Domino Metathesis of 2-Azanorbornenones: A New Strategy for the Enatioselective Synthesis of 1-Azabicyclic Compounds†

Odón Arjona,* Aurelio G. Csákÿ, Rocío Medel, and Joaquín Plumet*

Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, 28040 Madrid, Spain

plumety@eucmax.sim.ucm.es

Received August 3, 2001

Abstract: Domino metathesis of N-alkylated derivatives of (*1S*)-2-azanorborn-5-en-3-one allowed for the enantioselective synthesis of pyrrolizidine, quinolizidine, pyrrolidinoazepine, and pyrrolidinoazocine derivatives in a straightforward process.

Alkaloids with pyrrolizidine **1**, quinolizidine **2**, pyrrolidinoazepine **3**, and pyrrolidinoazocine **4** ring sistems have a wide and varied distribution in nature. These compounds display a broad range of interesting biological activities, and many of them serve as intermediates in the synthesis of more elaborated compounds. Accordingly, new strategies for the enantioselective synthesis of these azabicyclic skeletons continue to receive considerable attention.[1,2] In recent times, olefin metathesis has emerged as a powerful tool in organic synthesis.[3] In particular, ring-closing metathesis (RCM) has been extensively used for the preparation of cyclic compounds from acyclic precursors. However, the application of this procedure to the synthesis of azabicyclic compounds[4,5] usually requires the elaboration of suitably functionalized pyrrolidines from simple starting materials in stepwise procedures (Scheme 1).

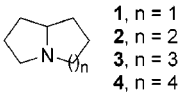
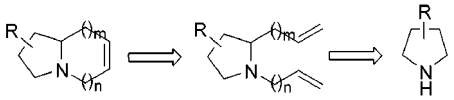
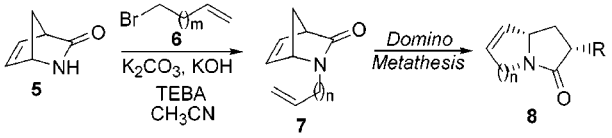


Figure 1.

Scheme 1



Scheme 2



We report herein (Scheme 2) a new method for the enantioselective synthesis of the azabicyclic γ-lactams **8** starting from (1*S*)-2-azanorborn-5-en-3-one[6] **5** as a common precursor in a two-step procedure: (i) N-alkylation of **5**, (ii) domino metathesis[7] (combination of ring opening (ROM), ring closing (RCM), and cross metatheses (CM)).

(1*S*)-2-Azanorborn-5-en-3-one **5** was akylated at the nitrogen atom with the corresponding alkyl halides **6** under solid−liquid PTC conditions to give compounds **7** (Scheme 2),[8] which were treated with Grubbs' ruthenium catalyst ([Ru]) in the presence of ethylene or allyl acetate (Scheme 3). The results are given in Table 1.

In the presence of [Ru] (5% mol), the reaction of compounds **7b**,**c** with ethylene afforded the expected domino metathesis bicyclic γ-lactones **8b**,**c**. On the other hand, compounds **7a** and **7d** did not cyclize under the aforementioned conditions, and the products of ring-opening−cross metathesis (ROM−CM)[9] **9a**,**d** were instead isolated as the only products (Table 1, entries 1 and 9). No significant improvements were noticed upon increasing [Ru] catalyst loading to 10% mol or when [Imes-Ru] was used as catalyst instead of [Ru] (Table 1, entries 2, 3; 5, 6; 9, 10). In a similar fashion, compound **7b** reacted with allyl acetate in the presence of [Ru] to afford compounds **8b** and **8e** (Table 1, entries 11 and 12). The best yield in **8e** was obtained with [Imes-Ru] (Table 1, entry 13). It is worth mentioning that no ROM−CM products were observed in these cases.[7]

However, the isolated ROM−CM products **9a**,**d** did cyclize under ring-closing metathesis (RCM) conditions with [Ru] or [Mo], giving rise to the expected domino metathesis products **8a** and **8d**. The results are gathered in Table 2.

The outcome of these reactions may be understood on the basis of the operation of two alternative equilibrating reaction pathways (Scheme 4).

† Dedicated to Prof. Marcial Moreno on occasion of his 60th birthday.

(1) For general references on the synthesis of alkaloids, see: (a) *Alkaloids, Vol. 55: Chemistry and Biology*, Cordell, G. A., Ed.; Academic Press: San Diego, 2001. (b) Enders, D.; Thiebes, C. *Pure Appl. Chem.* **2001**, *73*, 573. See also: (c) Liddell, J. R. *Nat. Prod. Rep.* **2000**, *17*, 455. (d) Michael, J. P. *Nat. Prod. Rep.* **1999**, *16*, 675. (e) Le Cont, D. J. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Gilchrist, T. L., Eds.; Pergamon: Oxford, 1999; Vol. 11, Chapter 7.

(2) For azabicycloalkanes as reverse-turn inducer dipeptide mimics, see: (a) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789. (b) Cativiela, C.; Díaz de Villegas, M. D. *Tetrahedron*: *Asymmetry* **2000**, *11*, 645. (c) Angiolini, M.; Araneo, S.; Belvisi, L.; Cesarotti, E.; Checchia, A.; Crippa, L.; Manzoni, L. Scolastico, C. *Eur. J. Org. Chem.* **2000**, 2571 and cited references therein.

(3) (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (d) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073. (e) Undheim, K.; Efskind, J. *Tetrahedron* **2000**, *56*, 48. (f) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2000**, *34*, 18 and references cited therein.

(4) For reviews, see: (a) Phillips, A. J.; Abell, A. D. *Aldrichim. Acta* **1999**, *32*, 75. (b) Schuster, M.; Stragies, R.; Blechert, S. In *Targets in Heterocyclic Systems. Chemistry and Properties*; Attanasi, O. A., Spinelli, D., Eds.; Italian Society of Chemistry: Rome, 1998; and references cited therein.

(5) See, for example: (a) Lennartz, M.; Steckhan, E. *Synlett* **2000**, 319. (b) Pandit, U. K.; Overkleeft, H. S.; Borer, B. C.; Bieräugel, H. *Eur. J. Org. Chem.* **1999**, 959. (b) Arisawa, M.; Takezawa, E.; Nishida, A.; Mori, M.; Nakagawa, M. *Synlett* **1997**, 1179. (c) Huwe, C. M.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2376. (d) Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y. *Tetrahedron* **1996**, *52*, 7251.

(6) For the chemistry of substituted 2-azanorbornenes (2-azabicyclo-[2.2.1]hept-5-enes), see: Brandt, P.; Andersson, P. G. *Synthesis* **2000**, 1092.

(7) Stragies, R.; Blechert, S. *Synlett* **1998**, 169.

(8) Compound **5** is commercially available in both optically pure forms.

(9) Schneider, M.; Lucas, N.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 257.

10.1021/jo016000e CCC: $22.00
Published on Web 01/30/2002

Scheme 3

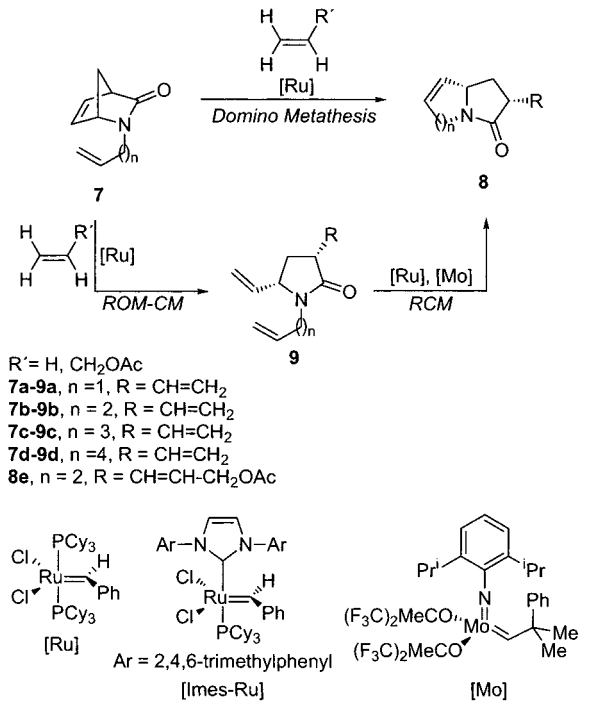


Table 1. RCM and Domino Metathesis of 7 with Ethylene

no.	7	[Ru] (mol %)	8[b] (%)	9[b] (%)	7[c] (%)
1	**7a**	[Ru] (5)[a]		**9a** (10)	80
2	**7a**	[Ru] (10)[a]		**9a** (25)	50
3	**7a**	[Imes-Ru] (5)[a]		**9a** (5)	80
4	**7b**	[Ru] (5)[a]	**8b** (60)	**9b** (7)	30
5	**7b**	[Ru] (10)[a]	**8b** (65)	**9b** (5)	30
6	**7b**	[Imes-Ru] (5)[a]	**8b** (55)	**9b** (35)	20
8	**7c**	[Ru] (10)[a]	**8c** (60)	**9c** (10)	20
9	**7d**	[Ru] (5)[a]		**9d** (30)	20
10	**7d**	[Ru] (10)[a]		**9d** (60)	20
11	**7b**	[Ru] (5)[d]	**8b** (20), **8e** (20)		
12	**7b**	[Ru] (10)[e]	**8b** (30), **8e** (40)		
13	**7b**	[Imes-Ru] (5)[d]	**8b** (30), **8e** (65)		

[a] Reactions carried out in CH_2Cl_2 (40 mL/mmol) and 1 atm ethylene. [b] Isolated yield. [c] Percent recovered. [d] Reactions carried out in CH_2Cl_2 (40 mL/mmol) and 1 equiv of allyl acetate. [e] Reactions carried out in CH_2Cl_2 (40 mL/mmol) and 10 equiv of allyl acetate.

Table 2. Ring-Closing Metathesis of 9a,d[a]

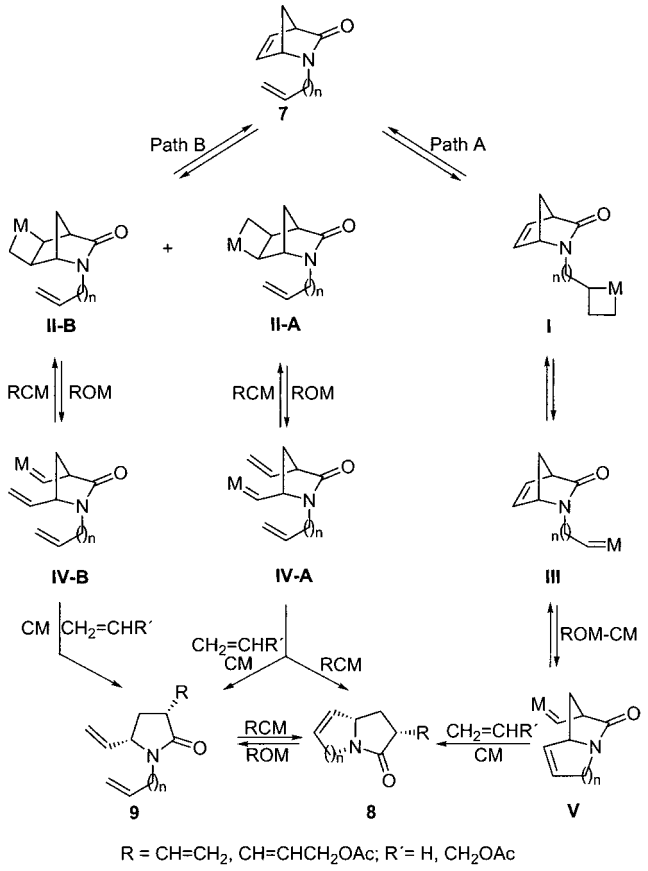
no.	9	[Ru] (mol %)	8[b] (%)	9[c] (%)
1	**9a**	[Ru] (5)	**8a** (22)	**9a** (60)
2	**9a**	[Ru] (10)	**8a** (60)	**9a** (30)
3	**9a**	[Mo] (5)	**8a** (50)	**9a** (20)
4	**9d**	[Ru] (5)	**8d** (30)	**9d** (50)
5	**9d**	[Ru] (10)	**8d** (50)	**9d** (40)
6	**9d**	[Mo] (5)	**8d** (45)	**9d** (30)

[a] Reactions carried out in CH_2Cl_2 (100 mL/mmol). [b] Isolated yield. [c] Percent recovered.

Initial cyclobutanametalation of the terminal alkene moiety of **7** may lead to intermediate **I** (path A). Intramolecular ROM−CM of **I** would lead to carbenes **III** and **V**, which would render the domino metathesis products **8** upon reaction with an external alkene by CM.

On the other hand, initial cyclobutanametalation of the endocyclic C=C bond of **7** may lead to the regioisomeric intermediates **II-A** or **II-B**, which lead, respectively, to carbenes **IV-A** and **IV-B** (path B). Intramolecular RCM of **IV-A** would afford the domino metathesis products **8**,

Scheme 4



whereas intermolecular CM with an external alkene would give rise to the ROM−CM products **9**. The latter may be interconverted to **8** by RCM. Also, intermediate **IV-B** could afford the ROM−CM products **9** by CM with an external alkene.

The operation of patway A is put forward by the results obtained in the reactions of compound **7a** ($n = 1$). In this case, the intermediate carbene **III** may be stabilized by coordination of the metal with the carbonyl group.[10] This extra-stabilization effect would account for the displacement of the equilibria toward **III**. The low conversion observed could be explained on the basis of the low reactivity of the stabilized carbene **III** due to this stabilization effect.

On the other hand, the operation of pathway B is put forward by the exclusive obtention of the ROM−CM products **9a**,**d** in the reactions of compounds **7a**,**d**. Intermediacy of species **IV-B** would render the direct domino metathesis a more difficult process, as the formation of **8** would require the CM of **9** in a second reaction step.

Also, the operation of pathway B is noted in the reactions of compound **7b** with allyl acetate. In this case, compound **8e**, which could stem from intermediate **V**, is obtained together with compound **8b**, which is the product or RCM of **IV-A**. However, as previously stated, compound **8e** could also be formed by CM of **8b** with allyl acetate.

The results described herein put forward the operation of different equilibrating reaction pathways, which ac-

(10) Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277.

count for the obtention of the ROM−CM or domino metathesis products in the reaction of **5** with [Ru] or [Mo] metathesis catalyst in the presence of an external alkene. In any case, the ROM−CM products could be converted to the final azabicyclic γ-lactams **8** by independent RCM. This procedure allows for the enantioselective synthesis of 1-azabicyclic compounds of different ring sizes from a single starting material, although the low yields obtained for the pirrolidizidine skeleton makes it of scarce preparative use in this case.

Experimental Part

All starting materials were commercially available research-grade chemicals and used without further purification. CH_2Cl_2 was distilled after refluxing over $CaCl_2$ under Ar. Silica gel 60 F_{254} was used for TLC, and the spots were detected with UV or vainillin solution. Flash column chromatography was carried out on silica gel 60. IR spectra have been recorded as $CHCl_3$ solutions. ^1H and ^{13}C NMR spectra were recorded at 200 and 50.5 MHz, respectively, in $CDCl_3$ solution with TMS as internal reference.

Synthesis of the *N*-Alkyl-2-azanorborn-5-enones 7. General Procedure. To a solution of (1*S*)-(−)-2-azabicyclo[2.2.1.]-hept-5-en-3-one **5** (109 mg, 1 mmol) in CH_3CN (6 mL) were succesively added K_2CO_3 (166 mg, 1.2 mmol), triturated KOH (168 mg, 3 mmol), and TEBA (30 mg, 0.013 mmol). After the mixture was stirred for 5 min at rt, the corresponding alkyl halide **6** (1.2 mmol) was added, and the resulting mixture was heated at reflux temperature for 3 h. After the mixture was cooled to room temperature, the solid was removed by filtration and washed with diethyl ether (3 × 10 mL) and the filtrate concentrated under reduced pressure. The residue was purified by chromatography (pentane/Et_2O = 1:1).

(1*S*)-2-(Allyl)-2-azabicyclo[2.2.1.]hept-5-en-3-one, 7a. Pale yellow oil, 90%. $[\alpha]^{25}_D = +189.1$ (*c* 0.11, $CHCl_3$). IR ($CHCl_3$): *ν* 2953, 1697, 1645. ^1H NMR ($CDCl_3$, 300 MHz): *δ* 2.09 (d, 1 H, *J* = 7.5 Hz), 2.27 (dd, 1 H, *J* = 1.6, 7.5 Hz), 3.33−3.32 (m, 1 H), 3.37 (ddd, 1 H, *J* = 1.4, 6.3, 15.5 Hz), 3.84 (dd, 1 H, *J* = 5.8, 15.4 Hz), 4.13 (dd, 1 H, *J* = 1.6, 3.6 Hz), 5.13 (dt, 1 H, *J* = 1.5, 10.0 Hz), 5.16 (dddd, 1 H, *J* = 0.8, 1.5, 3.0, 18.0 Hz), 5.72−5.58 (m, 1 H), 5.58 (ddd, 1 H, *J* = 1.4, 3.4, 4.9 Hz), 6.79 (dd, 1 H, J = 2.1, 5.2 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): *δ* 46.6, 53.8, 58.2, 62.5, 117.7, 133.1, 137.7, 139.5, 180.2. Anal. Calcd for $C_9H_{11}NO$: C, 72.48; H, 7.38. Found: C, 72.61; H, 7.30.

(1*S*)-2-(But-3-enyl)-2-azabicyclo[2.2.1.]hept-5-en-3-one, 7b. Pale yellow oil, 85%. $[\alpha]^{25}_D = +294.8$ (*c* 0.31, $CHCl_3$). IR ($CHCl_3$): *ν* 2851, 1691, 1641. ^1H NMR ($CDCl_3$, 300 MHz): *δ* 2.21−2.09 (m, 3 H), 2.27 (dt, 1 H, *J* = 1.5, 7.3 Hz), 2.93 (q, 1 H, *J* = 6.8 Hz), 3.25 (t, 1 H, *J* = 7.3 Hz), 3.32−3.30 (m, 1 H), 4.18 (td, 1 H, *J* = 2.0, 3.4 Hz), 5.01 (ddd, 1 H, *J* = 1.5, 2.9, 8.8 Hz), 5.05 (ddd, 1 H, *J* = 1.5, 3.4, 17.6 Hz), 5.79−5.65 (m, 1 H), 6.62 (ddd, 1 H, *J* = 1.5, 3.4, 5.4 Hz), 6.81 (dd, 1 H, *J* = 1.5, 5.4 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): *δ* 32.3, 43.0, 53.8, 58.9, 63.2, 116.6, 135.1, 138.1, 139.5, 180.3. Anal. Calcd for $C_{10}H_{13}NO$: C, 73.62; H, 7.97. Found: C, 73.75; H, 8.09.

(1*S*)-2-(Pent-4-enyl)-2-azabicyclo[2.2.1.]hept-5-en-3-one, 7c. Pale yellow oil, 80%. $[\alpha]^{25}_D = +239.6$ (*c* 0.54, $CHCl_3$). IR ($CHCl_3$): *ν* 2953, 1689, 1641. ^1H NMR ($CDCl_3$, 300 MHz): *δ* 1.48 (q, 2 H, *J* = 7.4 Hz), 1.98 (c, 2 H, *J* = 7.9 Hz), 2.09 (dt, 1 H, *J* = 1.5, 8.1 Hz), 2.25 (dt, 1 H, *J* = 1.6, 7.5 Hz), 2.86 (dt, 1 H, *J* = 7.1, 13.7 Hz), 3.16 (dt, 1 H, *J* = 7.4, 13.9 Hz), 3.29−3.28 (m, 1 H), 4.14 (dd, 1 H, *J* = 1.9, 3.7 Hz), 4.92 (dt, 1 H, *J* = 1.4, 10.3 Hz), 4.97 (ddd, 1 H, *J* = 1.6, 3.4, 17.5 Hz), 5.81−5.68 (m, 1 H), 6.60 (ddd, 1 H, *J* = 1.8, 3.3, 4.9 Hz), 6.79 (dd, 1 H, *J* = 1.5, 5.2 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): *δ* 27.0, 30.9, 43.1, 53.8, 58.8, 63.0, 114.9, 137.6, 138.0, 139.5, 180.3. Anal. Calcd for $C_{11}H_{15}NO$: C, 74.58; H, 8.47. Found: C, 74.67; H, 8.36.

(1*S*)-2-(Hex-5-enyl)-2-azabicyclo[2.2.1.]hept-5-en-3-one, 7d. Pale yellow oil, 80%. $[\alpha]^{25}_D = +229.2$ (*c* 0.67, $CHCl_3$). IR ($CHCl_3$): *ν* 2935, 1689, 1639. ^1H NMR ($CDCl_3$, 200 MHz): *δ* 1.49−1.22 (m, 4 H), 2.16−1.97 (m, 3 H), 2.26 (dt, 1 H, *J* = 1.5, 7.6 Hz), 2.85 (dt, 1 H, *J* = 6.8, 13.7 Hz), 3.17 (dt, 1 H, *J* = 6.8, 13.7 Hz), 3.25 (d, 1 H, *J* = 1.0 Hz), 4.14 (c, 1 H, *J* = 1.7 Hz), 4.95−4.89 (dm, 1 H, *J* = 10.3 Hz), 5.01−4.92 (dm, 1 H, *J* = 17.1 Hz), 5.74 (ddt, 1 H, *J* = 6.8, 10.3, 17.1 Hz), 6.61 (ddd, 1 H, *J* = 1.2, 3.2, 4.9 Hz), 6.80 (dd, 1 H, *J* = 2.0, 5.0 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): *δ* 25.9, 27.1, 33.2, 43.4, 53.8, 58.9, 63.0, 114.6, 138.0, 138.3, 139.5, 180.3. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.39; H, 8.90. Found: C, 75.51; H, 9.02.

Metathesis of Compounds 7 with Ethylene. General Procedure. A solution of **7** (0.31 mmol) in CH_2Cl_2 (12 mL) was saturated with ethylene and left under ethylene atmosphere (1 atm). [Ru] (0.015 or 0.031 mmol, see Table 1) dissolved in CH_2Cl_2 (4L or 9 mL ,respectively) was added, and the mixture was stirred for 24 h. The solvent was removed under reduced pressure, and the residue was purified by chromatography (pentane/Et_2O = 1:1).

(2*S*,8a*S*)-2-Vinyl-1,5,6,8a-tetrahydroindolizin-3-one, 8b. Pale yellow oil. $[\alpha]^{25}_D = -17.8$ (*c* 0.8, $CHCl_3$). IR ($CHCl_3$): *ν* 2928, 2852, 1678. ^1H NMR ($CDCl_3$, 300 MHz): *δ* 1.52 (c, 1 H, *J* = 11.8 Hz), 2.12−2.05 (m, 1 H), 2.32−2.18 (m, 1 H), 2.46 (ddd, 1 H, *J* = 6.7, 7.3, 12.1 Hz), 2.87 (td, 1 H, *J* = 4.5, 12.4 Hz), 3.21 (dt, 1 H, *J* = 7.3, 11.1 Hz), 4.11−4.06 (m, 1 H), 4.21 (dd, 1 H, *J* = 6.7, 13.2 Hz), 5.18 (dd, 1 H, *J* = 0.1, 17.1 Hz), 5.22 (dd, 1 H, *J* = 0.7, 10.4 Hz), 5.72−5.68 (m, 1 H), 5.83−5.78 (m, 1 H), 5.96 (ddd, 1 H, *J* = 6.7, 10.4, 17.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 24.5, 33.3, 36.3, 46.9, 52.8, 117.4, 125.0, 127.7, 135.3, 172.4. Anal. Calcd for $C_{10}H_{13}NO$: C, 73.62; H, 7.97. Found: C, 73.51; H, 8.10.

(2*S*,9a*S*)-2-Vinyl-1,2,5,6,7,9a-hexahydropyrrolo[1,2-*a*]azepin-3-one, 8c. Pale yellow oil. $[\alpha]^{25}_D = +37.1$ (*c* 0.07, $CHCl_3$). IR ($CHCl_3$): *ν* 2937, 1711, 1674. ^1H NMR ($CDCl_3$, 300 MHz): *δ* 1.73−1.62 (m, 1 H), 1.80−1.74 (m, 1 H), 1.92−1.82 (m, 1 H), 2.24−2.15 (m, 2 H), 2.47 (ddd, 1 H, *J* = 7.8, 8.8, 12.7 Hz), 3.10−2.96 (m, 2 H), 4.02 (ddd, 1 H, *J* = 4.9, 7.8, 13.2 Hz), 4.28−4.22 (m, 1 H), 5.14 (dd, 1 H, *J* = 1.5, 8.8 Hz), 5.17 (dd, 1 H, *J* = 1.5, 17.6 Hz), 5.46 (dd, 1 H, *J* = 1.9, 11.7 Hz), 5.72−5.64 (m, 1 H), 5.89 (ddd, 1 H, *J* = 6.8, 10.3, 17.1 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): *δ* 26.2, 27.9, 33.1, 43.0, 46.0, 57.0, 116.9, 129.9, 131.3, 135.8, 174.2. Anal. Calcd for $C_{11}H_{15}NO$: C, 74.58; H, 8.47. Found: C, 74.70; H, 8.35.

(3*S*,5*S*)-1-Allyl-3,5-divinylpyrrolidin-2-one, 9a. Pale yellow oil. $[\alpha]^{25}_D = +64.4$ (*c* 0.27, $CHCl_3$). IR ($CHCl_3$): *ν* 2928, 1678, 1643. ^1H NMR ($CDCl_3$, 300 MHz): *δ* 1.69 (ddd, 1 H, *J* = 7.8, 9.3, 12.7 Hz), 2.46 (ddd, 1 H, *J* = 7.3, 8.8, 13.2 Hz), 3.13 (c, 1 H, *J* = 8.3 Hz), 3.49 (dd, 1 H, *J* = 7.3, 15.1 Hz), 4.01 (c, 1 H, *J* = 7.8 Hz), 4.28 (dd, 1 H, *J* = 4.9, 15.1 Hz), 5.11 (dd, 1 H, *J* = 1.0, 17.1 Hz), 5.16 (d, 1 H, *J* = 10.3 Hz), 5.31−5.18 (m, 4 H), 5.60 (ddd, 1 H, *J* = 1.5, 8.8, 17.1 Hz), 5.76−5.64 (m, 1 H), 5.96 (ddd, 1 H, *J* = 6.8, 9.8, 17.1 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): *δ* 32.2, 43.3, 45.6, 59.5, 117.1, 117.8, 119.0, 132.2, 135.6, 138.1, 174.3. Anal. Calcd for $C_{11}H_{15}NO$: C, 74.58; H, 8.47. Found: C, 74.43; H, 8.60.

(3*S*,5*S*)-2-(But-3-enyl)-3,5-divinylpyrrolidin-2-one, 9b. Pale yellow oil. IR ($CHCl_3$): *ν* 2928, 1690, 1650. ^1H NMR ($CDCl_3$, 300 MHz): *δ* 1.71−1.63 (m, 1 H), 2.36−2.18 (m, 2 H, Hz), 2.43 (ddd, 1 H, *J* = 6.9, 8.8, 13.0 Hz), 3.02 (ddd, 1 H, *J* = 5.5, 7.8, 13.3 Hz), 3.10 (c, 1 H, *J* = 8.4 Hz), 3.66 (dt, 1 H, *J* = 7.8, 13.7 Hz), 4.01 (c, 1 H, *J* = 8.1 Hz), 5.03 (dt, 1 H, *J* = 1.5, 8.9 Hz), 5.07 (dt, 1 H, *J* = 1.5, 15.6 Hz), 5.18 (dt, 1 H, *J* = 1.1, 8.0 Hz), 5.24 (dt, 1 H, *J* = 0.7, 9.5 Hz), 5.26 (dt, 1 H, *J* = 0.7, 19.0 Hz), 5.34 (dt, 1 H, *J* = 0.7, 17.1 Hz), 5.70−5.58 (m, 1 H), 5.82−5.71 (m, 1 H), 5.95 (ddd, 1 H, *J* = 6.9, 10.7, 17.1 Hz). Anal. Calcd for $C_{12}H_{17}NO$: C, 75.39; H, 8.90. Found: C, 75.49; H, 9.02.

(3*S*,5*S*)-1-(Pent-4-enyl)-3,5-divinylpyrrolidin-2-one, 9c. Pale yellow oil. IR ($CHCl_3$): *ν* 2932, 1709, 1676. ^1H NMR ($CDCl_3$, 300 MHz): *δ* 1.70−1.43 (m, 3 H), 2.02 (c, 2 H, *J* = 6.8 Hz), 2.48−2.39 (m, 1 H), 2.97 (ddd, 1 H, *J* = 4.9, 8.8, 13.7 Hz), 3.09 (c, 1 H, *J* = 8.3 Hz), 3.55 (ddd, 1 H, *J* = 1.9, 6.8, 13.2 Hz), 3.98 (c, 1 H, *J* = 7.8 Hz), 4.96 (d, 1 H, *J* = 11.2 Hz), 5.01 (d, 1 H, *J* = 19.5 Hz), 5.34−5.14 (m, 4 H), 5.60 (ddd, 1 H, *J* = 3.4, 8.8, 17.1 Hz), 5.79 (m, 1 H), 5.95 (m, 1 H). ^{13}C NMR ($CDCl_3$, 50 MHz): *δ* 26.4, 31.0, 32.3, 40.4, 45.7, 60.0, 114.9, 117.0, 118.8, 135.7, 137.7, 138.4, 174.4. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.10; H, 9.27. Found: C, 75.98; H, 9.43.

(3*S*,5*S*)-(Hex-5-enyl)-3,5-divinylpyrrolidin-2-one, 9d. Pale yellow oil. $[\alpha]^{25}_D = +18.2$ (*c* 0.22, $CHCl_3$). IR ($CHCl_3$): *ν* 2932, 1678, 1641. ^1H NMR ($CDCl_3$, 300 MHz): *δ* 1.35 (c, 2 H, *J* = 7.2 Hz), 1.56−1.40 (m, 2 H), 1.64 (ddd, 1 H, *J* = 8.1, 9.6, 13.2 Hz), 2.05 (c, 2 H, *J* = 6.9 Hz), 2.42 (ddd, 1 H, *J* = 6.9, 9.0, 12.9 Hz), 2.94 (ddd, 1 H, *J* = 5.4, 8.4, 13.8 Hz), 3.09 (cd, 1 H, *J* = 1.5, 8.4

Hz), 3.52 (ddd, 1 H, J = 6.9, 8.1, 13.8 Hz), 3.97 (c, 1 H, J = 8.4 Hz), 4.94 (dt, 1 H, J = 1.5, 10.8 Hz), 4.99 (dt, 1 H, J = 1.5, 17.1 Hz) 5.33−5.15 (m, 4 H), 5.62 (dt, 1 H, J = 9.3, 16.5 Hz), 5.77 (ddt, 1 H, J = 6.6, 10.5, 17.1 Hz), 5.94 (ddd, 1 H, J = 6.3, 10.8, 17.1 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 26.0, 26.6, 32.3, 33.3, 40.6, 45.7, 59.9, 114.7, 117.0, 118.7, 135.7, 138.4, 138.4, 174.3. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.71; H, 9.59. Found: C, 76.85; H, 9.48.

Acetic Acid 3-[(2*S*,8a*S*)-3-Oxo-1,2,3,5,6,8a-hexahydroindolizin-2-yl]allyl Ester, 8e. To a solution of **7b** (0.31 mmol) in CH_2Cl_2 (12 mL) was added allyl acetate (0.31 mmol) followed by a solution of [Imes-Ru] (0.015 mmol) in CH_2Cl_2 (4 mL). The mixture was was stirred for 24 h at rt. The solvent was removed under reduced pressure, and the residue was purified by chromatography (pentane/Et_2O = 1:1). Pale yellow oil, 65%. IR ($CHCl_3$): ν 2854, 1734, 1682. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.50 (c, 1 H, J = 11.8 Hz), 2.07 (s, 3 H), 2.13−2.09 (m, 1 H), 2.28−2.17 (m, 1 H), 2.47 (ddd, 1 H, J = 6.3, 7.8, 12.1 Hz), 2.87 (tdd, 1 H, J = 1.2, 5.1, 12.7 Hz), 3.28−3.20 (m, 1 H), 4.11−4.07 (m, 1 H), 4.20 (dd, 1 H, J = 6.6, 13.0 Hz), 4.54 (d, 1 H, J = 12.9 Hz), 4.61 (d, 1 H, J = 12.6 Hz), 5.96−5.75 (m, 4 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.5, 30.3, 33.5, 36.3, 45.5, 52.8, 64.6, 125.1, 126.7, 127.5, 131.9, 170.7, 176.6. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.38; H, 7.23.Found: C, 66.50; H, 7.37.

Ring-Closing Metathesis of 8. General Procedure. A solution of **8** (0.16 mmol) and [Mo] or [Ru] (8×10^{-3} mmol, see Table 2) in anhydrous, degassed CH_2Cl_2 (15 mL) was stirred at room temperature for 12 h. After removal of the solvent under reduced pressure, the crude reaction product was purified by chromatography (pentane/Et_2O = 1:1).

(3*S*,7a*S*)-2-Vinyl-1,5,6,7a-tetrahydropyrrolizin-3-one, 8a. Pale yellow oil. $[\alpha]^{25}_D = -8.0$ (*c* 0.15, $CHCl_3$). IR ($CHCl_3$): ν 2930, 1688, 1643. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.75 (td, 1 H, J = 9.8, 12.2 Hz), 2.62 (dt, 1 H, J = 6.7, 11.9 Hz), 3.49 (dt, 1 H, J = 6.9, 12.6 Hz), 3.72 (dd, 1 H, J = 4.0, 15.5 Hz), 4.42 (dd, 1 H, J = 3.9, 15.7 Hz), 4.64−4.56 (m, 1 H), 5.16 (d, 1 H, J = 17.2 Hz), 5.22 (d, 1 H, J = 10.4 Hz), 5.91 (s, 2 H), 5.95 (ddd, 1 H, J = 6.6, 10.6, 17.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 36.5, 48.6, 50.0, 65.1, 117.4, 128.4, 130.2, 134.8, 177.2. Anal. Calcd for $C_9H_{11}NO$: C, 72.48; H, 7.38. Found: C, 72.60; H, 7.29.

(2*S*,10a*S*)- 2-Vinyl-1,5,6,7,8,10a-hexahydro-2*H*-pyrrolo[1,2-*a*]azocin-3-one, 8d. Pale yellow oil. $[\alpha]^{25}_D = +67.6$ (*c* 0.17, $CHCl_3$). IR ($CHCl_3$): ν 2928, 1672, 1558. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.55−1.47 (m, 2 H), 1.76−1.66 (m, 2 H), 1.99−1.90 (m, 1 H), 2.22−2.11 (m, 1 H), 2.37−2.25 (m, 1 H), 2.52 (ddd, 1 H, J = 6.7, 8.5, 15.4 Hz), 3.22−3.10 (m, 2 H), 3.70 (dd, 1 H, J = 9.3, 14.5 Hz), 4.27 (c, 1 H, J = 7.5 Hz), 5.21 (d, 1 H, J = 10.0 Hz), 5.21 (d, 1 H, J = 17.4 Hz), 5.40 (dd, 1 H, J = 7.0, 10.8 Hz), 6.04−5.88 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.2, 27.3, 27.3, 33.0, 40.9, 46.7, 54.2, 117.0, 129.5, 134.1, 135.7, 173.8. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.39; H, 8.90. Found: C, 75.50; H, 9.02.

Acknowledgment. Ministerio de Ciencia y Tecnología (Project No. BQU2000-0653) is gratefully thanked for financial support. One of us (R.M.) thanks the Ministerio de Educación y Cultura (Spain) for a predoctoral grant.

JO016000E