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Regioselective Ring-Opening Metathesis–Cross Metathesis of Bridgehead-Substituted 7-Azanorbornene†

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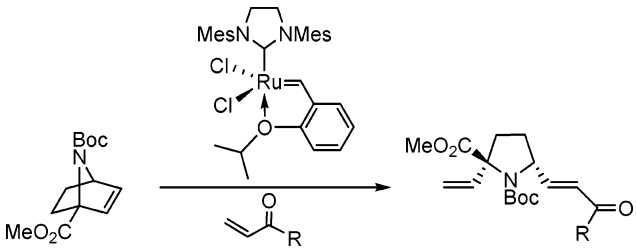
ABSTRACT



In this paper we describe a highly regioselective ring-opening metathesis–cross metathesis (ROM–CM) process between methyl *N*-Boc-7-azabicyclo[2.2.1]hept-2-en-1-carboxylate, a bridgehead-substituted 7-azanorbornene system, and electron-poor olefins. The reaction opens the way to the synthesis of interesting α-amino diacids and pyrrolizinone derivatives that incorporate quaternary stereocenters.

The metathesis reaction has appeared in recent times as a powerful tool for the construction of complex organic molecules.[1] This reaction allows the production of highly functionalized unsaturated polymers and small molecules. The development of new, well-defined catalysts tolerant to most functional groups has allowed this reaction to be carried out on new substrates.[2] In this sense, the ring-opening metathesis−cross metathesis (ROM−CM or ROCM) reaction of norbornene or oxanorbornene derivatives has received a great deal of attention because it is a powerful entry for the synthesis of highly substituted five-membered rings.[3] When azanorbornenes are used in ROCM reactions with the aim to synthesize polysubstituted pyrrolidines, particular attention must be rendered on regioselectivity of this process.[4] Nevertheless, in this context little is known about the use of 7-azanorbornenes as starting materials. Indeed, we have only found four recent examples in the literature.[5]

As a part of our research project on the chemistry of azanorbornanes,[6] we planned to apply the ROCM reaction to methyl *N*-Boc-7-azabicyclo[2.2.1]hept-2-en-1-carboxylate (**6**) to study the metathesis reaction in bridgehead-substituted systems to give interesting pyrrolidine derivatives. In par-

† Dedicated to Prof. Miguel Yus on the occasion of his 60th birthday.

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(1) (a) Chauvin, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3740−3747. (b) Schrock, R. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 3748−3759. (c) Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3760−3765. (d) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238.

(2) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29.

(3) (a) Schneider, M. F.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 411−412. (b) Arjona, O.; Csáky, A. G.; Murcia, M. C.; Plumet, J. *J. Org. Chem.* **1999**, *64*, 9739−9741. (c) Mayo, P.; Tam, W. *Tetrahedron* **2002**, *58*, 9513−9525. (d) Morgan, J. P.; Morril, C.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 67−70. (e) Katayama, H.; Nagao, M.; Ozawa, F. *Organometallics* **2003**, *22*, 586−593. (f) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592−4633.

(4) (a) Schneider, M. F.; Lucas, N.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 257−259. (b) Arjona, O.; Csáky, A. G.; Plumet, J. *Synthesis* **2000**, 857−861. (c) Arjona, O.; Csáky, A. G.; Plumet, J. *Eur. J. Org. Chem.* **2003**, 611−622. (d) Ishikura, M.; Saijo, M.; Hino, A. *Heterocycles* **2002**, *57*, 241−244. (e) Ishikura, M.; Saijo, M.; Hino, A. *Heterocycles* **2003**, *59*, 573−579. (f) Ishikura, M.; Hasunuma, M.; Saijo, M. *Heterocycles* **2004**, *63*, 5−8. (g) Ishikura, M.; Hasunuma, M.; Yanada, K. *Heterocycles* **2005**, *65*, 2587−2592. (h) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693−3712.

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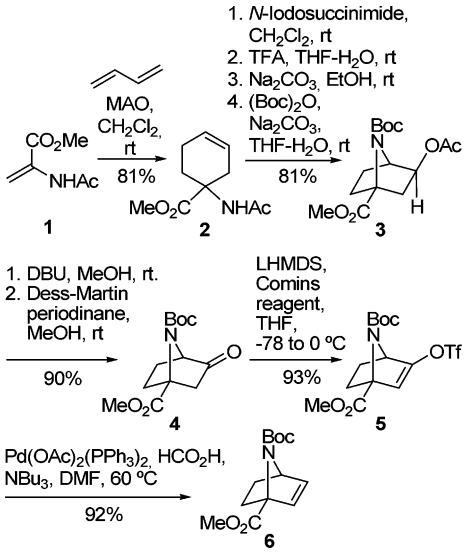
ticular, we became interested in the participation of electron-poor olefins, such as methyl acrylate, in the cross metathesis process to obtain amino diacids with the pyrrolidine substructure.[7]

In order to prepare compound **6** on a multigram scale, we designed a synthetic pathway (Scheme 1) starting from

Scheme 1. Synthetic Route To Obtain Compound **6**



ketone **4**, which was obtained by using an improved route based on our previously reported method[8] (see Supporting Information).

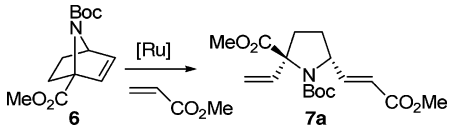
The synthesis of ketone **4** started from commercially available methyl 2-acetamidoacrylate (**1**), whose Diels−Alder reaction with 1,3-butadiene to give cleanly compound **2** was optimized for a multigram scale using methylaluminoxane (MAO) instead of $TiCl_4$ as a Lewis acid. In this sense, it is important to notice that MAO is not an usual Lewis acid for these processes; rather it was found to be an efficient cocatalyst for olefin polymerization reactions.[9] To the best of our knowledge, only Yamamoto described its use as a very strong and quite bulky Lewis acid in Diels−Alder reactions,[10] and recently, it has been used for the synthesis of cyclobutanes by a formal [2 + 2] process.[11]

From this compound **2** and following a previously published protocol[8a,b] that involves several steps, the corresponding 7-azabicyclic system was obtained, which was protected with $(Boc)_2O$ to obtain the new compound **3**. Deprotection of the *O*-acetyl group in derivative **3** with DBU, followed by oxidation with Dess−Martin periodinane gave the required ketone **4**.

The enol triflate **5** was obtained from **4** by treatment with LHMDS as a base and Comins triflating reagent.[12] In an effort to obtain the required olefin **6**, we tried the reduction of the enol triflate with Bu_3SnH in the presence of lithium chloride and palladium(0),[13] which gave the desired compound in good yield but accompanied by an excess of organotin byproducts. We attempted to avoid the presence of these byproducts by carrying out the reduction using tributylammonium formate and $Pd(OAc)_2(PPh_3)_2$ in DMF.[14] In this case compound **6** was obtained in good yield on a multigram scale (Scheme 1).

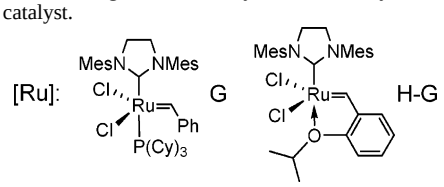
When **6** was exposed to ROCM reaction conditions with methyl acrylate (10 equiv) in dichloromethane using Grubbs second generation catalyst, pyrrolidine **7a** was exclusively obtained but with a poor yield (Table 1, entry 1). Some

Table 1. Highly Regio- and Stereoselective ROCM Process for Compound **6** and Methyl Acrylate



entry	catalyst[a] (equiv)	solvent	temp	time	yield (%)[b]
1	G (0.08)	CH_2Cl_2	rt	6 days	15
2	G (0.08)	$CHCl_3$	55 °C	48 h	50
3	G (0.04)	$PhCH_3$	80 °C	24 h	76
4	H-G (0.04)	$PhCH_3$	80 °C	4 h	92

[a] G: Grubbs second generation catalyst, H-G: Hoveyda-Grubbs second generation catalyst.



[b] Reaction followed by GC−MS and yield obtained from isolated product after column chromatography.

changes of solvent, temperature, and equivalents of Grubbs catalyst led to an increase in the yield of the ROCM reaction. Indeed, the use of chloroform at 55 °C and toluene at 80 °C

(5) (a) Weeresakare, G. M.; Liu, Z.; Rainier, J. D. *Org. Lett.* **2004**, *6*, 1625−1627. (b) Liu, Z.; Rainier, J. D. *Org. Lett.* **2005**, *7*, 131−133. (c) Liu, Z.; Rainier, J. D. *Org. Lett.* **2006**, *8*, 459−462. (d) Büchert, M.; Meinke, S.; Prenzel, A. H. G. P.; Deppermann, N.; Maison, W. *Org. Lett.* **2006**, *8*, 5553−5556.

(6) (a) Avenoza, A.; Cativiela, C.; Busto, J. H.; Peregrina, J. M.; *Tetrahedron Lett.* **1995**, *36*, 7123−7126. (b) Avenoza, A.; Cativiela, C.; Busto, J. H.; Fernández-Recio, M. A.; Peregrina, J. M.; Rodríguez, F. *Tetrahedron* **2001**, *57*, 545−548. (c) Avenoza, A.; Barriobero, J. I.; Busto, J. H.; Cativiela, C.; Peregrina, J. M. *Tetrahedron: Asymmetry* **2002**, *13*, 625−632. (d) Avenoza, A.; Barriobero, J. I.; Busto, J. H.; Peregrina, J. M. *J. Org. Chem.* **2003**, *68*, 2889−2894.

(7) (a) Ma, D.; Yang, J. *J. Am. Chem. Soc.* **2001**, *123*, 9706−9707. (b) Watanabe, H.; Okue, M.; Kobayashi, H.; Kitahara, T. *Tetrahedron Lett.* **2002**, *43*, 861−864.

(8) (a) Avenoza, A.; Cativiela, C.; Fernández-Recio, M. A.; Peregrina, J. M. *Synlett* **1995**, 891−892. (b) Avenoza, A.; Cativiela, C.; Fernández-Recio, M. A.; Peregrina, J. M. *Synthesis* **1997**, 165−167. (c) Avenoza, A.; Cativiela, C.; Fernández-Recio, M. A.; Peregrina, J. M. *Tetrahedron: Asymmetry* **1999**, *10*, 3999−4007.

(9) Zurek, E.; Ziegler, T. *Prog. Polym. Sci.* **2004**, *29*, 107−148.

(10) Akakura, M.; Yamamoto, H. *Synlett* **1997**, 277−278.

(11) Avenoza, A.; Busto, J. H.; Canal, N.; Peregrina, J. M.; Pérez-Fernández, M. *Org. Lett.* **2005**, *7*, 3597−3600.

(12) (a) Comins, D. L.; Dehghani, A.; Foti, C. J.; Joseph, S. P. *Org. Synth.* **1997**, *74*, 77−83. (b) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299−6302.

(13) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630−4632.

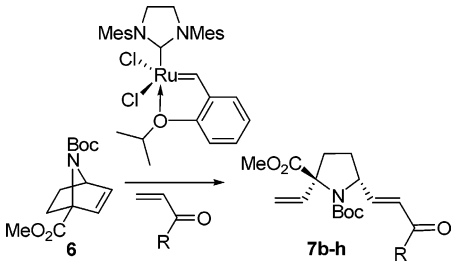
(14) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *25*, 4821−4824.

gave yields of 50% and 76%, respectively (Table 1, entries 2 and 3). However, the best conditions involved the use of Hoveyda−Grubbs catalyst,[15] highly indicated for cross metathesis reaction with electron-poor olefins. Indeed, the use of toluene and 4 mol % of catalyst gave a 92% yield (Table 1, entry 4).

In all conditions tested the reaction gave a single product. However, the ^{1}H NMR spectra are complex due the presence of two conformers for the *tert*-butoxycarbonyl group (Boc).[16] When the ^{1}H NMR spectra were recorded at different temperatures, we observed a single compound at 340 K (Supporting Information). Therefore, it is important to notice that this reaction gave a single regio- and stereoisomer and the (*Z*) isomer was not detected. Although a few studies on the effect of a remote substituent on the regioselectivity of the ROCM reactions of unsymmetrical bicyclic systems have been reported,[3b,4c,5a,b,17] to the best of our knowledge, this is the second time that a substituent in an allylic position induced a complete regioselectivity, since we have only found a single case in the literature and it refers to unpublished work cited in a review.[4c]

To expand the reactivity of compound **6** to other electron-poor olefins, we examined the ROCM reaction with several acrylates. Isobutyl, *tert*-butyl, and ethyl acrylates reacted under the same conditions to give excellent yields of a single stereoisomer (Table 2, entries 1−3), meaning that the size

Table 2. ROCM Reaction of Compound **6** with Electron-Poor Olefins, Using Hoveyda-Grubbs Second Generation Catalyst



entry	R (equiv)	product	time (h)	yield (%)[a]
1	O^{i}Bu (10)[b]	**7b**	4	89
2	O^{t}Bu (10)[b]	**7c**	4	90
3	OEt (10)[b]	**7d**	4	93
4	OH (10)[c]	**7e**	48	23
5	Me (2)[c]	**7f**	24	87
6	Et (2)[c]	**7g**	24	89
7	H (2)[c]	**7h**	48	76

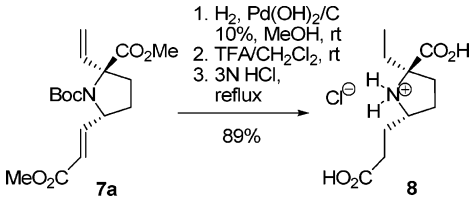
[a] Yield obtained from isolated product after column chromatography. [b] Equivalents of electron-poor olefin used in the conditions: toluene at 80 °C and 4 mol % of catalyst. [c] Another addition of 4 mol % was made.

of the ester group does not affect the regioselectivity of ROCM reaction. Acrylic acid was also tested, but the reaction gave only a moderate yield of the metathesis product (Table 2, entry 4).

Under the same reaction conditions, ketones such as methyl vinyl ketone and ethyl vinyl ketone and aldehydes as acrolein afforded poor yields of the required products (**7f**−**h**), probably due to their high reactivity (i.e., auto-cross metathesis). To prevent these side reactions, fewer equivalents (2 equiv) of electron-poor olefin and 8 mol % (instead of 4 mol %) of catalyst were used, obtaining good yields (Table 2, entries 5−7).

Compound **7a** and related systems (**7b**−**h**) are interesting substrates to obtain amino diacids. Consequently, hydrogenation with Pd−C as a catalyst, subsequent hydrolysis of the Boc group with TFA, and final acid hydrolysis of the methyl ester group afforded an interesting amino acid with a quaternary stereocenter at the α carbon. This α-amino diacid **8** is a "chimera" of natural amino acids proline and 2-aminosuberic acid (Scheme 2). Moreover, it is important

Scheme 2. Synthesis of Amino Diacid **8**



to note that compound **8** incorporates the substructure of GABA,[18] an inhibitory neurotransmitter found in the nervous system, with a limited flexibility due to the restriction imposed by the five-membered ring.

β,γ-Unsaturated amino acid derivatives have received a great deal of attention since they are potential precursors to new α-branched α-amino acids as building blocks for de novo peptide design.[19] Moreover, they are also important enzyme inhibitors;[20] for example, α-vinyl-α-amino acids are known to inhibit amino acid decarboxylases.[21] Therefore, given the stability of these compounds to racemization, in order to apply a similar vinyl-triggering strategy to the mechanism-based inactivation of amino acid decarboxylase enzymes, quaternary β,γ-unsaturated amino acids become attractive targets.[22] Given this background and the fact that there are few methods available for the stereocontrolled

(15) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179. (b) Randl, S.; Gessler, S.; Wakamatsu, H.; Blechert, S. *Synlett* **2001**, *3*, 430−432.

(16) Avenoza, A.; Busto, J. H.; Corzana, F.; Jiménez-Osés, G.; Peregrina, J. M. *Tetrahedron* **2003**, *59*, 5713−5718.

(17) Cuny, G. D.; Cao, J.; Shidu, A.; Hauske, J. R. *Tetrahedron* **1999**, *55*, 8169−8178.

(18) (a) GABA: Chebib, M.; Johnston, G. A. R. *J. Med. Chem.* **2000**, *43*, 1427−1447. (b) GABA-3-substituted: Bryans, J. S.; Wustrow, D. J. *Med. Res. Rev.* **1999**, *19*, 149−177.

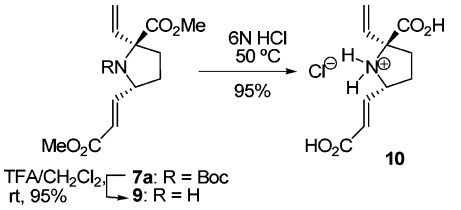
(19) (a) Altmann, E.; Nebel, K.; Mutter, M. *Helv. Chim. Acta* **1991**, *74*, 800−806, and references cited therein. (b) Baldwin, J. E.; Haber, S. B.; Hoskins, C.; Kruse, L. I. *J. Org. Chem.* **1977**, *42*, 1239−1241. (c) Rose, N. G. W.; Blaskovich, M. A.; Wong, A.; Lajoie, G. A. *Tetrahedron* **2001**, *57*, 1497−1507.

(20) (a) Rando, R. R. *Biochemistry* **1974**, *13*, 3859−3863. (b) Metcalf, B. W.; Jund, K. *Tetrahedron Lett.* **1977**, *41*, 3689−3692.

(21) (a) Maycock, A. L.; Aster, S. D.; Patchett, A. A. *Dev. Biochem.* **1979**, *6*, 115−129. (b) Danzin, C.; Casara, P.; Claverie, N.; Metcalf, B. W. *J. Med. Chem.* **1981**, *24*, 16−20. (c) Tendler, S. J. B.; Threadgill, M. D.; Tisdale, M. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2617−2623.

synthesis of quaternary β,γ-unsaturated amino acids,[22] the unsaturated quaternary amino diacid **10** is particularly attractive (Scheme 3). This compound is a proline-derived

Scheme 3. Synthesis of Unsaturated Amino Diacid **10**

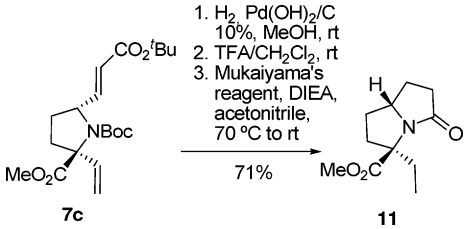


α-vinyl-α-amino acid, whose synthesis was achieved by a simple acid hydrolysis of compound **9**, which was obtained from compound **7a**. Therefore, the *tert*-butoxycarbonyl group of **7a** was removed using TFA to give compound **9**, whose structure was confirmed by COSY, HSQC, and 2D-NOESY experiments (see Supporting Information).

Hydrogenation of compound **7c**, using $Pd(OH)_2/C$ as catalyst in MeOH, gave the corresponding saturated compound. Selective hydrolysis of the *tert*-butyl ester group of this saturated compound was possible, and the use of TFA allowed the concomitant hydrolysis of the *N*-Boc group to give the corresponding γ-amino acid. Subsequent cyclization using Mukaiyama's reagent gave lactam **11** (Scheme 4).

This compound **11** is a pyrrolam[23] derivative and contains the pyrrolizinone core that is present in bioactive compounds such as the telomerase inhibitor UCS1025A.[24] In addition,

Scheme 4. Synthesis of Pyrrolizinone Core



this pyrrolizinone core is present in azabicyclo[3.3.0]octanone amino acids, particularly in 3-amino-2-oxo-1-azabicyclo-[3.3.0]octane-8-carboxylic acid derivatives,[25] which have been used as restricted dipeptide surrogates in which the peptide backbone is constrained within a fused bicyclic skeleton.

In conclusion, we have achieved a highly regioselective ROCM process between compound **6**, a bridgehead-substituted 7-azanorbornene, and electron-poor olefins. The reaction opens the way to obtain interesting quaternary amino diacids and the pyrrolizidinone core. In future works, we aim to study the role of the bridgehead methyl ester in the regiochemistry of this reaction.

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Supporting Information Available: Experimental details, spectroscopic characterization of all compounds, and variable temperature NMR experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) (a) Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **1999**, *10*, 4653−4661. (b) Berkowitz, D. B.; Chisowa, E.; McFadden, J. M. *Tetrahedron* **2001**, *57*, 6329−6343.

(23) (a) Majik, M. S.; Shet, J.; Tilve, S. G.; Parameswaran, P. S. *Synthesis* **2006**, 663−665. (b) Watson, R. T.; Gore, V. K.; Chandupatla, K. R.; Dieter, R. K.; Snyder, J. P. *J. Org. Chem.* **2004**, *69*, 6105−6114.

(24) (a) Lambert, T. H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 426−427. (b) Hoye, T. R.; Dvornikovs, V. *J. Am. Chem. Soc.* **2006**, *128*, 2550−2551. (c) Hoye, T. R.; Dvornikovs, V.; Sizova, E. *Org. Lett.* **2006**, *8*, 5191−5194.

(25) (a) Dietrich, E.; Lubell, W. D. *J. Org. Chem.* **2003**, *68*, 6988−6996. (b) Salvati, M.; Cordero, F. M.; Pisaneschi, F.; Bucelli, F.; Brandi, A. *Tetrahedron* **2005**, *61*, 8836−8847. (c) Cordero, F. M.; Pisaneschi, F.; Meschini Batista, K.; Valenza, S.; Machetti, F.; Brandi, A. *J. Org. Chem.* **2005**, *70*, 856−867.