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A Concise Asymmetric Route to the Bridged Bicyclic Tropane Alkaloid Ferruginine Using Enyne Ring-Closing Metathesis

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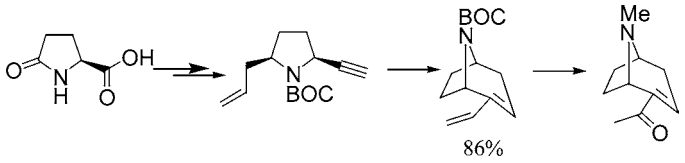
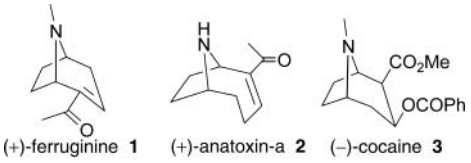
ABSTRACT



Enyne metathesis has been used to prepare bridged azabicycles and applied in a short asymmetric synthesis of the tropane ferruginine. A Grubbs first generation catalyst proved to be superior to the second generation catalyst in the enyne metathesis reaction.

Bridged azabicycles, like the well-known compound cocaine, show a broad range of neurochemical activity.[1] For example, both anatoxin and ferruginine have potential in the treatment of the neurodegenerative disorder Alzheimer's disease.[2] Their biological activity coupled with an interesting architecture has stimulated considerable synthetic activity, and azabicycles have acted as important vehicles for the development of new methods and strategies.[1] As a novel strategy, we considered the possibility of carrying out RCM of a suitable precursor to assemble the bridged azabicycle. Although RCM has been widely employed to construct cyclic and fused bicyclic compounds,[3] the construction of bridged bicycles is much less common.[4]

For successful RCM, it is important that the substrate should easily be able to adopt the conformation required for cyclization. Thus, to construct bridged azabicycles, the precursor must be able to adopt a conformation in which the two substituents are diaxial. This can best be achieved using acyl or alkoxycarbonyl groups on nitrogen as $A^{1,3}$ strain (between the carbonyl oxygen and substituents α to the nitrogen)[5] will result in the diaxial conformer being favored.

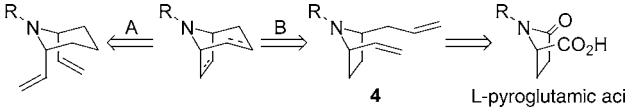


(+)-ferruginine **1** (+)-anatoxin-a **2** (−)-cocaine **3**

Figure 1.

Indeed, during the course of our work, Martin described such a strategy utilizing disconnection A (Scheme 1).[6] As we wanted to access tropane alkaloids, e.g., ferruginine **1**, we

Scheme 1. Retrosynthetic Analysis of the Tropane Bicycle Based on Ring-Closing Metathesis



4 L-pyroglutamic acid

[†] F. Hoffmann-La Roche Ltd., Pharmaceuticals Division, Lead Generation, PRBC-CI, Bldg 65/416, CH-4070 Basel, Switzerland.

(1) For a general review, see: Lounasmaa, M.; Tamminen, T. *The Alkaloids, The Tropane Alkaloids*; Academic Press: New York, 1993; Vol. 44, pp 1−114.

(2) Swanson, K. L.; Albuquerque, E. X. *Handb. Exp. Pharmacol.* **1992**, *102*, 620−621.

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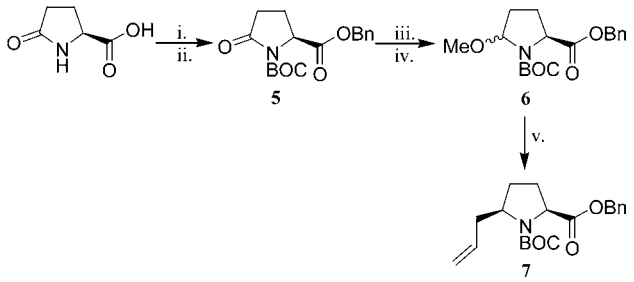
needed to be able to introduce functionality in the six-membered ring, and clearly this could most easily be done through disconnection B with suitably substituted alkenes. Furthermore, unlike disconnection A, disconnection B would enable us to easily access enantiomerically pure material as **4** could potentially be obtained from L-pyroglutamic acid.

Pyroglutamic acid was first converted into the known aminal **6**[7j] in four steps. Treatment with $BF_3{\cdot}OEt_2$ and allyltrimethylsilane gave the required *cis* product as the major diastereomer (Scheme 2).[7]

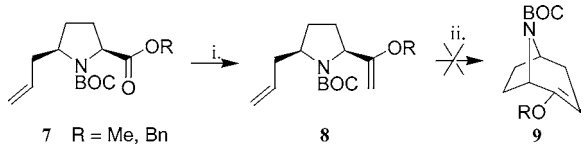
Scheme 2. Preparation of Allyl-ester **7**[a]



[a] (i) $^{i}Pr_2EtN$ (1.2 equiv), BnBr (1.0 equiv), 0 to 55 °C, CH_2Cl_2, 5 h. (ii) BOC_2O (1.2 equiv), DMAP (0.1 equiv), 25 °C, MeCN, 3 h, 92% over two steps. (iii) $LiEt_3BH$ (1.2 equiv), −78 °C, THF, 2 h, 88%. (iv) MeOH, *p*TSA (0.1 equiv), 25 °C, 5 h, 98%. (v) $BF_3.OEt_2$ (1.03 equiv), allyltrimethylsilane (4.5 equiv), −78 to 25 °C, Et_2O, 15 h, 93% (80:20, *cis*:*trans*).

The ester was converted into the enol ether **8** by the modified Takai procedure[8] (Scheme 3), but we were unable

Scheme 3. Enol Ether Preparation and Attempts at RCM[a]



[a] (i) $TiCl_4$ (4.0 equiv), TMEDA (8 equiv), Zn (9 equiv), $PbCl_2$ (0.046 equiv), CH_2Br_2 (2.2 equiv), 25 °C, 4.5 h, THF, 45%. (ii) RCM.[13]

to effect RCM using the Ru and Mo catalysts **I**,[9] **II**,[10] **III**,[11] and **IV**[12] (Figure 2).[13] Only unreacted starting material was

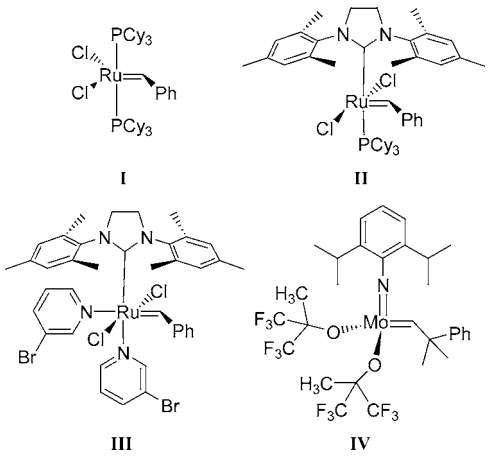


Figure 2. Structures of the 1st, 2nd, and 3rd generation Grubbs and Schrocks catalysts.

observed. To determine whether active catalyst was still present, dimethyl diallymalonate was added to the reaction mixture after 1 h. Rapid ring closure of the malonate proved that the catalyst had not become deactivated by the enol ether or other adventitious impurities.

To test whether the problem lay with enol ether metathesis (which is known to be a more difficult cyclization than simple diene metathesis)[14] or substrate conformation, we prepared diene **10**, and this time RCM occurred uneventfully to give the bridged azabicycle **11** in good yield (Scheme 4).

This showed that our strategy for controlling the diaxial conformation had been successful, but to easily access the enone required for the synthesis of ferruginine we needed a

(3) For reviews of RCM, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (c) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75−89. (d) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (e) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073−2077. (f) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (g) Semeril, D.; Bruneau, C.; Dixneuf, P. H. *Adv. Synth. Catal.* **2002**, *344*, 585−595. (h) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, *1*, 1−18. (i) Hoveyda A. H.; Gillingham D. G.; Van Veldhuizen J. J.; Kataoka O.; Garber S. B.; Kingsbury J. S.; Harrity J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8−23.

(4) Neipp, C. E.; Martin, S. F. *J. Org. Chem.* **2003**, *68*, 8867−8878 and references therein.

(5) For a review, see: Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.

(6) Neipp, C. E.; Martin, S. F. *Tetrahedron Lett.* **2002**, *43*, 1779−1782.

(7) Although this reaction has been described to furnish a 95:5 (*cis*:*trans*) ratio of diastereomers we have not been able to reproduce this result (80:20, *cis*:*trans* obtained). See: (a) Shono, T.; Fujita, T.; Matsumura, Y. *Chem. Lett.* **1991**, 81−84. (b) Ma, D.; Yang, J. *J. Am. Chem. Soc.* **2001**, *123*, 9706−9707. Other workers have also reported levels of selectivity similar to our own. See: (c) Chiesa, M. V.; Manzoni, L.; Scalastico, C. *Synlett* **1996**, 441−443. (d) Beal, L. M.; Moeller, K. D. *Tetrahedron Lett.* **1998**, *39*, 4639−4642. (e) Grossmith, C. E.; Senia, F.; Wagner, J. *Synlett* **1999**, *10*, 1660−1662. (f) Mulzer, J.; Schulzchen, F.; Bats, J.-W. *Tetrahedron* **2000**, *56*, 4289−4298. (g) Tong, Y.; Forbian, Y. M.; Wu, M.; Boyd, N. D.; Moeller, K. D. *J. Org. Chem.* **2000**, *65*, 2484−2493. (h) Manzoni, L.; Colombo, M.; May, E.; Scolastico, C. *Tetrahedron* **2001**, *57*, 249−255. (i) Zhang, X.; Schmitt, A. C.; Jiang, W. *Tetrahedron Lett.* **2001**, *42*, 5335−5338. (j) Kim, S.; Hayashi, K.; Kitano, Y.; Tada, M.; Chiba, K. *Org. Lett.* **2002**, *4*, 3735−3737. (k) Harris, P. W. R.; Brimble, M. A.; Gluckman, P. D. *Org. Lett.* **2003**, *5*, 1847−1850.

(8) Takai, K.; Kataoka, Y.; Miyai, J.; Okazoe, T.; Oshima, K.; Utimoto, K. *Org. Synth.* **1996**, *73*, 73−84.

(9) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039−2041.

(10) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

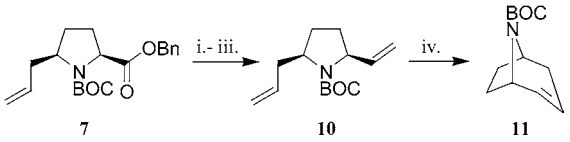
(11) Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 4035−4037.

(12) Murdzek, J. S.; Schrock, R. R. *Organometallics* **1987**, *6*, 1373−1374.

(13) Grubbs 1st, 2nd, and 3rd generation catalysts in either dichloromethane or benzene, Schrocks catalyst in degassed pentane, at both room temperature and reflux, with concentrations ranging from 0.005 to 0.1 M.

(14) (a) Louie, J.; Grubbs, R. H. *Organometallics* **2002**, *21*, 2153−2164 and references therein. (b) Aggarwal, V. K.; Daly, A. D. *Chem. Commun.* **2002**, 2490−2491.

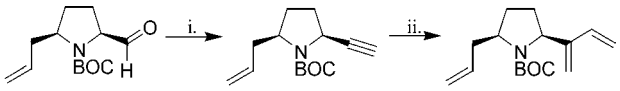
Scheme 4. Diene Preparation and RCM[a]



[a] (i) $LiAlH_4$ (2 equiv), 0 °C, THF, 10 min., 78% (pure *cis* isomer). (ii) Dess−Martin periodinane (2.1 equiv), 25 °C, DCM, 30 min, 85%. (iii) CH_3PPh_3Br (1.1 equiv), *n*-BuLi (1.1 equiv), 25 °C, THF, 16 h, 93%. (iv) 2nd generation Grubbs **II** (10 mol %), reflux, 0.005 M in C_6H_6, 90 min, 87%.

differentially functionalized alkene. We therefore considered the possibility of enyne metathesis, as this should generate a diene. However, literature precedent for enyne metathesis to furnish bridged bicycles was particularly rare.[15] The required enyne **13** was prepared by reduction of the ester **7** to the aldehyde **12** as described in Scheme 4 followed by homologation using a modified version of the Gilbert reagent[16] (Scheme 5).

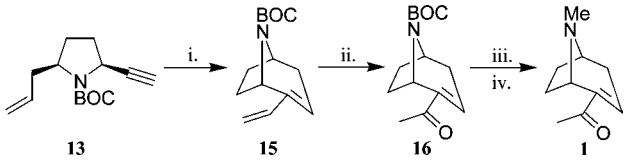
Scheme 5. Enyne Preparation and Attempted RCM[a]



[a] (i) $CH_3COCN_2PO(OEt)_2$ (1.2 equiv), K_2CO_3 (2 equiv), 25 °C, MeOH, 1.5 h, 93%. (ii) Catalysts **I**−**III** (10 mol %), $CH_2{=}CH_2$, reflux, 0.01 M in CH_2Cl_2 or C_6H_6.

We began our investigation using conditions that are commonly used for ring closure of terminal enynes: the Grubbs second generation catalyst **II** under an atmosphere of ethylene.[17] However, under these conditions and employing any of the metathesis catalysts **I**−**III**, the major product was triene **14** (Scheme 5). As ethylene was clearly becoming incorporated, we decided to conduct the metathesis under an inert atmosphere. Although we obtained clean conversion by GC−MS to the desired tropane **15** (Scheme 6) with catalysts **II** or **III**, our isolated yields were very low. To determine whether the problem occurred during product isolation (active catalyst present with product diene could cause dimerization) or during the course of the reaction (e.g., ring-opening polymerization/acyclic diene polymerization) the reaction was monitored by GC−MS with an internal standard. This clearly showed a buildup in the concentration of the product to a steady-state level followed by a slow

Scheme 6. Enyne RCM and Wacker Oxidation[a]



[a] (i) 1st generation Grubbs **I** (10 mol %), reflux, 0.01 M in CH_2Cl_2, 50 °C, 10 h, 86%. (ii) $PdCl_2$ (0.1 equiv), $CuCl_2$ (2.1 equiv), H_2O, 95 °C, DMF, 6 h, 81%. (iii) TFA, 25 °C, CH_2Cl_2, 3 h, then K_2CO_3 (aq) (1 M), 93%. (iv) CH_2O (5 equiv), $NaCNBH_3$ (1.6 equiv), CH_3CN, 15 min, 97%.

decline. Thus, the active metathesis catalyst was destroying the product during the reaction.[18] This led us to test the less active first generation Grubbs catalyst **I**. This time the metathesis reaction resulted in clean buildup of the required tropane **15** in high isolated yield. Examples where the Grubbs first generation catalyst is superior to the later generations are rare. This important example of enyne metathesis adds to this growing list.[19]

Wacker oxidation of the terminal alkene gave methyl ketone **16** (Scheme 6), which has been deprotected and N-methylated in 90% yield,[20] thus completing the synthesis of ferruginine **1**.

In summary, we have developed an efficient asymmetric synthesis of ferruginine (12 steps and 29% overall yield)[21] using inexpensive L-pyroglutamic acid. The key step involved enyne metathesis, which required the first generation Grubbs catalyst as the more active second generation catalyst caused subsequent destruction of the diene. The synthesis was completed with a Wacker oxidation giving the enone **16**. As enones are common motifs in bridged azabicycles and many other natural products, this strategy could find wide usage.

Acknowledgment. We thank Hoffman-La Roche for financial support.

Supporting Information Available: Experimental procedures and full characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) (a) Rodríguez, J. R.; Castedo, L.; Mascareñas. J. L. *Chem. Eur. J.* **2002**, *8*, 2923−2930. (b) Neipp, C. E.; Martin, S. F. *J. Org. Chem*. **2003**, *68*, 8867−8878 and references therein.

(16) (a) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem*. **1982**, *47*, 1837−1845. (b) Ohira, S. *Synth. Commun*. **1989**, *19*, 561−564. (c) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521−522.

(17) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 3, 6082−6083. For a review of enyne metathesis see ref 3h.

(18) GC−MS analysis of the reaction mixture only showed product and starting material, implying that the byproducts formed are nonvolatile. We speculate that the active metathesis catalyst was converting the desired product **15** into the (nonvolatile) homodimer.

(19) For recent examples, see: (a) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204−2207. (b) Boiteau, J.; Van de Weghe, P.; Eustache, J. *Org. Lett.* **2001**, *3*, 2737−2740. (c) Fürstner, A.; Guth, O.; Düffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R. *Chem. Eur. J.* **2001**, *7*, 4811−4820. (d) Clark, J. S.; Elustondo, F.; Trevitt, G. P.; Boyall, D.; Robertson, J.; Blake, A. J.; Wilson, C.; Stammen, B. *Tetrahedron* **2002**, 58, 1973−1982. (e) Poulsen, C. S.; Madsen, R. *J. Org. Chem.* **2002**, *67*, 4441−4449.

(20) Hernandez, A. S.; Thaler, A.; Castells, J.; Rapoport,H. *J. Org. Chem.* **1996**, *61*, 314−323.

(21) For one of the best previous syntheses of ferruginine (8 steps, 11% overall yield), see: Gauthier, I.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1997**, *62*, 6704−6705.