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

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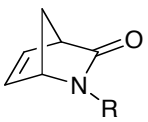
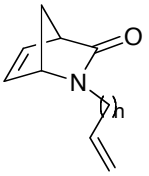
**Abstract** – A concise method for the synthesis of enantiopure 3,5-disubstituted pyrrolidines from 2-azanorbornene derivatives is described. The method is also applied to the synthesis of 3,5-disubstituted prolines.

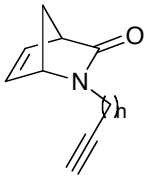
Ring-opening/cross-metathesis (ROM-CM) of bicyclic substrates is an important task in organic synthesis[1,2] by two main reasons: a) the sequence results in the rapid generation of complex skeletons from relatively simple starting materials and, b) the chiral information inherent in the ring system is transferred into the stereochemistry of the cyclic product. Despite this synthetic potential that has been largely considered in norbornene and 7-oxanobornene[3] (the group of Rainier[3d,e] also considered with the 7-oxanobornene 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[4] and Ishikura[5] 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*-trialkylsilyl substituted derivatives.




**1a** R=H
**1b** R=Boc
**1c** R=Ac
**1d** R=benzyl or silyl derivative




**2**

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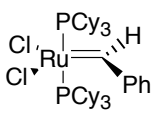
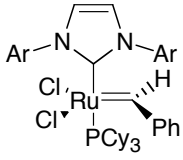



**A**

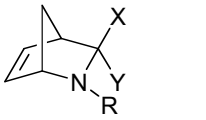



**B**
Ar=2,4,6-trimethylphenyl

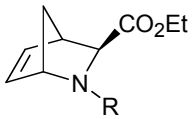
Figure 1

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-azanorbornene 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.



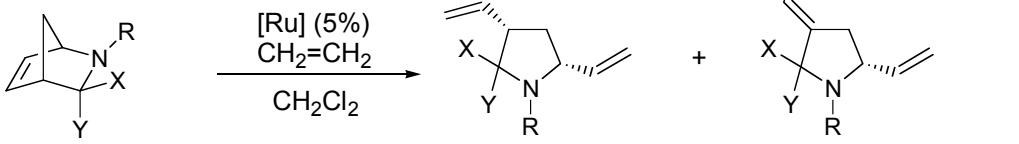

**1a** R= H; X,Y= O
**1b** R= Boc; X,Y= O
**4** R= Boc; X=Y= H




**5** R= CHMePh
**6** R= Boc

Figure 2

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).




**(-)-1a** R= H; X,Y= O
**(+)-4** R= Boc; X=Y= H
**(-)-1b** R= Boc; X,Y= O

**(-)-7a** R= H; X,Y= O
**(+)-8a** R= Boc; X=Y= H
**(+)-9a** R= Boc; X,Y= O

**(+)-9b** R= Boc; X,Y= O

Scheme 1

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

| Entry | Compound | Time (h) | Product (isolated yield) |
|---|---|---|---|
| 1 | (-)-**1a** | 12 | (-)-**7a** (30%) |
| 2 | (-)-**1a** | 2.5 | (-)-**7a** (70%) |
| 3[b] | (+)-**4** | 2.5 | (+)-**8a** (60%) |
| 4 | (-)-**1b** | 2.5 | (+)-**9a** (15%); (-)-**9b** (65%) |
| 5[c] | (-)-**1b** | 2.5 | (-)-**9b** (80%) |

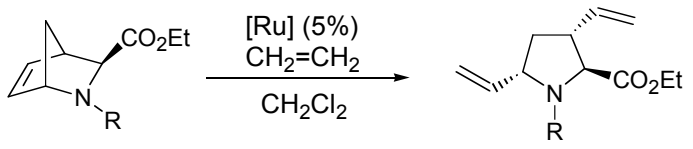
[a] Reaction conditions: All the reactions were performed in $CH_2Cl_2$, 5 mol % of catalyst (**B**), 1 atm ethylene and room temperature.

[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).




**5** R= CHMePh
**6** R= Boc

**10** R= CHMePh
**11** R= Boc

Scheme 2

Table 2. Metathesis reactions of compounds (**5**) and (**6**) with ethylene[a]

| Entry | Compound | Catalyst | Time (h) | Product (isolated yield) |
|---|---|---|---|---|
| 1 | **5** | **A** | 12 | **10** (15%) |
| 2 | **5** | **B** | 12 | **10** (30%) |
| 3 | **6** | **B** | 2.5 | **11** (70%) |
| 4 | **6** | **B** | 12 | **--** |

[a] Reaction conditions: All the reactions were performed in $CH_2Cl_2$, 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)[15] 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. $CH_2Cl_2$ was distilled after refluxing over $CaCl_2$ under Ar. Silica gel 60 $F_{254}$ was used for TLC. Flash column chromatography was carried out on silica gel 60. $^1H$ and $^{13}C$ NMR spectra were recorded at 200 MHz or 300MHz and 50.5 MHz or 75 MHz respectively in $CDCl_3$ solution with TMS as internal reference. Melting points are uncorrected. Elemental analyses were performed at the Complutense University of Madrid.

***tert*-Butyl (1*R*,4*S*)-(-)-3-oxo-2-azabicyclo[2.2.1]hept-5-ene-2-carboxylate [(-)-1b]**. To a solution of (-)-**1a** (570mg, 5.2 mmol) in $CH_2Cl_2$ (20 ml) were added $NEt_3$ (0.7 ml, 5.2 mmol), di-*tert*-butyldicarbonate (2.27 g, 10.4 mmol) and DMAP (630 mg, 5.2 mmol) at rt. After stirring for 24h at the same temperature, the mixture was evaporated *in vacuo* and the residue was diluted with water and extracted with $Et_2O$. The organic extract was dried over $MgSO_4$ 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 ºC. $[\alpha]_D^{25}$= -189.1(c = 2.0, $CHCl_3$). IR (neat) 1790, 1755 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): 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). $^{13}C$ NMR (50.5 MHz, $CDCl_3$): δ = 176.0, 150.2, 139.8, 138.0, 82.4, 62.2, 54.7, 54.3, 27.9. *Anal*. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.92; H, 7.35; N, 6.80

***tert*-Butyl (1*R*,4*S*)-(+)-2-azabicyclo[2.2.1]hept-5-ene-2-carboxylate [(+)-4]**. A solution of (-)-**1a** (320 mg, 2.95 mmol) in $Et_2O$ (20 ml) and THF (5 ml) was added dropwise to a suspension of $LiAlH_4$ (420 mg, 11 mmol) in $Et_2O$ 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 dropwise 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 $MgSO_4$, 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). $[\alpha]_D^{25}$= +198.4 (c = 1.75, $CHCl_3$). IR (neat) 1700 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$) 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). $^{13}C$ NMR (50.5 MHz, $CDCl_3$) 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 $C_{11}H_{17}NO_2$: 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 $CH_2Cl_2$ (39 ml/mmol 2-azanorbornene derivative) was saturated with ethylene and left under ethylene atmosphere (1 atm). [Ru] catalyst dissolved in $CH_2Cl_2$ (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).

**(3*S*,5*R*)-(-)-3,5-divinylpyrrolidin-2-one [(-)-7a]**, white solid, mp 67-68°C (hexane:AcOEt). $[\alpha]_D^{25}$ -7.6 (c = 0.5, $CHCl_3$). IR (neat) 1728 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): 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). $^{13}C$ NMR (50.5 MHz, $CDCl_3$): δ = 177.8, 138.6, 135.2, 117.6, 116.6, 55.3, 46.2, 34.9. *Anal*. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.85; H, 8.16; N, 10.09.

***tert*-Butyl (2*R*,4*S*)-(+)-2,4-divinylpyrrolidine-1-carboxylate [(+)-8a]**, (two rotamers), colorless oil. $[\alpha]_D^{25}$ +1.71 (c = 1.4, $CHCl_3$). IR (neat) 1782 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): 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). $^{13}$C NMR (50.5 MHz, $CDCl_3$): 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 $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.75; H, 9.32; N, 6.12.

***tert*-Butyl (3*S*,5*R*)-(+)-2-oxo-3,5-divinylpyrrolidine-1-carboxylate [(+)-9a]**, pale yellow oil. $[\alpha]_D^{25}$ +4.0 (c = 0.7, $CHCl_3$). IR (neat) 1780, 1730 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): 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). $^{13}$C RMN (50.5 MHz, $CDCl_3$): 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 $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.67; H, 8.15; N, 5.78.

***tert*-Butyl (5*R*)-(-)-(3E)-3-ethylidene-2-oxo-5-vinylpyrrolidine-1-carboxylate [(-)-9b]**, pale yellow oil. $[\alpha]_D^{25}$ -13.0 (c = 1.8, $CHCl_3$). IR (neat) 1775, 1712 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): 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 ). $^{13}$C NMR (50.5 MHz, $CDCl_3$): 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 $C_{13}H_{19}NO_3$: 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$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): 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). $^{13}$C NMR (50.5 MHz, $CDCl_3$): 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 $C_{19}H_{25}NO_2$: 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$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): 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). $^{13}$C NMR (50.5 MHz, $CDCl_3$): 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 $C_{16}H_{25}NO_4$: C, 65.06; H, 8.53; N, 4.74. Found: C, 64.95; H, 8.42; N, 4.62.

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