Synthesis of Polycyclic Lactams and Sultams by a Cascade Ring-Closure Metathesis/Isomerization and Subsequent Radical Cyclization

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Received 24 November 2004

Abstract: Starting from readily available substrates, a new one-pot procedure has been devised to prepare polycyclic lactams and sultams. 2-Pyrrolines obtained from *N*,*N*-bisallylamides by ring-closure metathesis and subsequent isomerization promoted by ruthenium hydride complexes can undergo radical cyclization to furnish polycyclic lactams in good yields. The process was successfully conducted on bisallylsulfonamides to give the corresponding sultams.

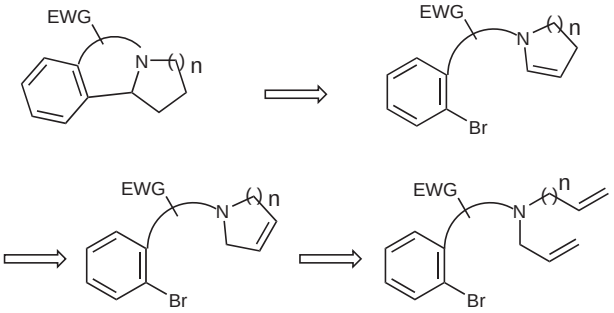
Key words: polycyclic lactams, 2-pyrrolines, ring-closure metathesis

The discovery of powerful ruthenium and molybdenum catalysts has considerably improved the scope of metathesis. Ring-closure reactions (RCM) considered nowadays as a cornerstone to prepare cyclic alkenes have been deeply studied and fruitfully applied to the synthesis of numerous natural products.[1–5] The success of these strategies is also connected to the tolerance of the catalysts to a wide number of functionalities present on the substrates. Even sulfur derivatives which commonly interfere in a number of organometallic processes have been converted into cyclized products under RCM conditions.[6]

Of great synthetic interest, unsaturated amines and nitriles are less reactive under neutral conditions but this lack of reactivity can be overtaken by performing the reaction in acidic media or in the presence of a Lewis acid like copper(I) chloride[7] which prevent the deactivation of the catalyst. Another possibility with aza compounds is offered by decreasing the nucleophilicity of the nitrogen atom. This can be conveniently achieved by using amides or sulfonamides instead of amines. By this way, the formation of medium-sized unsaturated lactams and sultams has been developed and applied to the synthesis of natural or biologically active compounds.[8,9] In some cases, the first cyclization procedure has been also combined with subsequent reactions in order to gain in complexity. Grigg et al. and later Evans have combined a RCM process with a further intramolecular Heck reaction to have an access to aza-bridged compounds.[10]

Other reactions have been associated with metathesis in order to gain in complexity. For example, Diels–Alder reactions have been carried out in one pot to prepare new polycyclic structures from dienes easily available from RCM of enynes.[4,5]

In connection with our interest in metathesis reactions,[11] we have explored a new approach to polycyclic aza compounds by using a RCM process combined with a subsequent radical cyclization an overall process which has been to date scarcely investigated.[12] The overall strategy is depicted in Scheme 1.

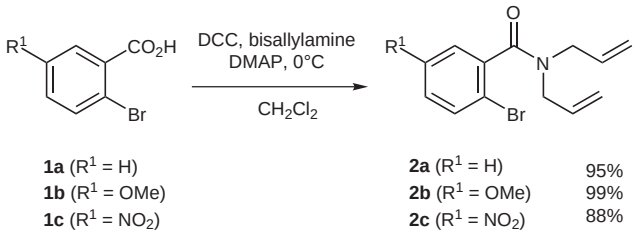


Scheme 1 Retrosynthetic analysis for the preparation of aza polycyclic compounds from bromoarylamides and sulfonamides

As already pointed out, the presence of an electron-withdrawing group (EWG) like a sulfonamide or an amide group is essential for the success of the first process. After migration of the new carbon-carbon double bond, the homolytic cleavage of the C-Br bond was expected to generate a free radical, which could interact with the enamino subunit. By this way, fused polycyclic aza compounds **4** could be prepared from easily available starting materials **1**. There are some precedents for migration of double bonds under metathesis conditions.[13] For example, Snapper et al. have performed a related reaction under a hydrogen atmosphere,[14] while Schmidt was able to isolate rearranged compounds after the addition in the medium of hydride species like NaH or $NaBH_4$, in a short and efficient dihydropyran synthesis.[15] Under these conditions new catalysts which are responsible for the isomerization step have been identified as ruthenium hydride complexes.

Amides **2a**–**c** were conveniently prepared by condensation of commercially 2-bromobenzoic acids with bisallylamine as depicted in Scheme 2.[16] Acid **1d** prepared from piperonyl alcohol[17–19] was condensed with the same amine to give compound **2d** (Scheme 3).

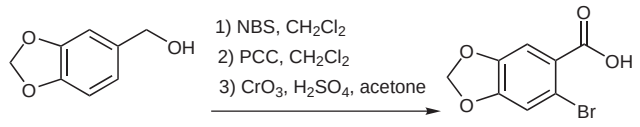
SYNLETT 2005, No. 4, pp 0577–0582
Advanced online publication: 22.02.2005
DOI: 10.1055/s-2005-862386; Art ID: D35104ST



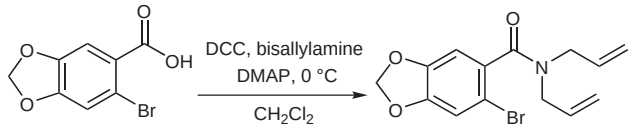
1a (R^1 = H)
1b (R^1 = OMe)
1c (R^1 = NO_2)

2a (R^1 = H) 95%
2b (R^1 = OMe) 99%
2c (R^1 = NO_2) 88%

Scheme 2



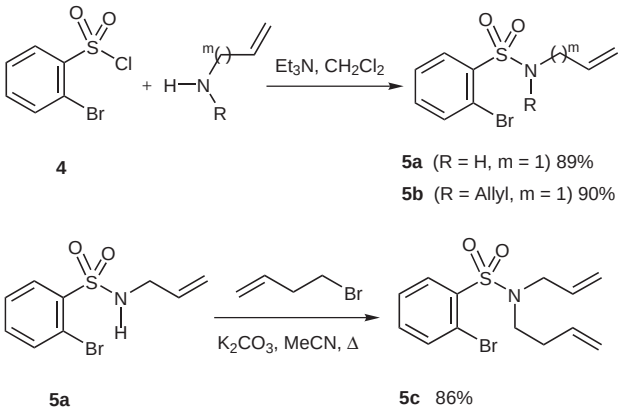
3 **1d** 42%



1d **2d** 63%

Scheme 3

Similarly, sulfonamides **5a**,**b** were obtained by condensation of 2-bromobenzenesulfonyl chloride **4** with allylamine and bisallylamine, respectively (Scheme 4). N-substitution of secondary sulfonamide **5a** was achieved with 4-bromobutene under mild conditions[20] and delivered **5c** in high yield.



4

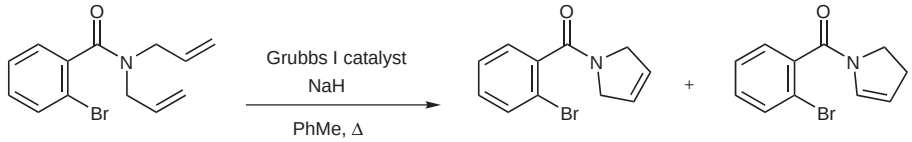
5a (R = H, m = 1) 89%
5b (R = Allyl, m = 1) 90%

5a **5c** 86%

Scheme 4

o-Bromobenzamide **2a** was first engaged in a RCM process in the presence of bis(tricyclohexylphosphine) benzylidene ruthenium(IV) dichloride known as Grubbs' type I catalyst and delivered as expected the pyrrolinyl amide **6a** in 96% (Scheme 5, Table 1).

In a next experiment, after total conversion of **2a**, sodium hydride was added in small portion in the media and the resulting suspension was heated to reflux. The new organometallic species generated by this way were expected to promote the isomerization of the new double bond formed. Fortunately, we were pleased to observe the migration of the double bond as reported in the oxygenated series.[15] By careful adjustment of the amounts of hydride and the ruthenium catalyst added, we obtained after complete conversion, amide **7a** with yield up to 72%. Best



2a **6a** **7a**

Scheme 5

Table 1 Tandem RCM/Isomerization of Bisallylamide **2a**

Entry	Catalyst (mol%)	NaH (mol%)	Concentratin (mol/L)	Time (h)	Yield of **6a** (%)	Yield of **7a** (%)
1	2.5	–	10^{-2}	24	96	–
2	5	30	10^{-2}	21	51	48
3	2 × 2.5	2 × 30	$4{\cdot}10^{-2}$	24	20	55
4	3 × 2.5	3 × 30	$4{\cdot}10^{-2}$	36	22	60
5	4 × 2.5	4 × 30	$4{\cdot}10^{-2}$	48	–	68
6	4 × 2.5	4 × 30	10^{-2}	48	–	72
7	4 × 2.5	4 × 30[a]	10^{-2}	48	48	43

[a] $NaBH_4$ used instead of NaH.

results required 10% of Grubbs' I catalyst and 120 mol% of NaH as shown in Table 1 (entry 5).[21]

Other amides were submitted to these selected conditions (Scheme 6) and the results are collected in Table 2. The reaction was effective in almost all cases except with amide **2c**. The presence of the nitro group seems compatible with the metathesis but problematic for the isomerization step promoted by the in situ generated ruthenium hydride complex.

Table 2 Tandem RCM/Isomerization of Amides **2a**–**d**

Amide	R^1	R^2	Yield of **6** (%)	Yield of **7** (%)
2a	H	H	–	**7a** (68)
2b	OMe	H	–	**7b** (86)
2c	NO_2	H	31	**7c** (43)
2d	-O-CH_2-O-		–	**7d** (71)

While an alternative and apparently more direct approach from enamides could be also considered,[22] our strategy described therein seems more attractive if considering the availability and stability of the required substrates.

We next considered the free radical cyclization[23,24] to reach tricyclic lactam structures and chose **7a** as a model (Scheme 7). The combination of Bu_3SnCl and sodium borohydride in toluene under high dilution, known as Stork's conditions,[25] afforded lactam **10a** in moderate yield and without significant formation of the reduced amide **11a**. To enhance the efficiency of the radical cyclization, tris(trimethylsilyl)silane (TTMSS)[26] was also used. A slow addition of this reagent to a highly diluted solution of **7a** gave in far better yield **10a**, which was easily isolated by chromatography with the reduced compound **11a**. Amides **7b** and **7d** resulting from the RCM/isomerization process were engaged under these conditions and converted into polycyclic derivatives in good yields (Table 3).[27] This overall sequence was applied to sulfonamides **5b**,**c**. As in the tetrahydropyranne series, the isomerization of **5c** was totally regioselective and delivered only enamide **9c**. Compared to results obtained with amides **2**, the yields for the RCM/isomerization and also for the radical cyclization were better in the sulfonamide series. No trace of compounds resulting from the reduction of the C-Br bond was noticed. The dimeric approach has been also investigated. In some cases, the formation of dimeric species has been suggested before the ring-closure.[28]

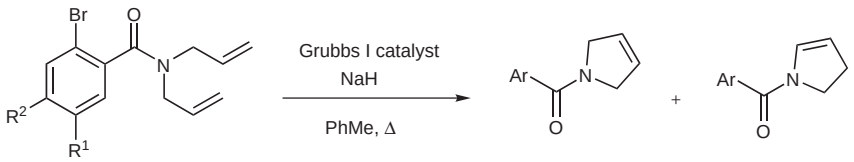
Table 3 RCM/Isomerization of Amides **7a**–**d**

Substrate	R^1	R^2	Conditions	Yield of **10** (%)	Yield of **11** (%)
7a	H	H	A[a]	**a** (45)	**a** (0)
7a	H	H	B[b]	**a** (77)	**a** (20)
7b	OMe	H	B[b]	**b** (52)	**b** (0)
7c	NO_2	H	B[b]	**c**[c] (–)	**c** (0)
7d	-O-CH_2-O-		B[b]	**d** (50)	**d** (0)

[a] Conditions A: Bu_3SnCl + $NaBH_4$, AIBN, PhMe, 130 °C.
[b] Conditions B: TTMSS (2 equiv) + AIBN, PhMe, 130 °C.
[c] Compound **10c** was obtained only in traces.

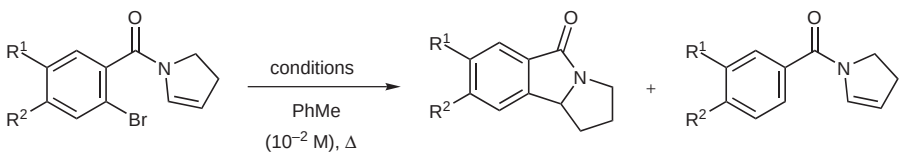
Bissulfonamide **5d** was easily prepared from **5a** (Scheme 8). Under the same tandem cyclization/isomerization conditions and after a similar time of reaction, an unseparable 1:3 mixture of **8b**:**9b** was isolated in 90% yield. This result shows that the formation of dimeric compounds as intermediate cannot be totally excluded during the first metathesis step.

Finally, we have investigated a one-pot procedure to prepare polycyclic lactams and sultams from amides **2** or sulfonamides **5**. According to the classification of tandem and sequential reactions,[29] this procedure could be described as a tandem RCM/isomerization followed by a sequential radical cyclization (Scheme 9). The reaction applied to compounds **2a**,**d** and **5c** gives the tricyclic



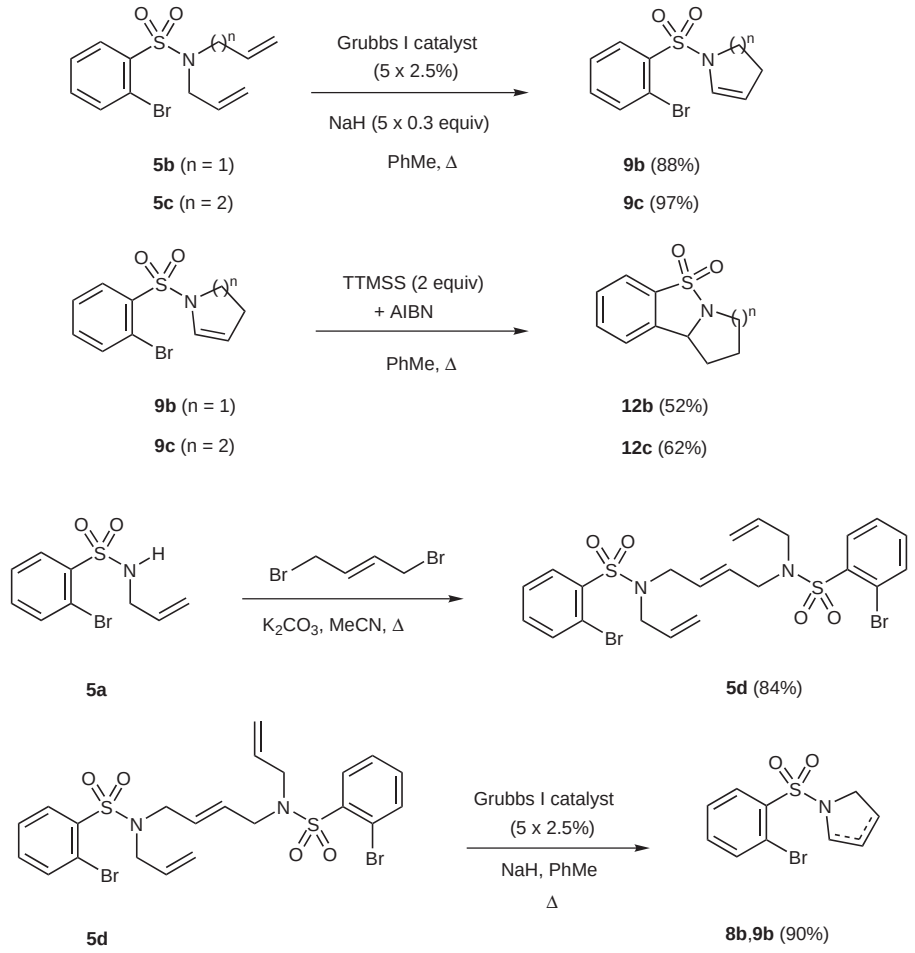
2 **6** **7**

Scheme 6



7 **10** **11**

Scheme 7



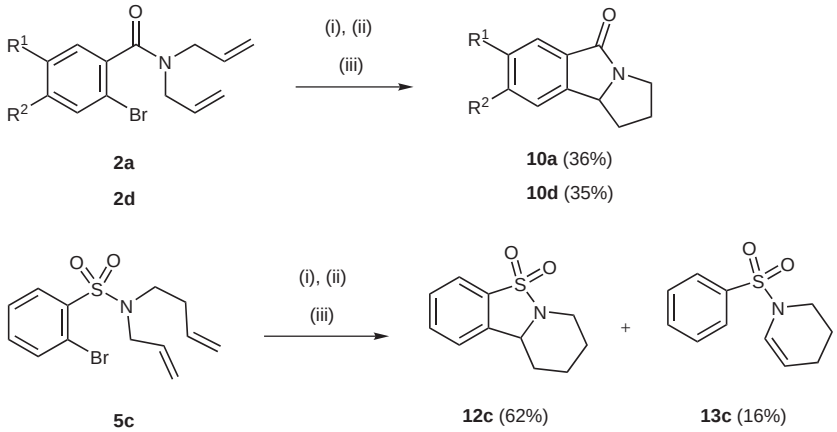
Scheme 8

lactams and sultam in moderate to good overall yields.[30] By this way, isolation of sensitive pyrroline intermediates is avoided.

In conclusion, we have combined a ring-closing metathesis, an isomerization step and a radical cyclization which could be carried out in a one-pot procedure and afford from readily available unsaturated amides and sulfonamides a short access to tri- or tetracyclic lactams and sultams. Work is under way to apply this cascade reaction to the synthesis of biologically active compounds.

Acknowledgment

C.B. and C.M. thank the 'Ministère de l'Education Nationale, de la Recherche et de la Technologie' for doctoral fellowships.



Scheme 9 *Reagents and conditions*: (i) Grubbs' I catalyst (2.5% mol), PhMe, 1 h; (ii) 5 × [Grubbs I catalyst (2.5% mol) + NaH (0.15 equiv)], PhMe, 130 °C, 60 h; (iii) TTMSS (2 equiv) + AIBN (10%), PhMe, 130 °C, 6 h.

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(16) **Preparation of the *N,N*-Bisallylamides 2.**
To a solution of acid (2 mmol) in CH_2Cl_2 (4 mL) were successively added DMAP (0.073 g, 0.6 mmol) and bisallylamine (0.195 g, 2 mmol). The reaction was next cooled to 0 °C and a solution of dicyclohexylcarbodiimide (0.412 g, 2 mmol) in the same solvent (1 mL) was added dropwise. After stirring 10 min at 0 °C, the ice-water bath was removed and the mixture stirred overnight at r.t. Urea was filtered off and the solvent removed by concentration under vacuo. Amide **2** was obtained pure by flash chromatography (eluent: EtOAc–hexanes 10:90).
Compound **2a** (95%): ^{1}H NMR ($CDCl_3$): δ = 3.65 (d, *J* = 4.5 Hz, 2 H), 3.75 (dd, *J* = 15.2, 6.8 Hz, 1 H), 4.48 (dd, *J* = 15.2, 3.7 Hz, 1 H), 5.03 (dd, *J* = 1.3, 16.9 Hz, 1 H), 5.10 (dd, *J* = 11.5, 1.3 Hz, 1 H), 5.18 (dd, *J* = 10.1, 1.3 Hz, 1 H), 5.23 (dd, *J* = 17.9, 1.3 Hz, 1 H), 5.59 (ddt, *J* = 16.9, 10.1, 5.8 Hz, 1 H), 5.83 (ddt, *J* = 16.9, 10.1, 5.4 Hz, 1 H), 7.13–7.31 (m, 3 H), 7.50 (d, *J* = 7.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ = 46.70, 50.60, 118.50, 118.51, 119.50, 127.90, 128.00, 130.60, 132.80, 133.00, 133.20, 138.50, 169.40. IR (film): 3080, 2923, 1637, 1415, 1285, 1115, 995, 925, 770 cm^{-1}.
Compound **2d** (63%): ^{1}H NMR ($CDCl_3$): δ = 3.74 (d, *J* = 5.6 Hz, 2 H), 3.80 (m, 1 H), 4.35–4.55 (m, 1 H), 5.11 (ddt, *J* = 17.0, 1.5, 1.5 Hz, 1 H), 5.18 (ddt, *J* = 10.2, 1.5, 1.5 Hz, 1 H), 5.23 (ddt, *J* = 10.4, 1.5, 1.5 Hz, 1 H), 5.27 (ddt, *J* = 15.6, 1.5, 1.5 Hz, 1 H), 5.67 (ddt, *J* = 17.0, 10.4, 5.6 Hz, 1 H), 5.87 (ddt, *J* = 16.4, 10.2, 6.0 Hz, 1 H), 6.00 (s, 2 H), 6.71 (s, 1 H), 6.98 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ = 46.7, 50.5, 102.4, 107.8, 110.4, 113.1, 118.4, 131.3, 132.6, 133.0, 147.7, 149.1, 168.9. HRMS: *m/z* calcd [MH$^+$]: 324.02353; found: 324.02315.
To a solution of *N*-allyl-2-bromobenzene sulphonamide (**5a**, 276 mg, 1 mmol) in MeCN (4 mL) was added 4-bromo-butene (148 mg, 1.1 mmol) and K_2CO_3 (553 mg, 4 mmol). The resulting suspension was heated for 16 h. After filtration and concentration, the product was purified by flash chromatography (eluent: EtOAc–hexanes 10:90).
Compound **5c** (86%): ^{1}H NMR ($CDCl_3$): δ = 2.27 (t, *J* = 7.4 Hz, 2 H), 3.36 (t, *J* = 7.4 Hz, 2 H), 3.99 (d, *J* = 6.4 Hz, 2 H), 4.95–5.15 (m, 2 H), 5.15–5.35 (m, 2 H), 5.59–5.85 (m, 2 H), 7.37 (dt, *J* = 1.8, 7.5 Hz, 1 H), 7.45 (dt, *J* = 1.8, 7.5 Hz, 1 H), 7.75 (dd, *J* = 7.5, 1.3 Hz, 1 H), 8.18 (dd, *J* = 8.7, 2.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ = 32.7, 46.6, 50.3, 117.5, 119.3, 120.7, 127.9, 132.5, 133.4, 133.9, 134.8, 136.0, 139.8. IR (film): 3070, 2985, 1640, 1575, 1445, 1340, 1155, 915, 755 cm^{-1}.
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(20) Selvamurugan, V.; Aidhen, I. S. *Synthesis* **2001**, 2239.
(21) **Metathesis and Isomerization of Amides 2, Typical Procedure.**
To a solution of amide **2a** (140 mg, 0.5 mmol) in toluene was added first generation Grubbs' catalyst (11 mg, 2.5% mol). After stirring at r.t. for 1 h and complete disappearance of the starting material, NaH (7 mg, 1.5 mmol) was added at once and the mixture was heated to reflux. A new addition of both Grubbs' catalyst (11 mg, 2.5% mol) and NaH (7 mg, 1.5 mmol) was performed after 12 h of heating and this sequence was repeated three times more. After cooling to r.t., the solvent was removed by concentration and the resulting crude mixture was purified by flash chromatography on silica (eluent: hexanes–EtOAc 7:3).
Compound **7a** (72%): ^{1}H NMR ($CDCl_3$) 2 rotamers (ratio 4.2:1): δ (major rotamer) = 2.76 (dt, *J* = 8.6, 2.4 Hz, 2 H), 4.07 (t, *J* = 9.0 Hz, 2 H), 5.23 (dt, *J* = 4.3, 2.4 Hz, 1 H), 6.02 (dt, *J* = 6.4, 1.2 Hz, 1 H), 7.35 (m, 3 H), 7.60 (d, *J* = 7.5 Hz, 1 H); δ (minor rotamer) = 2.76 (dt, *J* = 8.6, 2.4 Hz, 2 H), 3.58 (t, *J* = 9.0 Hz, 2 H), 5.42 (dt, *J* = 4.3, 2.4 Hz, 1 H), 7.11 (dt, *J* = 6.4, 2.1 Hz, 1 H), 7.35 (m, 3 H), 7.60 (d, *J* = 7.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ (major rotamer) = 27.6, 43.8, 111.8, 118.4, 126.7, 127.4, 128.6, 129.7, 131.9, 136.9, 173.4; δ (minor rotamer) = 28.8, 45.7, 111.8, 117.7, 126.7, 127.4, 128.6, 129.7, 131.9, 137.6, 173.4. IR (film): 3065, 2955, 1645, 1420, 1045, 1025, 830 cm^{-1}. HRMS: *m/z* calcd [MH$^+$]: 252.00240; found: 252.00229.
Compound **7d** (71%): yellow oil. ^{1}H NMR ($CDCl_3$): δ = 2.73 (dt, *J* = 6.0, 0.8 Hz, 2 H), 4.01 (t, *J* = 8.3 Hz, 2 H), 5.22 (dt, *J* = 5.3, 2.6 Hz, 1 H), 6.02 (s, 2 H), 6.06 (dt, *J* = 4.3, 2.1 Hz, 1 H), 6.80 (s, 1 H), 7.01 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ = 28.9, 45.1, 102.4, 108.2, 108.5, 110.9, 113.0, 113.1, 130.0, 147.7, 149.4, 164.5. HRMS: *m/z* calcd [MH$^+$]: 294.98441; found: 294.98497.
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(27) **Radical Cyclization of Amides 7, Typical Procedure Described from Amide 7a.**
A solution of amide **7a** (100 mg, 0.4 mmol) in toluene (40 mL) containing small amounts of AIBN (7 mg, 0.04 mmol) was bubbled by a dried stream of nitrogen for 10 min and heated to reflux. A solution of tristrimethylsilylsilane (140 μL, 0.44 mmol) in toluene (10 mL) was carefully added drop by drop in 15 min. The reaction was heated for additional 6 h. The solvent was removed by concentration and the crude mixture was purified by flash chromatography on silica (eluent: EtOAc–hexanes 50:50) and gave lactam **10a**.
Compound **10a** (77%): viscous oil. ^{1}H NMR ($CDCl_3$): δ = 1.25 (m, 2 H), 2.34 (m, 2 H), 3.43 (m, 1 H), 3.72 (dt, *J* = 11.3, 8.3 Hz, 1 H), 4.68 (dd, *J* = 10.3, 5.3 Hz, 1 H), 7.45 (m, 3 H), 7.80 (d, *J* = 7.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ = 28.2, 28.7, 40.9, 63.7, 114.9, 121.7, 122.9, 127.3, 130.6, 145.4, 170.6. IR: 3075, 2960, 1685, 1385, 1220, 1145, 740 cm^{-1}. HRMS: *m*/*z* calcd [MH^+]: 174.09189; found: 174.09163.
Compound **12c** (62%): white solid; mp 103–109 °C. ^{1}H NMR ($CDCl_3$): δ = 1.40–1.85 (m, 4 H), 2.03 (dt, *J* = 11.3, 3.0 Hz, 1 H), 2.28 (dd, *J* = 3.0, 11.3 Hz, 1 H), 3.02 (dt, *J* = 3.2, 11.3 Hz, 1 H), 3.86 (dt, *J* = 10.2, 2.7 Hz, 1 H), 4.20 (dd, *J* = 3.2, 11.3 Hz, 1 H), 7.37 (dd, *J* = 1.1, 7.5 Hz, 1 H), 7.50 (t, *J* = 7.5 Hz, 1 H), 7.58 (dt, *J* = 1.1, 7.5 Hz, 1 H), 7.79 (d, *J* = 7.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ = 23.9, 24.3, 30.5, 40.4, 58.8, 121.4, 123.2, 129.3, 132.8, 135.4, 138.8. IR: 3080, 2955, 2850, 1645, 1450, 1285, 1170, 1130 cm^{-1}. HRMS: *m*/*z* calcd [MH^+]: 224.07452; found: 224.07453.

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(30) **Tandem Process from Amides 2a,d, Typical Procedure.**
To a solution of amide **2a** (140 mg, 0.5 mmol) in toluene was added first generation Grubbs' catalyst (11 mg, 2.5% mol). After stirring at r.t. for 1 h and complete disappearance of the starting material, NaH (7 mg, 1.5 mmol) was added at once and the mixture was heated to reflux. A new addition of both Grubbs' catalyst (11 mg, 2.5% mol) and NaH (7 mg, 1.5 mmol) was performed after 12 h of heating and this sequence was repeated three times more. After cooling to r.t., AIBN (8 mg, 0.05 mmol) was added. The mixture was bubbled with a dried nitrogen stream and next heated. A solution of TTMSS (320 μL, 1 mmol) in toluene (10 mL) containing AIBN (8 mg, 0.05 mmol) was slowly added to the reaction mixture in 10 min. After heating at 130 °C for 6 h, the mixture was cooled to r.t., and the solvent removed by concentration under vacuum. The products were purified after flash chromatography on silica.