Synthesis of Cyclic Enehydrazides by Ring-Closing Metathesis

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Abstract: A series of five- and six-membered unsaturated hydrazides were efficiently prepared from precursor dienehydrazides through a ring-closing metathesis (RCM) reaction. The parent compounds were easily obtained by sequential acylation and alkylation of appropriate hydrazines.

Key words: metathesis, ring closure, heterocycles, enehydrazides

During the past decade the ring-closing metathesis (RCM) reaction has emerged as a powerful synthetic tool for the creation of carbon–carbon bonds and this annulation technique ranks henceforth highly in the hierarchy of synthetic tactics for the elaboration of small-, medium- and large-sized unsaturated heterocycles.[1] The propulsion of the RCM reaction to the forefront of contemporary organic chemistry stems also mainly from the advent of an array of efficient homogeneous ruthenium catalysts,[2] the three most common of which, **1**–**3**, are shown in Figure 1.

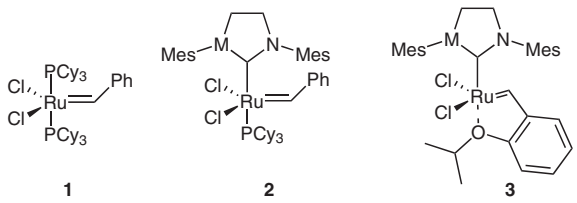

Figure 1 Common ruthenium catalysts used in RCM reactions

In the case of nitrogen containing heterocycles, the synthesis of five- and six-membered ring systems is well documented[3] as witnessed by the numerous total syntheses of complex molecules, alkaloids[4] and amino acid derivatives[5] that include this versatile technique as the synthetic key step. Paradoxically, the synthesis of small- and medium-sized azaheterocycles such as unsaturated five- and six-membered hydrazides **4**–**7** has not been investigated in detail. The rising interest in these classes of azacycles as putative pharmaceuticals, namely as potent potassium channel activators,[6] prompted us to develop a synthetic sequence leading to this class of compounds via an RCM approach.

As outlined in the retrosynthetic Scheme 1, our straightforward strategy towards the azacycles **4**–**7** hinges upon the annulation of the dienic hydrazides **8**–**12** which could be in turn assembled by sequential N-alkylation of enehydrazides **13**–**16** and N-acylation of the appropriate hydrazines **17**–**19** (Table 1). For the key step of this synthetic approach, which is based on inexpensive and readily accessible starting materials, only the commercially available Grubbs catalysts **1** and **2** were employed.

The first facet of the synthesis was the preparation of the diolefinic hydrazides **8a**,**b**–**10a**,**b**. These highly conjugated precursors were easily synthesized as depicted in Scheme 2 by treatment of the suitably substituted hydrazines **17**–**19** with acryloyl (**20a**; n = 0, R^1 = H), methacryloyl (**20b**; n = 0, R^1 = Me) and but-3-enoyl chloride (**21**; n = 1, R^1 = H), respectively. The mandatory installation of the second olefinic unit was readily accessed by N-alkylation of the resulting enehydrazide **13**–**16** with

Table 1 Compounds **4**–**19** Prepared

Compound(s)	R^1	R^2	R^3	m	n
17	–	Ph	Ph	–	–
18	–	$(CH_2)_5$		–	–
19	–	$(CH_2)_3CH(CH_2OMe)$		–	–
13a	H	Ph	Ph	–	0
13b	Me	Ph	Ph	–	0
14a	H	$(CH_2)_5$		–	0
14b	Me	$(CH_2)_5$		–	0
15a	H	$(CH_2)_3CH(CH_2OMe)$		–	0
15b	Me	$(CH_2)_3CH(CH_2OMe)$		–	0
16	H	Ph	Ph	–	1
8a, **4a**	H	Ph	Ph	1	0
8b, **4b**	Me	Ph	Ph	1	0
9a, **5a**	H	$(CH_2)_5$		1	0
9b, **5b**	Me	$(CH_2)_5$		1	0
10a, **6a**	H	$(CH_2)_3CH(CH_2OMe)$		1	0
10b, **6b**	Me	$(CH_2)_3CH(CH_2OMe)$		1	0
11a, **7a**	H	Ph	Ph	2	0
11b, **7b**	Me	Ph	Ph	2	0
12	H	Ph	Ph	1	1

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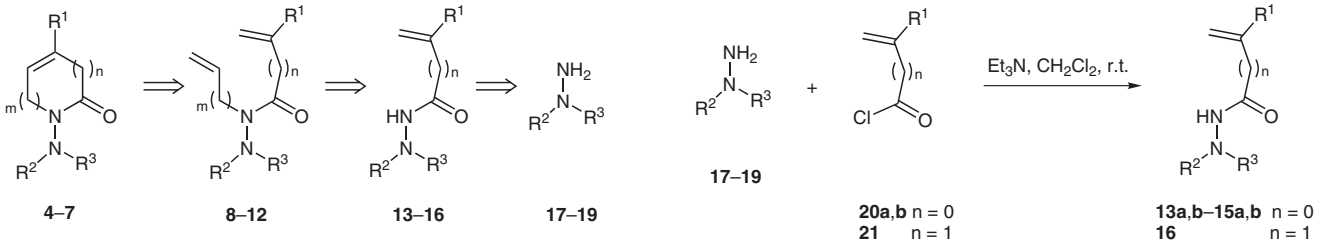
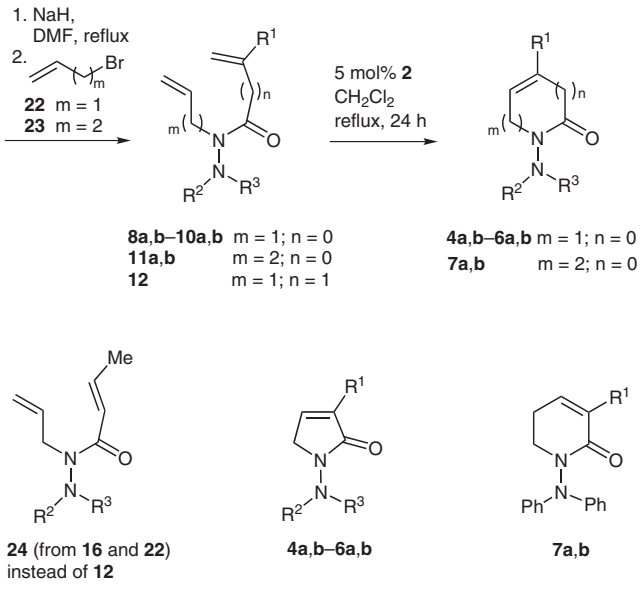


Scheme 1

allyl bromide **22** (m = 1) and this operation delivered our RCM precursors in excellent yields ranging from 52% to 75% (two steps, Table 2).

With the acyclic dienehydrazides **8a**,**b**–**10a**,**b** in hand we then studied the outcome of the RCM reaction and, in order to ensure the optimal formation of the target annulated compounds, variation of the nature of the catalyst, the amount of ruthenium catalyst, temperature profile and time were screened. The diolefinic hydrazide **8a** was chosen as the starting material for our study. Results are presented in Table 2 where it can be seen that as expected the Grubbs catalyst **2** performed significantly better than its analogue **1**. Best results were obtained by employing 5 mol% of this catalyst at reflux in CH_2Cl_2. These optimal conditions were then used to perform the annulation reactions of substrates **8b**–**10a**,**b** in which the structural environment of the non-acylated nitrogen has been changed. A representative series of compounds which have been prepared by this technique are presented in Table 2 where it can be seen that this simple procedure affords very satisfactory yields of the previously unknown cyclic enehydrazides **4a**,**b**–**6a**,**b**.

The promising results obtained for the five-membered enelactamic models prompted us to envisage an extension



Scheme 2

to the six-membered terms of the series. Disappointingly, initial attempts to assemble the diolefinic precursor **12** as outlined in Scheme 2 met with no success. Thus when the appropriate enehydrazide **16** was allowed to react with al-

Table 2 Reaction Conditions for the RCM Reaction

Entry	Substrate	Yield (%)[a]	Reaction time (h)	Temp (°C)	Annulated compound	Catalyst **1**		Catalyst **2**	
						mol%	Yield (%)	mol%	Yield (%)
1	**8a**	67	36	r.t.	**4a**	5	–	–	–
2	**8a**	–	36	reflux	**4a**	5	–	–	–
3	**8a**	–	36	reflux	**4a**	15	20	–	–
4	**8a**	–	24	reflux	**4a**	–	–	5	82
5	**8a**	–	24	reflux	**4a**	–	–	3	55
6	**8b**	73	24	reflux	**4b**	–	–	5	76
7	**9a**	75	24	reflux	**5a**	–	–	5	73
8	**9b**	69	24	reflux	**5b**	–	–	5	78
9	**10a**	70	24	reflux	**6a**	–	–	5	84
10	**10b**	66	24	reflux	**6b**	–	–	5	80
11	**11a**	52	24	reflux	**7a**	–	–	5	72
12	**11b**	56	24	reflux	**7b**	–	–	5	78

lyl bromide **22** under basic conditions the isomerized dienehydrazide **24** was solely obtained, probably due to the high degree of conjugation of the final compound. Alternatively, the structurally modified diolefinic precursors **11a**,**b** were synthesized as portrayed in Scheme 2 by N-alkylation of the suitable enehydrazides **13a**,**b** with butenyl bromide **23**. These compounds were then subjected to previously defined RCM reaction conditions and we were pleased to observe that the annulated compound **7a**,**b** were obtained in a very satisfactory yield (Table 2). The analytical and spectral data of the hydrazides prepared are given in Table 3.

Table 3 Spectroscopic and Physical Data of Hydrazides Prepared

Product[a,b]	Yield (%)[c]	Mp (°C)	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
13a	91	159–160[d]	5.69 (d, *J* = 10.2, 1 H_{vin}), 5.78 (d, *J* = 10.2, 1 H_{vin}), 6.21 (ddd, *J* = 2.3, 10.2, 16.9, 1 H_{vin}), 6.38 (d, *J* = 16.9, 1 H_{vin}), 6.51 (d, *J* = 16.9, 1 H_{vin}), 6.78 (ddd, *J* = 2.3, 10.2, 16.9, 1 H_{vin}), 6.96–7.35 (m, 20 H_{arom}), 7.76 (br s, 1 H, NH), 8.56 (br s, 1 H, NH)[e]	119.5, 119.6, 123.0, 123.7, 125.5, 128.0, 128.8, 129.2, 129.4, 131.1, 145.7, 146.3, 164.9, 170.3[e]
13b	93	173–174	2.00 (s, 3 H, CH_3), 5.42 (s, 1 H_{vin}), 5.80 (s, 1 H_{vin}), 6.88–7.31 (m, 10 H_{arom}), 8.42 (br s, 1 H, NH)	18.8, 119.4, 120.8, 122.9, 129.1, 138.5, 145.8, 167.6
14a	87	130–131	1.52–1.68 (m, 12 $H_{c\text{-}hex}$), 2.78–2.86 (m, 8 $H_{c\text{-}hex}$), 5.54 (dd, *J* = 1.6, 10.3, 1 H_{vin}), 5.63 (dd, *J* = 1.9, 10.4, 1 H_{vin}), 6.05 (dd, *J* = 10.3, 16.9, 1 H_{vin}), 6.26 (dd, *J* = 1.6, 16.9, 1 H_{vin}), 6.34 (dd, *J* = 1.9, 17.4, 1 H_{vin}), 6.85 (br s, 1 H, NH), 6.92 (dd, *J* = 10.4, 17.4, 1 H_{vin}), 7.20 (br s, 1 H, NH)[e]	22.9, 23.2, 25.2, 25.6, 56.8, 58.0, 126.7, 126.9, 128.4, 129.7, 163.0, 168.0[e]
14b	90	118–119	1.32-1.36 (m, 2 $H_{c\text{-}hex}$), 1.61–1.64 (m, 4 $H_{c\text{-}hex}$), 1.89 (s, 3 H, CH_3), 2.71–2.75 (m, 4 $H_{c\text{-}hex}$), 5.22 (s, 1 H_{vin}), 5.55 (s, 1 H_{vin}), 6.83 (br s, 1 H, NH)	18.8, 23.2, 25.3, 56.8, 119.1, 139.7, 166.2
15a	85	96–97	1.66–2.15 (m, 8 H), 2.58–2.66 (m, 1 H), 2.73–2.83 (m, 1 H), 3.01–3.09 (m, 1 H), 3.18–3.25 (m, 1 H), 3.30 (s, 3 H, OCH_3), 3.34 (s, 3 H, OCH_3), 3.38–3.51 (m, 6 H), 5.65–5.73 (m, 2 H_{vin}), 6.13 (dd, *J* = 10.4, 16.9, 1 H_{vin}), 6.32–6.43 (m, 2 H_{vin}), 6.61 (br s, 1 H, NH), 6.83 (br s, 1 H, NH), 6.95 (dd, *J* = 10.4, 16.4, 1 H_{vin})[e]	20.9, 21.4, 25.8, 26.6, 55.4, 57.1, 59.0, 59.2, 64.5, 65.5, 73.4, 74.8, 126.9, 127.4, 128.3, 129.5, 164.5, 169.3[e]
15b	81	111–112	1.46–2.05 (m, 7 H), 2.73–2.81 (m, 1 H), 3.08–3.35 (m, 7 H), 5.26 (s, 1 H_{vin}), 5.58 (s, 1 H_{vin}), 7.04 (br s, 1 H, NH)	18.7, 21.3, 26.3, 55.2, 59.2, 64.0, 75.1, 119.1, 139.9, 167.4
16	70	85–86	3.05 (d, *J* = 6.0, 2 H, CH_2), 3.22 (d, *J* = 6.0, 2 H, CH_2), 5.04–5.31 (m, 4 H_{vin}), 5.83–6.018 (m, 2 H_{vin}), 6.99–7.36 (m, 20 H_{arom}), 7.84 (br s, 1 H, NH), 8.38 (br s, 1 H, NH)[e]	36.4, 39.6, 118.9, 119.4, 119.9, 122.9, 123.8, 129.2, 129.5, 130.3, 130.5, 145.8, 146.0, 169.9, 176.5[e]
8a	80	72–73	4.33 (dt, *J* = 1.1, 6.7, 2 H, NCH_2), 5.02–5.11 (m, 2 H_{vin}), 5.69 (dd, *J* = 2.2, 10.1, 1 H_{vin}), 5.75–5.89 (m, 1 H_{vin}), 6.51 (dd, *J* = 2.2, 16.9, 1 H_{vin}), 6.71 (dd, *J* = 10.1, 16.9, 1 H_{vin}), 7.03–7.16 (m, 6 H_{arom}), 7.27–7.34 (m, 4 H_{arom})	50.5, 119.1, 119.2, 123.3, 127.1, 129.4, 130.2, 132.3, 144.4, 169.0
8b	81	oil	1.62 (s, 3 H, CH_3), 4.19 (d, *J* = 6.4, 2 H, NCH_2), 4.88–5.12 (m, 4 H_{vin}), 5.72–5.88 (m, 1 H_{vin}), 6.89–7.18 (m, 10 H_{arom})	20.3, 51.3, 117.1, 119.2, 119.5, 123.0, 129.2, 132.5, 140.1, 144.5, 174.2
9a	78	oil	1.51–1.72 (m, 6 $H_{c\text{-}hex}$), 2.56–2.75 (m, 4 $H_{c\text{-}hex}$), 4.01 (d, *J* = 5.5, 2 H, NCH_2), 5.05 (d, *J* = 10.2, 1 H_{vin}), 5.13 (d, *J* = 17.3, 1 H_{vin}), 5.54 (dd, *J* = 1.6, 10.2, 1 H_{vin}), 5.86 (m, 1 H_{vin}), 6.28 (dd, *J* = 1.6, 17.3, 1 H_{vin}), 7.12 (dd, *J* = 10.2, 17.3, 1 H_{vin})	23.3, 26.0, 42.0, 54.1, 116.7, 127.1, 127.8, 134.8, 167.6
9b	75	53–54	1.35–1.49 (m, 6 $H_{c\text{-}hex}$), 1.92 (s, 3 H, CH_3), 2.58–2.73 (m, 4 $H_{c\text{-}hex}$), 3.95 (d, *J* = 6.0, 2 H, NCH_2), 4.90 (s, 1 H_{vin}), 5.02 (s, 1 H_{vin}), 5.05 (dd, *J* = 1.2, 10.2, 1 H_{vin}), 5.14 (dd, *J* = 1.6, 17.2, 1 H_{vin}), 5.86 (m, 1 H_{vin})	20.1, 23.3, 25.8, 41.7, 53.8, 113.6, 116.5, 134.7, 143.8, 173.8
10a	79	oil	1.55–1.78 (m, 4 H), 2.81–2.95 (m, 2 H), 3.05–3.22 (m, 6 H, 3 H_{SMP} + OCH_3), 3.92–4.01 (m, 2 H), 5.04 (d, *J* = 10.2, 1 H_{vin}), 5.12 (d, *J* = 17.3, 1 H_{vin}), 5.54 (dd, *J* = 1.6, 10.2, 1 H_{vin}), 5.81–5.88 (m, 1 H_{vin}), 6.26 (dd, *J* = 1.6, 17.3, 1 H_{vin}), 7.07 (dd, *J* = 10.2, 17.3, 1 H_{vin})	20.6, 25.8, 42.6, 51.1, 58.3, 58.6, 73.1, 115.9, 126.3, 127.4, 134.0, 168.1

Table 3 Spectroscopic and Physical Data of Hydrazides Prepared (continued)

Product[a,b]	Yield (%)[c]	Mp (°C)	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
10b	72	oil	1.56–1.83 (m, 7 H, 4 H + CH_3), 2.83–2.89 (m, 2 H), 3.06–3.25 (m, 6 H, 3 H_{SMP} + OCH_3), 3.78 (d, *J* = 16.5, 1 H), 4.03 (d, *J* = 16.5, 1 H), 4.72 (s, 1 H_{vin}), 4.75 (s, 1 H_{vin}), 5.53 (dd, *J* = 2.3, 10.4, 1 H_{vin}), 6.26 (dd, *J* = 2.3, 17.3, 1 H_{vin}), 7.13 (dd, *J* = 10.4, 17.3, 1 H_{vin})	20.4, 21.3, 26.3, 45.4, 51.5, 58.7, 73.9, 110.4, 126.6, 127.9, 141.5, 168.8
11a	57	oil	2.22–2.26 (m, 2 H, CH_2), 3.81 (dd, *J* = 5.5, 10.4, 2 H, NCH_2), 4.91–4.97 (m, 2 H_{vin}), 5.67–5.72 (m, 2 H_{vin}), 6.51 (dd, *J* = 2.1, 16.9, 1 H_{vin}), 6.73 (dd, *J* = 10.1, 16.9, 1 H_{vin}), 7.04–7.18 (m, 6 H_{arom}), 7.24–7.35 (m, 4 H_{arom})	32.3, 47.7, 116.6, 119.1, 123.3, 127.2, 129.5, 130.1, 134.9, 144.5, 169.2
11b	55	oil	1.78 (s, 3 H, CH_3), 2.27–2.35 (m, 2 H, CH_2), 3.72–3.78 (m, 2 H, NCH_2), 4.94–5.05 (m, 3 H_{vin}), 5.18–5.26 (m, 1 H_{vin}), 5.61–5.74 (m, 1 H_{vin}), 7.04–7.18 (m, 6 H_{arom}), 7.23–7.35 (m, 4 H_{arom})	20.4, 32.3, 48.6, 116.6, 117.2, 119.4, 123.2, 129.3, 134.9, 140.3, 144.9, 170.2
24	80	oil	1.72 (d, *J* = 6.9, 3 H, CH_3), 4.21 (d, *J* = 6.7, 2 H, NCH_2), 4.88–4.92 (m, 2 H_l), 5.64–5.77 (m, 1 H_{vin}), 6.30 (d, *J* = 15.2, 1 H_{vin}), 6.94–6.98 (m, 1 H_{vin}), 7.02–7.09 (m, 6 H_{arom}), 7.15–7.26 (m, 4 H_{arom})	18.3, 50.4, 118.9, 119.2, 121.1, 123.0, 129.3, 132.5, 144.3, 144.5, 169.0
4a	82	84–85	4.25 (t, *J* = 1.9, 2 H, NCH_2), 6.33 (td, *J* = 1.9, 6.5, 1 H_{vin}), 7.05–7.12 (m, 6 H_{arom}), 7.17 (td, *J* = 1.9, 6.5, 1 H_{vin}), 7.26–7.34 (m, 4 H_{arom})	50.6, 119.6, 123.3, 127.8, 129.5, 142.7, 144.6, 169.1
4b	76	oil	2.08 (s, 3 H, CH_3), 4.20 (br s, 2 H, NCH_2), 6.87 (br s, 1 H_{vin}), 7.07–7.18 (m, 6 H_{arom}), 7.25–7.41 (m, 4 H_{arom})	11.8, 48.8, 119.6, 123.2, 129.4, 135.3, 144.7, 169.9
5a	73	oil	1.55–1.72 (m, 6 $H_{c\text{-hex}}$), 2.75–2.89 (m, 4 $H_{c\text{-hex}}$), 3.99 (br s, 2 H, NCH_2), 6.06 (br s, 1 H_{vin}), 6.92 (br s, 1 H_{vin})	23.2, 25.9, 48.4, 53.4, 128.5, 141.0, 169.5
5b	78	75–76	1.33–1.42 (m, 2 $H_{c\text{-hex}}$), 1.55–1.64 (m, 4 $H_{c\text{-hex}}$), 1.80 (s, 3 H, CH_3), 2.98 (t, *J* = 5.3, 4 $H_{c\text{-hex}}$), 3.84 (br s, 2 H, NCH_2), 6.52 (br s, 1 H_{vin})	11.5, 23.3, 25.9, 47.0, 53.1, 133.4, 136.0, 169.6
6a	84	oil	1.53–2.06 (m, 4 H), 3.08–3.41 (m, 6 H, 3 H_{SMP} + OCH_3), 3.52–3.60 (m, 2 H), 4.05 (d, *J* = 1.6, 2 H, NCH_2), 6.03 (d, *J* = 6.4, 1 H_{vin}), 6.96 (dt, *J* = 1.6, 6.4, 1 H_{vin})	21.2, 25.9, 50.7, 51.3, 58.4, 59.9, 74.9, 127.7, 141.1, 169.1
6b	80	oil	1.39–2.03 (m, 7 H, 4 H + CH_3), 3.04–3.30 (m, 7 H, 4 H_{SMP} + OCH_3), 3.51–3.59 (m, 1 H), 3.93 (br s, 2 H, NCH_2), 6.51 (br s, 1 H_{vin})	11.4, 21.9, 26.5, 49.6, 51.8, 58.9, 60.6, 75.2, 134.0, 135.7, 169.7
7a	72	71–72	2.53 (ddt, *J* = 1.8, 4.2, 7.2, 2 H, CH_2), 3.71 (d, *J* = 7.2, 2 H, NCH_2), 5.94 (dt, *J* = 1.8, 9.8, 1 H_{vin}), 6.57 (dt, *J* = 4.2, 9.8, 1 H_{vin}), 6.91–7.08 (m, 6 H_{arom}), 7.16–7.24 (m, 4 H_{arom})	25.3, 47.4, 119.4, 122.9, 125.5, 129.3, 129.5, 140.3, 144.1, 163.6
7b	75	79–80	1.94 (q, *J* = 1.6, 3 H, CH_3), 2.54–2.61 (m, 2 H, CH_2), 3.82 (t, *J* = 7.1, 2 H, NCH_2), 6.41 (dd, *J* = 4.2, 5.7, 1 H_{vin}), 7.00–7.03 (m, 2 H_{arom}), 7.05–7.13 (m, 4 H_{arom}), 7.22–7.29 (m, 4 H_{arom})	17.2, 24.8, 48.0, 119.4, 122.7, 129.2, 132.0, 134.5, 144.2, 164.9

[a] Satisfactory microanalyses obtained: C ± 0.29, H ± 0.26, N ± 0.31.
[b] IR (KBr): 1660–1674 (C=O), 1628–1637 (C=C) cm^{-1}. For **13a**,**b**–**15a**,**b**, **16**; IR (KBr): 3197–3240 (N–H) cm^{-1}.
[c] Yield of purified product.
[d] Lit.[8] mp 158 °C.
[e] Mixture of two rotamers (1:1).

In summary we have developed a short and efficient synthetic strategy towards a variety of hitherto unknown substituted cyclic enehydrazides based on inexpensive and readily available precursors. In contrast to structurally related N-containing substrates, where it has been shown that the efficacy of ring-closing metathesis is highly dependent upon the nature of the N-connected group,[7] the present method which makes use of the most popular metathesis reagents **1** and **2** tolerates the presence of diversely substituted hydrazido groups. The synthetic sequence gives rise to a number of α,β-unsaturated lactam-type compounds which can be regarded as versatile building blocks for further synthetic planning, e.g. functionalization including, but not limited to epoxidation and dihydroxylation. Applications of this strategy to natural product synthesis are underway and will be reported in due course.

Melting point determinations were carried out on a Reichert-Thermopan apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured at 300 MHz and 75 MHz, respectively, on a Bruker AM 300 spectrometer as solutions in $CDCl_3$ with TMS as internal standard. Elemental analyses were determined by the CNRS microanalysis center. For flash chromatography, silica gel 60 M (230400 mesh ASTM) was used. All solvents were dried and distilled according to standard procedures.

Hydrazides 13a,b–15a,b, 16; General Procedure
A solution of acryloyl chloride (**20a**; 1.99 g, 22 mmol), methacryloyl chloride (**20b**; 2.30 g, 22 mmol) or but-3-enoyl chloride (**21**; 2.01 g, 22 mmol) in anhyd CH_2Cl_2 (5 mL) was added dropwise under argon to a cooled (0 °C) solution of hydrazine **17**–**19** (0.02 mol) and Et_3N (0.03 mol) in anhyd CH_2Cl_2 (20 mL). The mixture was stirred at r.t. for 4 h, filtered and the filtrate was washed with H_2O (2×20 mL) and then dried ($MgSO_4$). Evaporation of the solvent in vacuo left a residue which was purified by column chromatography using EtOAc as eluent (for **14a**,**b** and **15a**,**b**) or EtOAc–hexanes (30:70) as eluent (for **13a**,**b** and **16**) (Table 3).

Diolefinic Hydrazides 8a,b–10a,b, 11a,b, 24; General Procedure
A solution of hydrazides **13a**,**b**–**15a**,**b** or **16** (9 mmol) in anhyd DMF (3 mL) was added dropwise at 0 °C under argon to a stirred suspension of NaH (24 mg, 10 mmol) in anhyd DMF (10 mL). The mixture was then stirred at r.t. for 30 min and allyl bromide (**22**; 1.21 g, 10 mmol for **8a**,**b**–**10a**,**b** and **24**) or 4-bromobut-1-ene (**23**; 1.35 g, 10 mmol, for **11a**,**b**) was slowly added. The mixture was subsequently refluxed for 5 h and, after cooling, was diluted with H_2O (10 mL) and CH_2Cl_2 (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were washed with brine (20 mL) and dried ($MgSO_4$). After evaporation of the solvent under vacuum the oily residue was purified by column chromatography using EtOAc as eluent (for **9a**,**b** and **10a**,**b**) or EtOAc–hexanes (20:80) as eluent (for **8a**,**b**, **11a**,**b** and **24**) (Tables 2 and 3).

Cyclic Enehydrazides 4a,b–7a,b; General Procedure
A solution of diolefinic hydrazides **8a**,**b**–**11a**,**b** (0.5 mmol) and second-generation Grubbs catalyst (5% mol, 21 mg, 0.025 mmol) in CH_2Cl_2 (10 mL) was carefully degassed by three freeze-thaw cycles and then refluxed for 24 h. Evaporation of the solvent in vacuo left a residue which was purified by column chromatography using acetone–hexanes (60:40) as eluent (for **5a**,**b** and **6a**,**b**) or EtOAc–hexanes (30:70) as eluent (for **4a**,**b** and **7a**,**b**) (Tables 2 and 3).

References

(1) For reviews, see: (a) Philips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75. (b) Schultz-Fademrecht, C.; Deshmukh, P. H.; Malagu, K.; Procopiou, P. A.; Barrett, A. G. M. *Tetrahedron* **2004**, *60*, 7515. (c) Dieters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.

(2) Grubbs, R. H. In *Handbook of Metathesis*, Vol. 1-3; Wiley-VCH: Weinheim, **2003**.

(3) For reviews, see: (a) Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Pätzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251. (b) Campagne, J.-M.; Ghosez, L. *Tetrahedron Lett.* **1998**, *39*, 6175. (c) Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3493. (d) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2553. (e) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862. (f) Briot, A.; Bujard, M.; Gouverneur, V.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2000**, *2*, 1517. (g) Gonzáles-Pérez, P.; Pérez-Serrano, L.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *Tetrahedron Lett.* **2002**, *43*, 4765. (h) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693. (i) Gille, S.; Ferry, A.; Billard, T.; Langlois, B. R. *J. Org. Chem.* **2003**, *68*, 8932. (j) Declerck, V.; Ribière, P.; Martinez, J.; Lamaty, F. *J. Org. Chem.* **2004**, *69*, 8372.

(4) (a) Arisawa, M.; Takezawa, E.; Nishida, A.; Mori, M.; Nakagawa, M. *Synlett* **1997**, 1179. (b) Paolucci, C.; Musiani, L.; Venturelli, F.; Fava, A. *Synthesis* **1997**, 1415. (c) Dyatkin, A. B. *Tetrahedron Lett.* **1997**, *38*, 2065. (d) White, J. D.; Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359. (e) Ahn, J.-B.; Yun, C.-S.; Kim, K. H.; Ha, D.-C. *J. Org. Chem.* **2000**, *65*, 9249. (f) White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129.

(5) For representative examples, see: (a) Hammer, K.; Undheim, K. *Tetrahedron: Asymmetry* **1998**, *9*, 2359. (b) Clark, J. S.; Middleton, M. D. *Org. Lett.* **2002**, *4*, 765. (c) Martín, R.; Alcón, M.; Pericás, M. A.; Riera, A. *J. Org. Chem.* **2002**, *67*, 6896.

(6) Matsumoto, Y.; Tsuzuki, R.; Matsuhisa, A.; Takayama, K.; Yoden, T.; Uchida, W.; Asano, M.; Fujita, S.; Yanagisawa, I.; Fujikura, T. *Chem. Pharm. Bull.* **1996**, *44*, 103.

(7) (a) Rutjes, F. P. J. T.; Schoemaker, H. E. *Tetrahedron Lett.* **1997**, *38*, 677. (b) Maier, M. E.; Lapeva, T. *Synlett* **1998**, 891.

(8) Bar, D.; Marcincal-Lefebvre, A. *Bull. Soc. Chim. Fr.* **1976**, 1207.