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# Tuning the Chemoselectivity of the Metathesis Reactions of *N*-Substituted 2-Azabicyclo[2.2.1]hept-5-en-3-one

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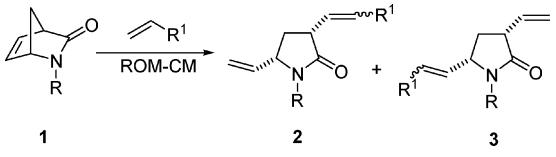
*Dedicated to Professor Ricardo Riguera on the occasion of his 60th birthday*

**Keywords:** Metathesis / Pyrrolidinone / Pyrrolizidinone / Hoveyda–Grubbs catalyst / Aza compounds / Bicyclic compounds

By using the second-generation Hoveyda–Grubbs precatalyst, the metathesis transformations of *N*-substituted 2-azabicyclo[2.2.1]hept-5-en-3-one derivatives have been explored. In the absence of any external alkene (cross-metathesis partner), substituted pyrrolizidin-3-one derivatives were obtained by ring-opening metathesis/ring-closing metathesis tandem reactions. In the presence of an external alkene, *N*-substituted 2-pyrrolidinones were isolated by ring-opening metathesis/cross metathesis tandem reactions. In this case, and by using an alkene other than ethylene (allyltrimethylsilane), the reaction was totally chemo- and diastereoselective.

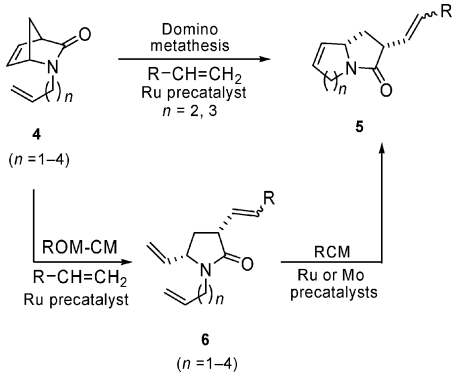

## Introduction

The ruthenium-catalyzed metathesis reactions of 2-azabicyclo[2.2.1]hept-5-en-3-one derivatives **1**, through the sequence ring-opening metathesis (ROM)/cross metathesis (CM) reactions, constitute a useful tool in the synthesis of functionalized pyrrolidinones (γ-lactams).[1] When an external alkene other than ethylene was used, two regioisomeric products **2** and **3** can be expected, and the ratio of **2**/**3** appears to be dependent on the nature of R, the precatalyst and other experimental conditions (Scheme 1).[2]




Scheme 1.

The *N*-substituted derivatives of **1** that bear a terminal double bond at the *N*-alkyl moiety, compounds **4** (Scheme 2), undergo the sequence ROM/CM/ring-closing metathesis (RCM) reactions (domino metathesis) to give fused bicyclic lactams **5**.[3]




Scheme 2.

However, although the method works well for $n = 2$ and 3 by using ruthenium precatalysts **7** and **8** (Figure 1), in the case of $n = 1$ only modest yields (5–25%) of pyrrolidinone **6** were obtained. RCM of isolated **6** gave 2-substituted pyrrolizidin-3-one **5** ($n = 1$) in 22–60% yields depending on the precatalyst used (**7**, **8** and Mo precatalyst **9**, Figure 1).

Pyrrolizidinones **10** (Scheme 3) have also been obtained in low (15%)[4] or moderate (56%)[5] yields starting from alkynyl derivatives **11** by the ROM/CM/RCM cascade reaction in the presence of precatalyst **8** under ethylene.

The *N*-acyl derivatives of **1** such as **12** (Scheme 4) have not, to the best of our knowledge, ever been used as the starting material in sequential metathesis reactions. In these cases ROM/CM tandem reactions by using an external alkene as the CM partner afford *N*-acylpyrrolidinones **13a** and/or **13b**, whereas ROM/RCM tandem reactions in the absence of any external alkene should give the bicyclic lac-

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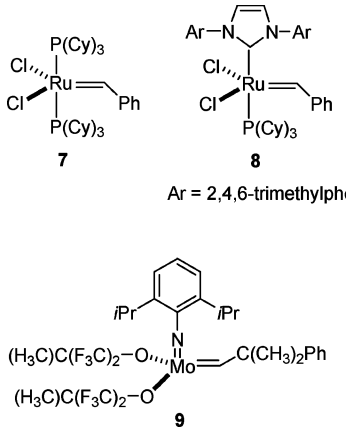
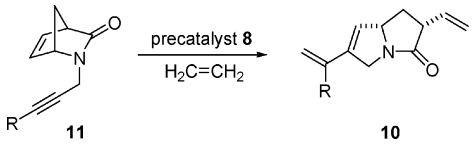
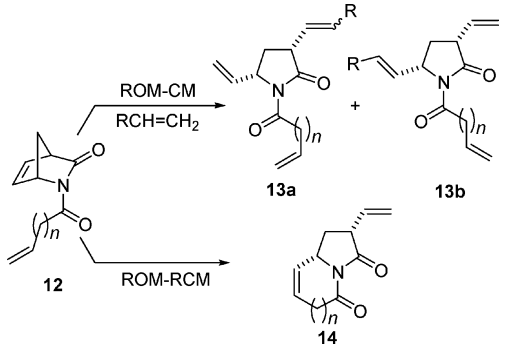



Figure 1. Ru and Mo precatalysts **7**–**9**.




Scheme 3.

tams **14**. The aim of this work was to find the best experimental conditions, based on reasonable mechanistic considerations, to achieve, in one synthetic step and starting from optically pure materials, the chemoselective transformation of compounds **12** into derivatives **13** and **14**.




Scheme 4.

An additional reason for pursuing this goal lies in the significance of the target structures. 1-Acyl-2-pyrrolidinone derivatives such as **15** (Figure 2) show anticonvulsant activity.[6] Also, the α,β-unsaturated amide **16** has been used as the starting material in several enantioselective transformations, including Diels–Alder,[7] 1,3-dipolar cycloadditions[8] and some conjugate addition reactions.[9] Polymerization reactions of **16** have also been reported,[10] and chiral 2-pyrrolidinones such as **17** have been employed as "Quat" chiral auxiliaries.[11] With regard to the bicyclic lactams, compound **18** (tetrahydro-6*H*-pyrrolizidine-3,5-dione, rolziracetam, Lukes–Sorin dilactam) is a well-known nootropic drug of the racetam family,[12] being also the starting material in some useful synthetic transformations.[13] Taking all this into account, the search for a convenient, general synthetic procedure for the preparation of the functionalized compounds **13** and **14** in optically pure form appears to be a reasonable goal.

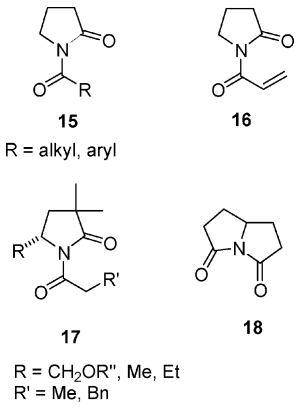
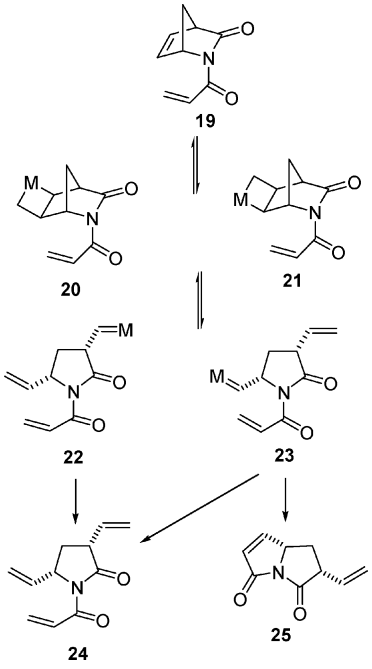



Figure 2. Useful 1-acyl-2-pyrrolidinone derivatives.

## Results and Discussion

We began our research by considering the synthesis of functionalized derivatives of compounds **16** and **18** (Figure 2) starting from the *N*-acyl derivatives of commercially available enantiomerically pure (–)-**1** (R = H). With compound **19** as the starting material and according to the generally accepted mechanism for metathesis reactions,[14] initial cyclobutametallation of the endocyclic double bond of **19** may lead, after cycloreversion of **20** and **21**, to the regioisomeric intermediates **22** and **23** (Scheme 5). In the absence of any external alkene (CM partner), the intramolecular RCM of **23** would afford the domino metathesis product **25**, whereas in the presence of ethylene as the external al-

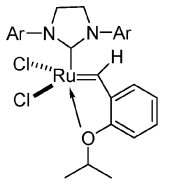



Scheme 5.

kene, CM reaction of both **22** and **23** should give the ROM/CM product **24**.

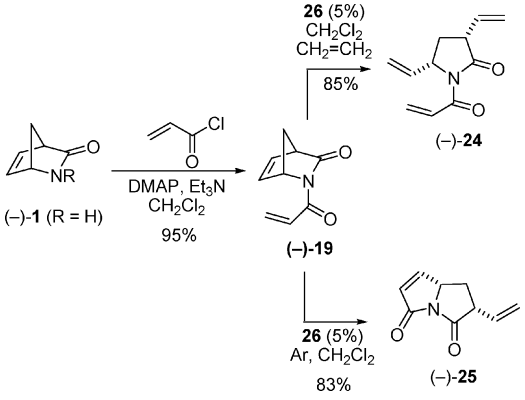
Thus, reaction of (–)-**1** (R = H) with acryloyl chloride (DMAP, $Et_3N$, $CH_2Cl_2$) gave (–)-**19** in 95% yield.[15] Treatment of (–)-**19** with the second-generation Hoveyda–Grubbs precatalyst **26**[16] (5% $CH_2Cl_2$, Figure 3) under ethylene afforded (–)-**24** (85%), whereas when the reaction was carried out under the same experimental conditions under argon, compound (–)-**25** was isolated in 83% yield (Scheme 6).




**26**

Ar = 2,4,6-$(Me)_3C_6H_2$

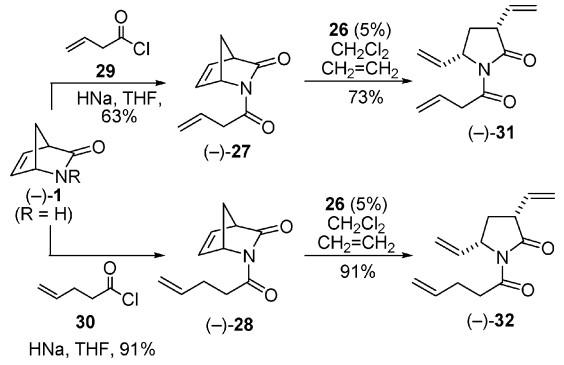
Figure 3. Second-generation Hoveyda–Grubbs catalyst **26**.




Scheme 6.

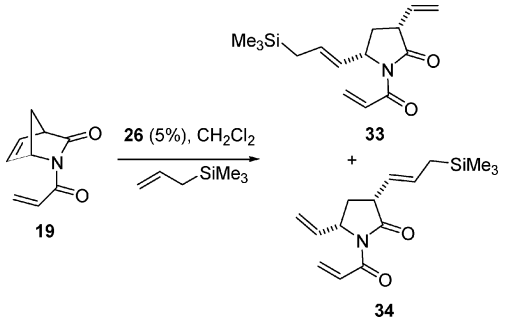
Next we tried to extend this experimental protocol to compounds **27** and **28**. Reaction of (–)-**1** (R = H) with acyl chlorides **29** and **30** (HNa, THF) gave compounds (–)-**27** and (–)-**28** in 63 and 91% yields, respectively. The ROM/CM (ethylene) sequence worked well for both compounds to give pyrrolidinones (–)-**31** and (–)-**32** in 73 and 91% yields, respectively. However, the ROM/RCM sequence (Ar) failed in both cases under a wide range of experimental conditions (temperature, solvent, precatalyst and reaction time). By using precatalyst **26** we observed the disappearance of the starting material (TLC), but we were unable to isolate any identifiable product from the crude reaction mixture. Moreover, all attempts to induce RCM reactions of isolated (–)-**31** and (–)-**32** were also unsuccessful (Scheme 7).

Next we explored the ROM/CM of compound **19** (in racemic form) in the presence of a CM partner other than ethylene (allyltrimethylsilane) by using precatalyst **26**. As indicated previously, two regioisomeric products **33** and **34** (Scheme 8) are now possible. In our hands, the reaction of **19** with equimolecular amounts of allyltrimethylsilane in $CH_2Cl_2$ and in the presence of 5% **26** over 4 h gave, after



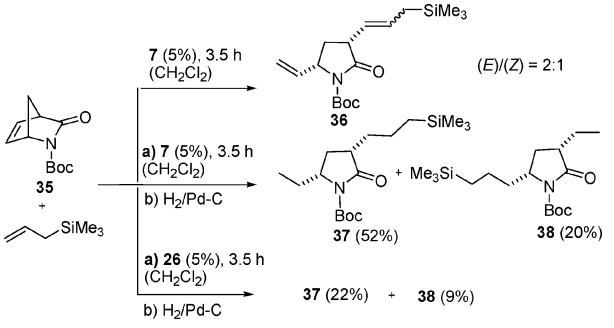

Scheme 7.

purification of the crude reaction mixture, 80% of compound **33** as sole regio- and diastereomer (*trans* stereochemistry with regard to the external double bond). The structure of compound **33** was secured by performing HMQC, HMBC and COSY-45 NMR experiments (see the Supporting Information).




Scheme 8.

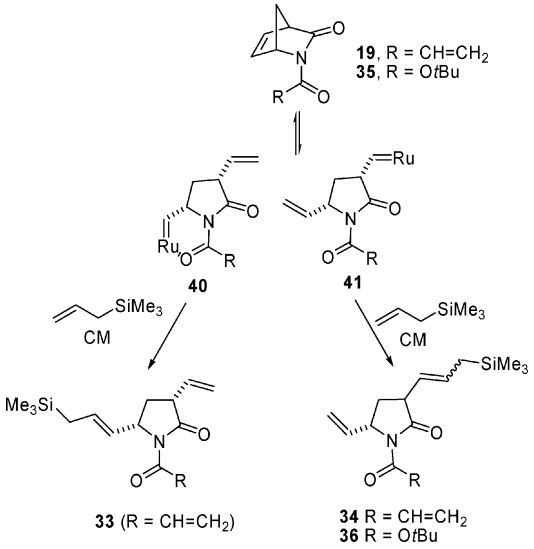
This result appears to be in sharp contrast with others previously described for *N*-substituted derivatives of **1**. For instance, the reaction of **35** with allyltrimethylsilane in the presence of Grubbs' Ru precatalyst **7** gave compound **36** as the sole regioisomer with an (*E*)/(*Z*) diastereomeric ratio of 2:1[2a] (Scheme 9). On the other hand, Ishikura et al.[2b] reported that, under the same experimental conditions and after catalytic hydrogenation of the reaction mixture, compounds **37** and **38** were isolated in 52 and 20% yields, respectively (based on **35**). Note that when precatalyst **26** was used[2c] compounds **37** and **38** were isolated in 22 and 9% yields, respectively.[17]




Scheme 9.

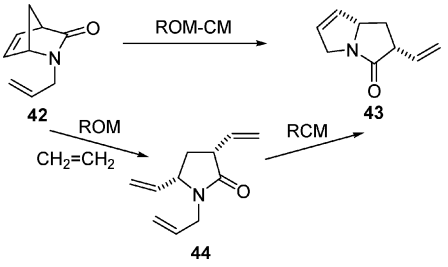
  

This discrepancy of results deserves some comment and can be explained as follows: the equilibrium position between carbenes **40** and **41** (Scheme 10) should be dictated by both steric and chelation effects of the metal centre.[18] On consideration of only steric arguments, intermediate **41** should be more stable than intermediate **40** and, if the final regioisomeric ratio reflects the equilibrium position of **40** and **41**, the CM product arising from **41** will be the major product in the final reaction mixture. That is the case in the experiments described in Scheme 9. However, the ability of amides to chelate to ruthenium during metathesis has been clearly established.[19] Thus, chelation effects would stabilize intermediate **40** in the case of the sterically less demanding vinyl moiety of **19** relative to the bulkier *tert*-butoxy group in **35**. Consequently, the balance between steric and chelation effects should, in our case, favour intermediate **40**.[20]




Scheme 10.

The efficacy of precatalyst **26** to achieve the chemoselective transformation of (–)-**19** into (–)-**25** (Scheme 6) prompted us to investigate the direct transformation of the allyl derivative **42** into pyrrolizidin-3-one **43**[21] by direct ROM/CM under argon. Although compound **43** has been synthesized by RCM reaction of **44** (see above), the direct synthesis of **43** from **42** has, to the best of our knowledge, never been reported (Scheme 11).[22]




Scheme 11.

In this way we were pleased to observe that the reaction of compound (–)-**42**[3] with 5% **26** in $CH_2Cl_2$ (12 h) under argon afforded 70% of compound (–)-**43**.

## Conclusions

The chemoselectivity of the metathesis reactions of *N*-substituted 3-oxo-2-azanorbornene derivatives may be tuned by using the second-generation Hoveyda–Grubbs catalyst **26**. Reactions in the presence of ethylene as the CM reagent afforded trisubstituted pyrrolidinone derivatives, whereas the reaction under argon in the absence of the CM partner gave functionalized tetrahydro-6*H*-pyrrolizidin-3-ones. In addition, the ROM/CM reaction of *N*-acryloyl-3-oxo-2-azanorbornene was totally regioselective in the presence of allyltrimethylsilane to give the sterically most hindered 3,5-disubstituted *N*-acryloylpyrrolidin-2-one.

## Experimental Section

**General Information:** All reactions were carried out under argon; materials were handled by employing standard techniques. All solvents were reagent grade. Dichloromethane was freshly distilled from calcium hydride. All other reagents and solvent were used as supplied. Flash chromatography was performed with silica gel 60 (230–400 mesh). Yields refer to chromatographically and spectroscopically pure compounds unless otherwise noted. $^1H$ and $^{13}C$ NMR spectra were recorded with Bruker 200-AM (200 MHz), AM-300 (300 MHz), and AM-500 (500 MHz) NMR spectrometers in deuteriochloroform. Chemical shifts are expressed as $\delta$ values in ppm, and coupling constants are given in Hz. Mass spectrometric data were recorded with a quadrupole HP-5989-A mass spectrometer at the University Complutense of Madrid. IR spectra were recorded with a Perkin-Elmer 781 apparatus in a solution of dichloromethane. Elemental analyses were performed with a Perkin-Elmer 2400CHN apparatus at the Complutense University Madrid.

**Starting Materials:** Compounds **1** and **30** are commercially available. Compounds **42** and **43** have been described previously.[3] Compound **29** was prepared from but-3-enoic acid by reaction with oxalyl chloride.[23]

**Compound (–)-19:** Acryloyl chloride (0.6 mL, 6.9 mmol), $Et_3N$ (0.95 mL, 6.9 mmol) and DMPA (60 mg, 0.46 mmol) were added to a solution of compound (–)-**1** (500 mg, 4.6 mmol) in $CH_2Cl_2$ (22 mL) under argon at 0 °C. The reaction mixture was stirred at room temp. overnight. After this time, 0.5 N HCl was added. The crude reaction mixture was washed with $NaHCO_3$ (saturated solution) and NaCl (saturated solution) and the organic layer dried with $MgSO_4$. After filtration, the solvent was removed in vacuo to give a yellow crude product which was purified by column chromatography ($SiO_2$, hexane/AcOEt, 4:1) to give 710 mg (95%) of pure (–)-**19** as a colourless oil. $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.26 (dd, $J$ = 17.0, 10.40 Hz, 1 H, $CH_2$=C*H*-CO-), 6.87 (dd, $J$ = 5.30, 2.30 Hz, 1 H, 5-H), 6.61 (ddd, $J$ = 5.30, 3.30, 1.50 Hz, 1 H, 5-H), 6.41 (dd, $J$ = 17.0, 1.90 Hz, 1 H, C$H_{2(E)}$=CH-CO-), 5.75 (dd, $J$ = 10.4, 1.9 Hz, 1 H, C$H_{2(Z)}$=CH-CO-), 5.27 (m, 1 H, 1-H), 3.40 (m, 1 H, 4-H), 2.29 (dt, $J$ = 8.65, 1.50 Hz, 1 H, -$CH_2$-), 2.17 (dt, $J$ = 8.65, 1.50 Hz, 1 H, -$CH_2$) ppm. $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): $\delta$ = 177.75 (C-3), 164.97 (-*C*O-CH=$CH_2$), 140.85 (C-6) 138.41 (C-5), 131.03 (-CO-CH=*C*$H_2$), 128.97 (-CO-*C*H=$CH_2$), 60.81 (C-1), 55.01 (C-4), 54.86 (C-7) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3057, 2937, 2872, 1732, 1442, 1418, 1373, 1271, 1115, 1045, 734, 704 $cm^{-1}$. MS (70 eV): $m/z$ (%) = 163 $[M]^+$, 149 (21) 99 (6), 71 (44), 66 (19), 57

(67), 43 (100). $C_9H_9NO_2$ (163.06): calcd. C 66.25, H 5.56; found C 66.38, H 7.68. $[a]_D^{24}$ = 133.67 (*c* = 0.9, $CHCl_3$).

**Compound (–)-27:** NaH (20 mg, 0.5 mmol) was added to a solution of compound (–)-**1** (50 mg, 0.92 mmol) in THF (2.3 mL) under argon at 0 °C. After 30 min, **29** (0.1 mL, 0.92 mmol) was added at 0 °C. The reaction mixture was stirred at room temp. overnight. After this time, 0.5 N HCl was added, and the mixture was extracted with $Et_2O$, washed with $NaHCO_3$ (saturated solution) and then NaCl (saturated solution), and the organic layer was dried with $MgSO_4$. After filtration, the solvent was removed in vacuo to give a yellow crude product which was purified by column chromatography ($SiO_2$, hexane/AcOEt, 4:1) to give 50 mg (63%) of pure (–)-**27** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 6.91 (dd, *J* = 5.25, 2.40 Hz, 1 H, 6-H), 6.67 (ddd, *J* = 5.25, 3.18, 1.45 Hz, 1 H, 5-H), 5.94 (m, 1 H, $CH_2$=C*H*-), 5.29 (m, 1 H, 1-H), 5.16 (dm, *J* = 11.30 Hz, 1 H, C$H_{2(Z)}$=CH-$CH_2$CO-), 5.15 (dm, *J* = 16.04 Hz, 1 H, C$H_{2(E)}$=CH-$CH_2$CO-), 3.55 (tt, *J* = 6.55, 1.45 Hz, 2 H, $CH_2$=CH-C$H_2$CO-), 3.45 (m, 1 H, 4-H), 2.31 (dt, *J* = 8.60, 1.60 Hz, 1 H, 7-H), 2.22 (dt, *J* = 8.60, 1.60 Hz, 1 H, 7′-H) ppm. $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ = 177.75 (C-3), 171.13 ($CH_2$=CH-$CH_2$*C*O-), 140.86 (C-6), 138.49 (C-5), 130.65 ($CH_2$=*C*H-$CH_2$CO-), 118.96 (*C*$H_2$=CH-$CH_2$CO-), 60.74 (C-1), 55.16 (C-7), 54.94 (C-4), 41.00 ($CH_2$=CH-*C*$H_2$-CO) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3020, 2976, 2957, 1751, 1686, 1423, 1357, 1340, 1217, 1149, 1018, 754, 669 cm$^{-1}$. MS (70 eV): *m*/*z* (%) = 177 $[M]^+$, 149 (8) 84 (16), 66 (100), 53 (17), 41 (50). $C_{10}H_{11}NO_2$ (177.08): calcd. C 67.68, H 6.26; found C 67.51, H 6.13. $[a]_D^{24}$ = –133.27 (*c* = 1.1, $CHCl_3$).

**Compound (–)-28:** NaH (88 mg, 3.67 mmol) was added to a solution of compound (–)-**1** (200 mg, 1.84 mmol) in THF (9.2 mL) under argon at 0 °C. After 30 min, **30** (0.1 mL, 0.92 mmol) was added at 0 °C. The reaction mixture was stirred at room temp. overnight. After this time, 0.5 N HCl was added and the mixture extracted with $Et_2O$, washed with $NaHCO_3$ (saturated solution) and then NaCl (saturated solution) and the organic layer dried with $MgSO_4$. After filtration, the solvent was removed in vacuo to give a yellow crude product which was purified by column chromatography ($SiO_2$, hexane/AcOEt, 7:3) to give 318 mg (91%) of pure (–)-**28** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 6.91 (ddd, *J* = 5.30, 2.40, 0.6 Hz, 1 H, 6-H), 6.67 (ddd, *J* = 5.30, 3.20, 1.50 Hz, 1 H, 5-H), 5.84 (ddt, *J* = 17.10, 10.30, 6.70 Hz, 1 H, $CH_2$=C*H*-$CH_2CH_2$CO-), 5.29 (m, 1 H, 1-H), 5.05 (dq, *J* = 17.10, 1.60 Hz, 1 H, C$H_{2(E)}$=CH-$CH_2CH_2$CO-), 4.99 (dt, *J* = 10.20, 1.60 Hz, 1 H, C$H_{2(Z)}$=CH-$CH_2CH_2$CO-), 3.45 (m, 2 H, 4-H), 2.87 (td, *J* = 4.00, 3.40 Hz, 1 H, $CH_2$=CH-$CH_2CH_2$CO-), 2.37 (dt, *J* = 7.40, 6.30, 1.40 Hz, 1 H, $CH_2$=CH-$CH_2CH_2$CO-), 2.26 (dt, *J* = 7.40, 6.30, 1.40 Hz, 1 H, $CH_2$=CH-$CH_2CH_2$CO-), 2.31 (dt, *J* = 8.80, 1.90 Hz, 1 H, 7a-H), 2.21 (dt, *J* = 8.80, 1.90 Hz, 1 H, 7b-H) ppm. $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ = 177.88 (C-3), 172.67 ($CH_2$=CH-$CH_2CH_2$*C*O-), 144.88 (C-6), 138.51 (C-5), 137.39 ($CH_2$=*C*H-$CH_2CH_2$CO-), 115.78 (*C*$H_2$=CH-$CH_2CH_2$CO-), 60.68 (C-1), 55.19 (C-7), 55.02 (C-4), 35.61 ($CH_2$=CH-$CH_2$*C*$H_2$CO-), 28.71 ($CH_2$=CH-*C*$H_2CH_2$CO-) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3080, 2952, 2877, 1751, 1683, 1406, 1321, 1166, 1145, 1002, 758, 667 cm$^{-1}$. MS (70 eV): *m*/*z* (%) = 191 $[M]^+$, 167 (11), 149 (28), 111 (16), 83 (26), 71 (37), 57 (59), 55 (100), 43 (44). $C_{11}H_{13}NO_2$ (191.09): calcd. C 69.09, H 6.85; found C 69.21, H 6.69. $[a]_D^{24}$ = –130.10 (*c* = 1.0, $CHCl_3$).

**Metathesis Reactions in the Presence of Ethylene:** Catalyst **26** (0.05 equiv.) in $CH_2Cl_2$ was added to a solution of compounds (–)-**19**, (–)-**27** and (–)-**28** (1.0 equiv.) in $CH_2Cl_2$ under argon. This mixture was stirred under ethylene at room temp. overnight. After this time, the solvent was removed in vacuo, and the reaction crude was purified as indicated in each case.

**Compound (–)-24:** From (–)-**19** (100.0 mg, 0.61 mmol) in $CH_2Cl_2$ (13.0 mL, 22 ml/mmol) and **26** (19.0 mg, 0.03 mmol) in $CH_2Cl_2$ (1.7 mL, 55 mL/mmol). Purification by column chromatography ($SiO_2$, hexane/AcOEt, 8:2) gave 99.0 mg (85%) of (–)-**24** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.42 (dd, *J* = 16.85, 10.40 Hz, 1 H, $CH_2$=C*H*-CO-), 6.50 (dd, *J* = 16.85, 1.90 Hz, 1 H, C$H_{2(E)}$=CH-CO-), 6.00–5.70 (m, 2 H, 2× $CH_2$=C*H*-), 5.86 (dd, *J* = 10.40, 1.90 Hz, 1 H, C$H_{2(Z)}$=CH-CO-), 5.28 (dm, *J* = 10.90 Hz, 1 H, C$H_{2(Z)}$=CH-), 5.27 (dm, *J* = 16.30 Hz, 1 H, C$H_{2(E)}$=CH-), 5.25 (dm, *J* = 17.00 Hz, 1 H, C$H_{2(E)}$=CH-), 5.20 (dm, *J* = 10.30 Hz, 1 H, C$H_{2(Z)}$=CH-), 4.77 (qm, *J* = 7.20 Hz, 1 H, 5-H), 3.31 (m, 1 H, 3-H), 2.53 (ddd, *J* = 13.30, 9.50, 8.00 Hz, 1 H, 4-H), 1.84 (ddd, *J* = 13.30, 7.20, 6.00 Hz, 1 H, 4′-H) ppm. $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ = 175.96 (C-2), 166.48 ($CH_2$=CH-*C*O-), 138.07 (-*C*H=$CH_2$), 134.27 (-*C*H=$CH_2$), 131.47 (*C*$H_2$=CH-CO-), 130.02 ($CH_2$=*C*H-CO-), 118.73 (-CH=*C*$H_2$), 116.68 (-CH=*C*$H_2$), 58.42 (C-5), 47.73 (C-3), 30.63 (C-4) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3020, 2979, 2939, 2887, 1733, 1684, 1406, 1348, 1186, 1059, 985, 756 cm$^{-1}$. MS (70 eV): *m*/*z* (%) = 191 $[M]^+$, 165 (32), 149 (45), 131 (63), 122 (69), 110 (42), 94 (46), 84 (28), 66 (57), 55 (100). $C_{11}H_{13}NO_2$ (191.09): calcd. C 69.09, H 6.85; found C 69.15, H 6.74. $[a]_D^{24}$ = –58.39 (*c* = 1.1, $CHCl_3$).

**Compound (–)-31:** From (–)-**27** (140.0 mg, 0.8 mmol) in $CH_2Cl_2$ (14.5 mL, 22 mL/mmol) and **26** (25.0 mg, 0.03 mmol) in $CH_2Cl_2$ (2.2 mL, 55 mL/mmol). Purification by column chromatography ($SiO_2$, hexane/AcOEt, 4:1) gave 115.0 mg (73%) of (–)-**31** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 6.06–5.70 (m, 3 H, 3× $CH_2$=C*H*-), 5.40–5.20 (m, 6 H, 3× C$H_2$=CH-), 4.73 (dm, *J* = 7.20 Hz, 2 H, 5-H), 3.71 (dm, *J* = 6.90 Hz, 2 H, $CH_2$=CH-C$H_2$CO-), 3.06 (m, 1 H, 3-H), 2.51 (ddd, *J* = 13.20, 9.30, 8.40 Hz, 1 H, 4-H), 1.83 (ddd, *J* = 13.20, 6.90, 5.70 Hz, 1 H, 4′-H) ppm. $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ = 175.71 (C-1), 172.55 ($CH_2$=CH-$CH_2$*C*O-), 138.16, 134.36 and 130.64 (3× $CH_2$=*C*H-), 119.13, 118.71 and 116.58 (3×-CH=*C*$H_2$), 58.33 (C-5), 47.67 (C-3), 42.48 ($CH_2$=CH-*C*$H_2$CO-), 30.56 (C-4) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3087, 3018, 2979, 2927, 1735, 1705, 1423, 1348, 1213, 1117, 1051, 758, 669 cm$^{-1}$. MS (70 eV): *m*/*z* (%) = 205 $[M]^+$, 145 (28), 131 (43), 122 (64), 85 (40), 83 (55), 71 (63), 57 (100), 41 (78). $C_{12}H_{15}NO_2$ (205.11): calcd. C 70.22, H 7.37; found C 70.37, H 7.49. $[a]_D^{24}$ = –41.35 (*c* = 1.3, $CHCl_3$).

**Compound (–)-32:** From (–)-**28** (100.0 mg, 0.52 mmol) in $CH_2Cl_2$ (11.5 mL, 22 mL/mmol) and **26** (16.4 mg, 0.027 mmol) in $CH_2Cl_2$ (1.5 mL, 55 mL/mmol of **26**). Purification by column chromatography ($SiO_2$, hexane/AcOEt, 4:1) gave 105.0 mg (91%) of (–)-**32** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 5.98–5.70 (m, 3 H, 3× $CH_2$=C*H*-), 5.27 (dm, *J* = 11.10 Hz, 1 H, C$H_{2(Z)}$=CH-), 5.26 (dm, *J* = 13.40 Hz, 1 H, C$H_{2(E)}$=CH-), 5.22 (dm, *J* = 17.20 Hz, 1 H, C$H_{2(E)}$=CH-), 5.17 (dm, *J* = 10.20 Hz, 1 H, C$H_{2(Z)}$=CH-), 5.08 (dm, *J* = 17.05 Hz, 1 H, C$H_{2(E)}$=CH-), 4.99 (dm, *J* = 10.30 Hz, 1 H, C$H_{2(Z)}$=CH-), 4.73 (qm, *J* = 7.00 Hz, 2 H, 5-H), 3.29 (qm, *J* = 6.80 Hz, 1 H, 3-H), 3.03 (td, *J* = 7.55, 2.60 Hz, 2 H, $CH_2$=CH-$CH_2$C$H_2$CO-), 2.50 (ddd, *J* = 13.20, 9.60, 8.40 Hz, 1 H, 4-H), 2.41 (qm, *J* = 6.70 Hz, 2 H, $CH_2$=CH-$CH_2$C$H_2$CO-), 1.82 (m, 1 H, 4′-H) ppm. $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ = 175.75 (C-2), 174.02 ($CH_2$=CH-$CH_2CH_2$*C*O-), 138.41, 137.43 and 134.44 (3× $CH_2$=*C*H-), 118.64, 116.37 and 115.79 (3× -*C*H=$CH_2$), 58.30 (C-5), 47.71 (C-3), 37.16 ($CH_2$=CH-$CH_2$*C*$H_2$CO-), 30.11 (C-4), 28.5174 ($CH_2$=CH-*C*$H_2CH_2$CO-) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3020, 2937, 1733, 1716, 1635, 1456, 1348, 1059, 929, 756 cm$^{-1}$. MS (70 eV): *m*/*z* (%) = 219 $[M]^+$, 149 (17), 125 (17), 111 (27), 86 (85), 71 (62), 57 (100), 43 (16). $C_{13}H_{17}NO_2$ (219.13): calcd. C 71.21, H 7.81; found C 71.37, H 7.72. $[a]_D^{24}$ = –30.36 (*c* = 0.8, $CHCl_3$).

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**Metathesis Reactions in the Presence of Allytrimethylsilane**

**Compound 33:** Catalyst **26** (19.2 mg, 0.03 mmol) in $CH_2Cl_2$ (1.6 mL) was added to a solution of **19** (100.0 mg, 0.62 mmol) and allyltrimethysilane (0.1 mL, 0.62 mmol) in $CH_2Cl_2$ (13.4 mL) under argon. This mixture was stirred at room temp. for 4 h. After this time, the solvent was removed in vacuo, and the crude product was purified by column chromatography ($SiO_2$, $CH_2Cl_2$/AcOEt, 9:1) to give 133.0 mg (80%) of **33** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.35 (dd, $J$ = 16.7, 10.2 Hz, 1 H, $CH_2$=C*H*-CO-), 6.45 (dd, $J$ = 16.7, 2.0 Hz, 1 H, C$H_{2(E)}$=CH-CO-), 5.96 (dd, $J$ = 10.9, 2.0 Hz, 1 H, C$H_{2(Z)}$=CH-CO-), 5.80 (dd, $J$ = 16.7, 10.2 Hz, 1 H, $CH_2$=C*H*-), 5.70 (dt, $J$ = 16.0, 8.6 Hz, 1 H, $Me_3$SiCH$_2$C*H*=CH-COO-), 5.30 (dm, $J$ = 16.04 Hz, 2 H, C$H_2$=CH-), 5.27 (dm, $J$ = 16.0 Hz, 1 H, $Me_3SiCH_2CH$=C*H*-), 4.72 (q, $J$ = 7.7 Hz, 1 H, 5-H), 3.28 (qm, $J$ = 7.7 Hz, 1 H, 3-H), 2.50 (m, 1 H, 4-H), 1.80 (ddd, $J$ = 13.0, 7.0, 5.4 Hz, 1 H, 4'-H), 1.47 (dm, $J$ = 8.5 Hz, 2 H, $Me_3SiCH_2$CH=CH-), –0.01 (s, 9 H, *Me*$_3$SiCH$_2$-CH=CH-) ppm. $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ = 177.69 (C-2), 168.04 ($CH_2$=CH-*C*O-), 136.25 ($CH_2$=*C*H-), 132.46 ($Me_3$-SiCH$_2$*C*H=CH-), 132.08 (*C*H$_2$=CH-CO-), 131.90 ($CH_2$=*C*H-CO-), 129.37 ($Me_3SiCH_2CH$=*C*H-), 120.09 (*C*H$_2$=CH-), 59.98 (C-5), 49.35 (C-3), 33.00 (C-4), 24.78 ($Me_3$Si*C*H$_2$CH=CH-), 0.05 [(*C*H$_3$)$_3$Si] ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3584, 3020, 1729, 1687, 1407, 1314, 1216, 854, 757, 666 cm$^{-1}$. MS (70 eV): *m*/*z* (%) = 277 [M]$^+$, 262 (30), 208 (7), 182 (7), 91 (11), 73 (100), 55 (72), 43 (22), 41 (14). $C_{15}H_{23}NO_2Si$ (277.15): calcd. C 64.94, H 8.36; found C 64.81, H 8.19.

**Metathesis Reactions in the Absence of Ethylene**

**Compound (–)-25:** Catalyst **26** (9.6 mg, 0.015 mmol) in $CH_2Cl_2$ (0.8 mL) was added to a solution of (–)-**19** (50.0 mg, 0.31 mmol) in $CH_2Cl_2$ (6.7 mL) under argon. This mixture was stirred at room temp. overnight. After this time, the solvent was removed in vacuo, and the crude product was purified by column chromatography ($SiO_2$, $CH_2Cl_2$/AcOEt, 4:1) to give 42 mg (83%) of (–)-**25** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.33 (dd, $J$ = 6.00, 1.80 Hz, 1 H, 7-H), 5.46 (m, 1 H, 6-H), 5.99 (ddd, $J$ = 17.10, 10.50, 6.20 Hz, 1 H, $CH_2$=C*H*-), 5.30 (dt, $J$ = 10.50, 1.50 Hz, 1 H, C$H_{2(Z)}$=CH-), 5.20 (dt, $J$ = 17.10, 1.50 Hz, 1 H, C$H_{2(E)}$=CH-), 4.82 (ddt, $J$ = 11.80, 5.90, 1.80 Hz, 1 H, 7a-H), 3.68 (q, $J$ = 6.20 Hz, 1 H, 2-H), 2.64 (ddd, $J$ = 11.80, 6.80, 5.90 Hz, 1 H, 1-H), 1.83 (c, $J$ = 11.80 Hz, 1 H, 1a-H) ppm. $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ = 171.35 (C-3), 167.76 (C-5), 150.77 (C-7), 132.51 ($CH_2$=*C*H-), 128.66 (C-6), 119.14 (*C*H$_2$=CH-), 62.60 (C-7a), 52.24 (C-2), 33.50 (C-1) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3391, 3087, 2926, 2853, 1772, 1696, 1406, 1272, 1229, 818 cm$^{-1}$. MS (70 eV): *m*/*z* (%) = 163 [M]$^+$, 121 (23), 109 (46), 83 (59), 71 (44), 57 (80), 43 (100), 41 (33). $C_9H_9NO_2$ (163.06): calcd. C 66.25, H 5.56; found C 66.15, H 5.53. $[\alpha]_D^{24}$ = –19.34 ($c$ = 0.6, $CHCl_3$).

**Compound (–)-43:** Catalyst **8** (8.6 mg, 0.010 mmol) in $CH_2Cl_2$ (0.8 mL) was added to a solution of (–)-**42** (30.0 mg, 0.20 mmol) in $CH_2Cl_2$ (4.5 mL) under argon. This mixture was stirred at room temp. overnight. After this time, the solvent was removed in vacuo, and the crude product was purified by column chromatography ($SiO_2$, $CH_2Cl_2$/AcOEt, 7:3) to give 21 mg (70%) of (–)-**43** as a colourless oil. $[\alpha]_D^{24}$ = –9.2 ($c$ = 1.1, $CHCl_3$) {ref.[3] $[\alpha]_D^{24}$ = –8.0 ($c$ = 0.15, $CHCl_3$)}.

**Supporting Information** (see footnote on the first page of this article): $^1$H and $^{13}$C NMR spectra for compounds (–)-**19**, (–)-**25** and (–)-**27** to (–)-**32**. $^1$H and $^{13}$C NMR, COSY (45), HMQC and HMBC NMR spectra for compound **33**.

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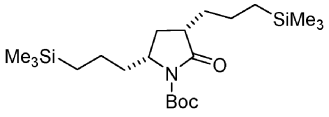


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[21] The occurrence of the structural motif pyrrolizidin-3-one is widespread in plants and, less extensively, in insects and molds. For a review on the synthetic approaches to these compounds, see: a) X. L. M. Despinoy, H. McNab, *Tetrahedron* **2000**, *56*, 6359; for two recent references, see: b) R. Schobert, A. Wicklein, *Synthesis* **2007**, 1499, and references cited therein; c) R. Zimmer, M. Collas, R. Czerwonka, U. Hain, H. U. Reissig, *Synthesis* **2008**, 237, and references cited therein; for the synthesis of enantiopure polyhydroxylated pyrrolizidine alkaloids by using RCM reactions, see: d) D. Muroni, M. Mucceda, A. Saba, *Tetrahedron Lett.* **2008**, *49*, 2373.

[22] Pyrrolizidine derivatives have been obtained from cyclopentene–yne compounds by means of ROM/CM in the presence of ethylene as the CM reagent and by using first- and second-generation Grubb's Ru precatalyst, see: H. Wakamatsu, Y. Sato, R. Fujita, M. Mori, *Heterocycles* **2006**, *67*, 89.

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