2H, *J* = 3.8, 3.8, 1.8 Hz, 5-H), 4.18 (dddd, 2H, *J* = 2.8, 2.8, 2.8, 1.0 Hz, 2-H), 2.42 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.5 (C-*i*, Ts), 142.9 (C-3), 140.0 (= CPh), 138.2 (C-*p*, Ts), 134.1 (C-*i*, Ph), 129.8 (C-*m*, Ts), 128.2 (C-*o*, C-*m*, Ph), 127.8 (C-*p*, Ph), 127.5 (C-*o*, Ts), 124.0 (C-4), 115.9 (= CH_2), 55.5 (C-2), 54.7 (C-5), 21.5 (CH_3).

MS (EI): *m/z* (%) = 325 (M^+, 34), 248 (3), 222 (11), 202 (2), 188 (3), 170 (29), 168 (18), 155 (25), 139 (8), 143 (21), 128 (22), 115 (28), 103 (30), 91 (100), 77 (20).

HRMS (EI): *m/z* calcd. for $C_{19}H_{19}NO_2S$: 325.1132. Found: 325.1136.

Anal. calcd. for $C_{19}H_{19}NO_2S$: C, 70.13; H, 5.88; N, 4.30; S, 9.85. Found: C, 69.86; H, 5.83; N, 4.18; S, 9.80.

Lewis Acid-catalyzed Diels–Alder Reaction of Diene 8 with Ethyl Acrylate (10); General Procedure

To a solution of ethyl acrylate **10** (6.5 μL, 0.06 mmol) in a solvent (2 mL) were added Lewis acid (2.50 equiv) and diene **9** (20 mg, 0.06 mmol) dropwise and the mixture was stirred for 5 h at r.t. (see Table 3). Then the mixture was poured onto sat. $NaHCO_3$, the layers were separated, the aqueous layer was extracted with the solvent (2 mL), and the combined organic layers were dried ($MgSO_4$). An aliquot was analyzed by capillary GC.

4-Carboxyethyl-7-phenyl-*N*-tosyl-1,3,3a,4,5,6-hexahydroisoindole (11)

To a solution of ethyl acrylate **10** (33 mg, 0.30 mmol) in toluene (10 mL) were added BCl_3 (0.75 mL, 0.75 mmol, 1 M solution in CH_2Cl_2) and diene **9** (98 mg, 0.30 mmol) dropwise and the mixture was stirred for 9 h at r.t. Hydrolysis and work-up was performed as described above. The crude product was purified by flash chromatography on SiO_2 (pentane/Et_2O, 70: 30) to give 83 mg (65%) of a colorless oil.

IR (KBr): ν = 3062, 3028, 2976, 2935, 2880, 1731, 1656, 1618, 1598, 1494, 1463, 1448, 1394, 1378, 1366, 1345, 1307, 1292, 1260, 1214, 1163, 1095, 1061, 1030, 1019, 953, 816 cm^{-1}.

UV/VIS (CH_3CN): λ_{max} (lg ε) = 260 (3.64), 232 (4.11) nm.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.55 [d, 2H, *J* = 8.3 Hz, *o*-H (Ts)], 7.25–7.16 [m, 5H, *m*-H (Ts), *p*-H, *m*-H (Ph)], 7.01 [d, 2H, *J* = 8.0 Hz, *o*-H (Ph)), 4.06 (br d, 1H, *J* = 14.2 Hz, 1-H_a), 3.97 (q, 2H, *J* = 7.1 Hz, OCH_2CH_3), 3.61 (ddd, 1H, *J* = 13.7, 9.6, 1.3 Hz, 3-H_a), 3.53 (br d, 1H, *J* = 14.1 Hz, 1-H_b), 2.86 (m, 3H, 4-H, 3a-H, 3-H_b), 2.60–2.49 (m, 1H, 6-H_a), 2.33 (s, 3H, CH_3), 2.13 (br s, 1H, 6-H_b), 2.02–1.94 (m, 1H, 5-H_a), 1.85–1.75 (m, 1H, 5-H_b), 1.07 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2 (CO), 143.3 (C-*i*, Ts), 140.8 (C-*p*, Ts), 133.4, 131.6 (C-7, C-7a), 129.9 (C-*i*, Ph), 129.5 (C-*m*, Ts), 128.2 (C-*o*, Ph), 127.4 (C-*o*, Ts), 127.0 (C-*p*, Ph), 126.9 (C-*m*, Ph), 60.1 (OCH_2CH_3), 50.2 (C-1), 49.7 (C-3), 40.0, 38.5 (C-4, C-3a), 27.2 (C-6), 24.6 (C-5), 21.4 (CH_3), 14.0 (OCH_2CH_3).

MS (EI): *m/z* (%) = 425 (M^+, 34), 380 (6), 352 (2), 348 (3), 270 (100), 242 (7), 224 (6), 196 (29), 182 (4), 169 (17), 155 (6), 141 (5), 128 (3), 118 (3), 91 (6), 77 (1).

One-pot Enyne Metathesis/Diels–Alder Reaction of 8

To a solution of Grubbs catalyst (25 mg, 0.03 mmol) in toluene (10 mL) was added enyne **8** (98 mg, 0.30 mmol) and the mixture was stirred for 2 min at r.t. Then a solution of ethyl acrylate **10** (33 mg, 0.30 mmol) in toluene (1 mL) and BCl_3 (0.75 ml, 0.75 mmol, 1 M solution in CH_2Cl_2) were added. The remaining mixture was stirred for 9 h at r.t. After hydrolysis, work-up, and flash chromatography, as described above, 77 mg (60%) of a colorless oil was obtained.

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