SYNTHESIS OF ENANTIOPURE 3,5-DISUBSTITUTED PYRROLIDINES
BY RING-OPENING/CROSS-METATHESIS REACTION OF 2-AZANORBORNENE DERIVATIVES

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Abstract – A concise method for the synthesis of enantiopure 3,5-disubstituted pyrrolidines from 2-azanorbornene derivatives is described. The method is also applied to the synthesis of 3,5-disubstituted prolines.

Ring-opening/cross-metathesis (ROM-CM) of bicyclic substrates is an important task in organic synthesis by two main reasons: a) the sequence results in the rapid generation of complex skeletons from relatively simple starting materials and, b) the chiral information inherent in the ring system is transferred into the stereochemistry of the cyclic product. Despite this synthetic potential that has been largely considered in norbornene and 7-oxanorbornene (the group of Rainier also considered with the 7-oxanorbornene system its 7-aza analogue) the metathesis of 2-azanorbornene systems has received less attention. Thus, the metathesis of N-substituted 2-azabicyclo[2.2.1]hept-5-en-3-one (1) (Figure 1) has been studied by three different groups. The groups of Blechert and Ishikura reported the regiochemistry of the ROM-CM sequence of 1a-d with allylsilanes in the presence of Grubbs' first or second generation catalyst (A or B respectively), resulting in general with fair regioselectivity except in the case of large N-trialkysilyl substituted derivatives.

Figure 1
On the other hand, the domino metathesis, ROM-CM-RCM sequence, has been described by our group\(^6\) as new enantioselective synthesis of 1-azabicyclic systems of different ring sizes, starting from \(N\)-alkenyl or \(N\)-alkynyl derivatives of \((-)-1a\) (Figure 1). In both cases the 1-azabicyclic system was obtained besides the pyrrolidinones (ROM-CM) depending on the structure of the starting materials and the reaction conditions.

In this context and following with our general interest in applying ring opening metathesis of strained systems in synthesis, we decided to applied the ROM-CM sequence to 2-azonorbornene derivatives (1a-b), (4) and (5), (6)\(^7\) (Figure 2) with ethylene using Grubbs' catalysts (A) or (B) as a convenient method to prepare enantiomerically pure substituted pyrrolidines or prolines.

![Figure 2](image)

The synthesis of the substrates has been achieved following literature procedures describe for racemic derivatives. Thus, the commercially available \((R)\)-(\(-\))\(-2\)azabicyclo[2.2.1]hept-5-en-3-one [(\(-\)\(-1a\)] was protected as its Boc carbamate\(^8\) and resulted in \((-\)\(-1b\). Selective reduction of the lactam carbonyl group in \((-\)\(-1a\) with LiAlH\(_4\) followed by in situ protection as Boc carbamate yielded \((+)-4\)\(^9\). The derivatives of 2-azabicycle[2.2.1]heptane-3-carboxylic acid ethyl esters 5 and 6 were obtained, following literature procedures, by aza-Diels-Alder of imine, derived from the condensation of 1-phenylethylamine with ethyl glyoxylate, and cyclopentadiene for 5\(^10\) or aza-Wittig, aza-Diels-Alder sequence for 6\(^11\). The reactions of compounds \((-\)\(-1b\), \((+)-4\) and \((-\)\(-1a\) with ethylene (1 atm) in the presence of the Grubbs' second generation catalyst (B)\(^12\) afforded pyrrolidines (7-9) in variable amounts depending on the structure of the starting materials and the reaction conditions (Scheme 1, Table 1).

![Scheme 1](image)
Table 1. Metathesis reactions of compounds [(−)-1a, (+)-4 and (−)-1b] with ethylene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Time (h)</th>
<th>Product (isolated yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(−)-1a</td>
<td>12</td>
<td>(−)-7a (30%)</td>
</tr>
<tr>
<td>2</td>
<td>(−)-1a</td>
<td>2.5</td>
<td>(−)-7a (70%)</td>
</tr>
<tr>
<td>3b</td>
<td>(+)-4</td>
<td>2.5</td>
<td>(+)-8a (60%)</td>
</tr>
<tr>
<td>4</td>
<td>(−)-1b</td>
<td>2.5</td>
<td>(+)-9a (15%); (−)-9b (65%)</td>
</tr>
<tr>
<td>5c</td>
<td>(−)-1b</td>
<td>2.5</td>
<td>(−)-9b (80%)</td>
</tr>
</tbody>
</table>

* Reaction conditions: All the reactions were performed in CH2Cl2, 5 mol % of catalyst (B), 1 atm ethylene and room temperature.

b In this case double dilution was required and catalyst (A) showed better yield than catalyst (B) (45%).

c Purification using a basic silica gel.

The results in Table 1 show that the conversion of the bicycle system to the 3,5-disubstituted pyrrolidines (7-9) proceeded stereospecifically in fair to good yields. The transformation appears with better results in a shorter time of reaction and with the presence of a carbonyl function in position C-3 of the bicycle. It should be pointed out that in the case of compound [(−)-1b] the reaction allowed, after chromatography, as a minor component the expected (+)-9a and as a major one the isomerised compound [(−)-9b] (Entry 4, Table 1). A similar product was obtained by Ishikura et al.5a,b as a minor component in the reaction of 1b with allyltrimethylsilane. They assume that the initial ring-opening/cross-metathesis products isomerize through double bond migration during silica gel column chromatography. This isomerized pyrrolidine [(−)-9b] could be obtained as the only product and with good yield by column chromatography using a basic silica gel (Entry 5, Table 1). This isomerisation requires an N-Boc substituent that increases the acidity of protons in C-3, since in the other cases it does not take place. The isomerisation was stereoselective and the E-diastereomer was obtained selectively.13 This process allows to differentiate both positions, C-3 and C-5,14 from simple way and can be a good alternative to the cross-metathesis with substituted terminal alkenes because the usual regio- and stereoselective problems founded in these reactions.

We next undertook the reaction of 2-azabicyclo[2.2.1]heptane-3-carboxilic acid ethyl ester derivatives (5) and (6) in the same conditions as before (Scheme 2, Table 2).
Table 2. Metathesis reactions of compounds (5) and (6) with ethylenea

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Product (isolated yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>A</td>
<td>12</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>B</td>
<td>12</td>
<td>10 (30%)</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>B</td>
<td>2.5</td>
<td>11 (70%)</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>B</td>
<td>12</td>
<td>--</td>
</tr>
</tbody>
</table>

a Reaction conditions: All the reactions were performed in CH₂Cl₂, 5 mol % of catalyst, 1 atm ethylene and room temperature.

Ring opening metathesis of derivative (5) with Grubbs first generation catalyst (A) gave poor results and 83% of starting material was recovered (Entry 1, Table 2). The use of the catalyst (B) only increases to 30% the yield of 10. This result can be due to the nature of the nitrogen (amine) in compound (5) since when changing the protecting group by a Boc, compound (6), (carbamate vs amine) the yield increase up to 70% of the 3,5-divynil proline derivative (11) (Entry 3, Table 2). Longer reaction time fails to increase the yield of the reaction due to the polymerization of the product.

In summary, we have developed a useful synthesis of enantiopure cis-3,5-disubstituted pyrrolidines bearing unsaturated side chains. The reaction also allows the differentiation of both positions and the application to the synthesis of cis-3,5-divinylprolines derivatives. Other applications of these transformations are being investigated and will be reported in due course.

ACKNOWLEDGEMENTS

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EXPERIMENTAL

All starting materials were commercially available research-grade chemicals and used without further purification. CH₂Cl₂ was distilled after refluxing over CaCl₂ under Ar. Silica gel 60 F₂₅₄ was used for TLC. Flash column chromatography was carried out on silica gel 60. ¹H and ¹³C NMR spectra were recorded at 200 MHz or 300MHz and 50.5 MHz or 75 MHz respectively in CDCl₃ solution with TMS as internal reference. Melting points are uncorrected. Elemental analyses were performed at the Complutense University of Madrid.
**tert-Butyl (1R,4S)-(-)-3-oxo-2-azabicyclo[2.2.1]hept-5-ene-2-carboxylate [(−)-1b]**. To a solution of (-)-1a (570mg, 5.2 mmol) in CH₂Cl₂ (20 ml) were added NEt₃ (0.7 ml, 5.2 mmol), di-tert-butyl dicarbonate (2.27 g, 10.4 mmol) and DMAP (630 mg, 5.2 mmol) at rt. After stirring for 24 h at the same temperature, the mixture was evaporated in vacuo and the residue was diluted with water and extracted with Et₂O. The organic extract was dried over MgSO₄ and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (hexane:AcOEt, 5:1) to give (-)-1b (980 mg, 90%) as white solid, mp 56-57 °C. [α]D²⁵ = -189.1 (c = 2.0, CHCl₃). IR (neat) 1790, 1755 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ = 1.44 (s, 9H), 2.08 (d, 1H), 2.28 (d, 1H), 3.33 (m, 1H), 4.89 (m, 1H), 6.60 (m, 1H), 6.83 (m, 1H). ¹³C NMR (50.5 MHz, CDCl₃): δ = 176.0, 150.2, 139.8, 138.0, 82.4, 62.2, 54.7, 54.3, 27.9. Anal. Calcd for C₁₁H₁₅NO₂: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.92; H, 7.35; N, 6.80

**tert-Butyl (1R,4S)-(+)-2-azabicyclo[2.2.1]hept-5-ene-2-carboxylate [(+)-4]**. A solution of (-)-1a (320 mg, 2.95 mmol) in Et₂O (20 ml) and THF (5 ml) was added dropwise to a suspension of LiAlH₄ (420 mg, 11 mmol) in Et₂O with stirring under argon at rt, and the mixture was refluxed for 7 h. It was cooled in an ice bath, then water (2 ml) was added with vigorous stirring, and the precipitate was filtered off. Di-tert-butyl dicarbonate (647 mg, 3.3 mmol) was added to the filtrate, and the mixture was stirred for 14 h at rt. After addition of benzene (40 ml) the mixture was dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residual was purified by flash chromatography on silica gel (hexane:AcOEt, 9:1) to give (+)-4 (300 mg, 52%) as a colorless oil (two rotamers). [α]D²⁵ = +198.4 (c = 1.75, CHCl₃). IR (neat) 1700 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ = 1.44 (s, 9H), 1.51-1.60 (m, 2H), 2.55-2.71 (m, 1H), 3.16 (br s, 1H), 3.30 (dd, 1H, J=9.2, 2.9 Hz), 4.57 (br s, 1H), 4.71 (br s, 1H), 6.27 (s, 1H), 6.38 (s, 1H). ¹³C NMR (50.5 MHz, CDCl₃): δ = 155.9, 136.1, 134.4, 133.7, 79.0, 61.1, 59.9, 48.1, 46.3, 45.9, 43.4, 42.9, 28.5. Anal. Calcd for C₁₁H₁₅NO₂: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.35; H, 8.65; N, 7.05.

**General procedure for the metathesis reactions.** A solution of the 2-azanorbornene derivative in CH₂Cl₂ (39 ml:mmol 2-azanorbornene derivative) was saturated with ethylene and left under ethylene atmosphere (1 atm). [Ru] catalyst dissolved in CH₂Cl₂ (12 ml:mmol 2-azanorbornene derivative) was added and the mixture was stirred for the time showed in Tables 1 and 2. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (hexane:AcOEt, 5:1).

**(3S,5R)-(−)-3,5-divinylpyrrolidin-2-one [(−)-7a]**. white solid, mp 67-68°C (hexane:AcOEt). [α]D²⁵ -7.6 (c = 0.5, CHCl₃). IR (neat) 1728 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ = 1.60-1.80 (m, 1H), 2.41-2.62 (m, 1H), 3.01-3.20 (m, 1H), 4.02-4.20 (dd, 1H, J=7.5Hz), 5.01-5.30 (m, 4H), 5.60-6.02 (m, 2H), 6.80 (s, 1H). ¹³C NMR (50.5 MHz, CDCl₃): δ = 177.8, 138.6, 135.2, 117.6, 116.6, 55.3, 46.2, 34.9. Anal. Calcd for C₇H₁₃NO: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.85; H, 8.16; N, 10.09.

**tert-Butyl (2R,4S)-(−)-2,4-divinylpyrrolidine-1-carboxylate [(−)-8a]**. (two rotamers), colorless oil. [α]D²⁵ +1.71 (c = 1.4, CHCl₃). IR (neat) 1782 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ = 1.35 (s, 9H),...
2.01-2.30 (m, 1H), 2.50-2.71 (m, 1H), 2.80-3.02 (m, 2H), 3.51-3.80 (br s, 1H), 3.90-4.21 (br s, 1H), 4.91-5.12 (m, 4H), 5.50-5.81 (m, 2H). 13C NMR (50.5 MHz, CDCl3): δ = 154.9, 140.2, 132.0, 131.5, 116.2, 114.6, 114.5, 79.9, 79.8, 60.5, 60.4, 55.5, 52.3, 41.1, 40.2, 36.8, 28.9, 28.8. Anal. Calcd for C13H12NO2: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.75; H, 9.32; N, 6.12.

tert-Butyl (3S,5R)-(+-)-2-oxo-3,5-divinylpyrrolidine-1-carboxylate [(+-)-9a], pale yellow oil. [α]25D +4.0 (c = 0.7, CHCl3). IR (neat) 1780, 1730 cm⁻¹. 1H NMR (200 MHz, CDCl3): δ = 1.44 (s, 9H), 2.07 (m, 2H), 3.21 (m, 1H), 4.58 (t, 1H), 5.16 (m, 4H), 5.84 (m, 2H). 13C NMR (50.5 MHz, CDCl3): δ = 174.0, 150.5, 136.6, 134.1, 118.4, 115.8, 83.2, 57.7, 45.6, 36.5, 28.4. Anal. Calcd for C13H19NO2: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.67; H, 8.15; N, 5.78.

tert-Butyl (5R)-(+-)(3E)-3-ethylidene-2-oxo-5-vinylpyrrolidine-1-carboxylate [(-)-9b], pale yellow oil. [α]25D -13.0 (c = 1.8, CHCl3). IR (neat) 1775, 1712 cm⁻¹. 1H NMR (200 MHz, CDCl3): δ = 1.44 (s, 9H), 1.73 (dt, 3H), 2.36 (br d, 1H), 2.78 (m, 1H), 4.57 (td, 1H), 5.09 (m, 2H), 5.71 (m, 1H), 6.70 (m, 1H). 13C NMR (50.5 MHz, CDCl3): δ = 166.6, 150.3, 137.9, 133.5, 130.7, 115.4, 82.7, 56.7, 28.6, 28.0, 14.8. Anal. Calcd for C13H19NO2: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.70; H, 8.00; N, 5.82.

Ethyl (±)-cis-1-(1-phenylethyl)-3,5-divinylpyrrolidine-2-carboxylate (10), colorless oil. IR (neat) 1725 cm⁻¹. 1H NMR (200 MHz, CDCl3): δ = 1.22 (t, 3H, J=7.1Hz), 1.34 (d, 3H, J=6.7Hz), 1.48 (ddd, J=13.0, 4.2, 3.2), 2.55 (dt, 1H, J=13.0, 8.8 Hz), 2.66-2.76 (m, 1H), 3.54 (d, 1H, J=2.7 Hz), 3.93 (td, 1H, J=8.8, 4.3 Hz) 3.98 (q, 1H, J=6.7 Hz), 4.00 (q, 2H, J=7.1 Hz), 4.68-5.06 (m, 4H), 5.47-5.62 (m, 1H), 6.70-6.02 (m, 1H), 7.10-7.40 (m, 5H). 13C NMR (50.5 MHz, CDCl3): δ = 175.3, 145.1, 142.1, 142.0, 128.6, 128.1, 127.2, 114.4, 114.3, 68.3, 65.3, 60.6, 58.2, 46.5, 38.6, 20.2, 14.6. Anal. Calcd for C19H23NO2: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.05; H, 8.30; N, 4.52.

Ethyl (±)-cis-1-tert-butoxycarbonyl-3,5-divinylpyrrolidine-2-carboxylate (11), colorless oil. IR (neat) 1772, 1739 cm⁻¹. 1H NMR (200 MHz, CDCl3): δ = 1.24 (m, 3H), 1.34 (s, 9H), 1.56 (m, 1H), 2.22 (m, 1H), 2.76 (dd, 1H), 4.23 (m, 4H), 5.03 (m, 2H), 5.73 (m, 2H). 13C NMR (50.5 MHz, CDCl3): δ = 172.5, 140.2, 138.2, 116.0, 114.3, 80.2, 65.4, 60.9, 46.3, 38.0, 28.2. Anal. Calcd for C19H23NO2: C, 65.06; H, 8.53; N, 4.74. Found: C, 64.95; H, 8.42; N, 4.62.

REFERENCES
2. For reviews on the use of norbornenes in ROM-CM sequences, see: (a) O. Arjona, A. G. Csáký, and


12. The use of Grubbs second generation catalyst (B) gave better results, in general, than the use of
catalyst (A). For instance see reference 5.

13. The stereochemistry of the new double bond was determined by NOE experiments.

14. Also the isomerised product [(-)-9b] was obtained in a one pot reaction from [(-)-7a] (45% yield), by protection with (Boc)_2O, Et_3N/DMAP in CH_2Cl_2.

15. The protection of an amine is especially important in cross-metathesis chemistry since most catalysts are poisoned by this functional group, see: A. J. Vernall and A. D. Abell, *Aldrichimica Acta*, 2003, 36, 93.