

Concise Formal Synthesis of (–)-Peduncularine via Ring-Closing Metathesis

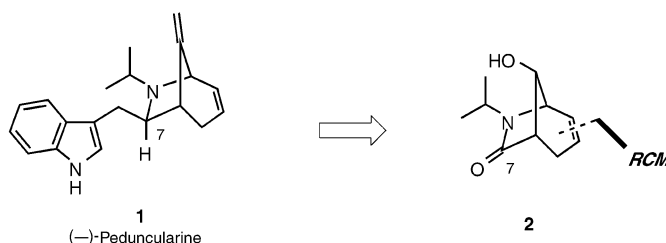
David G. Washburn, Richard W. Heidebrecht, Jr., and Stephen F. Martin*

Department of Chemistry and Biochemistry, The University of Texas,
Austin, Texas 78712

sfmartin@mail.utexas.edu

Received July 26, 2003

ABSTRACT



A synthesis of the 6-aza[3.2.1]bicyclooctene (–)-2 has been completed by a short sequence of reactions that required only six operations from (S)-malic acid and featured a novel ring-closing metathesis to form the bridged bicyclic ring. Because 2 was previously converted into (–)-peduncularine (1), its preparation constitutes a formal enantioselective synthesis of 1.

(–)-Peduncularine (**1**) is the principal alkaloid in the Tasmanian shrub *Aristotelia peduncularis*,¹ from which a number of structurally related alkaloids have also been isolated.² Interest in peduncularine has been stimulated by the combination of its anticancer activity and the presence of an unusual 6-azabicyclo[3.2.1]oct-3-ene subunit that is believed to be biosynthetically derived from tryptamine and a rearranged geranyl fragment. The first total synthesis of (–)-peduncularine was reported by Hiemstra and Speckamp in 1989.³ A key intermediate in this synthesis was the bicyclic lactam **2**, which has been subsequently prepared in racemic form by Weinreb.⁴ Moreover, the ketone corresponding to **2** has been prepared in racemic form independently by the groups of Rigby⁵ and Woerpel.⁶ In a nice extension of his

original work, Woerpel has recently completed a total synthesis of racemic **1** in which a solution to the problem of controlling the stereochemistry at C(7) of the natural product is described.⁷

Our retrosynthetic analysis of peduncularine (**1**) was inspired by our longstanding interest in applying ring-closing metatheses (RCM) reactions to problems in alkaloid synthesis.^{8,9} We focused our initial efforts upon the enantioselective synthesis of the 6-azabicyclo[3.2.1]octene **2**, envisioning that it would be accessible via a RCM of the pyrrolidinone derivative **4** (Scheme 1). A significant feature of this approach is that it also allows for the possible stereoselective introduction of an indole side chain, or a precursor thereof, onto **4** leading to **3**. This strategy thus offers an alternative tactic for controlling the stereochemistry

(1) (a) Bick, I. R. C.; Bremner, J. B.; Preston, N. W.; Calder, I. C. *J. Chem. Soc., Chem. Commun.* **1971**, 1155–1156. (b) Ros, H.-P.; Kyburz, R.; Preston, N. W.; Gallagher, R. T.; Bick, I. R. C.; Hesse, M. *Helv. Chim. Acta* **1979**, *62*, 481–487.

(2) Bick, I. R. C.; Hai, M. A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 24, pp 113–151.

(3) Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *J. Am. Chem. Soc.* **1989**, *111*, 2588–2595.

(4) Lin, X.; Stien, D.; Weinreb, S. M. *Tetrahedron Lett.* **2000**, *41*, 2333–2337.

(5) Rigby, J. H.; Meyer, J. H. *Synlett* **1999**, *SI*, 860–862.

(6) Roberson, C. W.; Woerpel, K. A. *Org. Lett.* **2000**, *2*, 621–623.

(7) Roberson, C. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 11342–11348.

(8) For recent reviews of RCM in synthesis, see: (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037–2056. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. (c) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211–240. (d) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043.

Scheme 1

Wittig

Nucleophilic Addition

1

2: Z = O

3: Z = R

4

5

The known imide **5** was first converted into the ethoxy aminal **6** by regioselective hydride reduction to give the ethoxy aminal **6**. Although **6** could be reacted with various vinyl organometallic reagents, the yield of the desired adduct was low, so we investigated other leaving groups. Inspired by the work of Ley,¹⁰ we converted **6** into the sulfone **7** by reaction with freshly prepared benzenesulfinic acid; the quality of this reagent was essential to the success of the reaction. When **7** was allowed to react with vinylmagnesium bromide in the presence of ZnCl₂ followed by workup with concentrated sulfuric acid, a separable mixture (ca. 4:1) of epimeric vinyl pyrrolidinones was obtained from which the desired **8** was isolated in 65% yield. It then remained to introduce the allyl group by stereoselective alkylation of **8**. Indeed, when a homogeneous solution of the dianion of **8** was treated with allyl bromide, the desired product **9** was formed as a single diastereomer in 71% yield, thereby setting the stage for the key RCM reaction.

Initial experiments to effect the RCM of **9** using the first generation Grubbs catalyst **10**¹¹ under a variety of conditions were unsuccessful. This result was rather surprising because **10** has been shown to be tolerant to the presence of free hydroxyl groups, although there are scattered reports of problems with this catalyst.¹² That the hydroxyl group was indeed the source of the problem was confirmed in a separate

(10) Brown, D. S.; Charreau, P.; Hansson, T.; Ley, S. V. *Tetrahedron* **1991**, *47*, 1311–13128.

Scheme 2

Scheme 2 illustrates the synthesis of bicyclic enone **2** from a substituted pyrrolidinone **5**. The scheme is divided into three main steps:

Step 1: A substituted pyrrolidinone **5** (where Z = O or H, OEt) reacts with PhSO_2H and CaCl_2 in CH_2Cl_2 at room temperature to yield intermediate **7** in 82% yield. The structure of **5** is defined by the reagents: NaBH_4 and EtOH/HCl give 89% yield for **6** (Z = H, OEt).

Step 2: Intermediate **7** is treated with $\text{CH}_2=\text{CHMgBr}$ and ZnCl_2 in THF at room temperature, followed by H_2SO_4 , to give intermediate **8** in 65% yield.

Step 3: Intermediate **8** is treated with LDA in THF at $0\text{ }^\circ\text{C}$, followed by $\text{CH}_2=\text{CHCH}_2\text{Br}$ from $-78\text{ }^\circ\text{C}$ to $-20\text{ }^\circ\text{C}$, to give intermediate **9** in 71% yield.

Step 4: Intermediate **9** is treated with **11** at $40\text{ }^\circ\text{C}$ to yield the final bicyclic enone **2** in 96% yield.

Structure 10: A ruthenium complex with two PCy_3 ligands, two Cl ligands, and a Ph ligand.

Structure 11: A ruthenium complex with one PCy_3 ligand, two Cl ligands, and a Ph ligand, with a MesN and NMes group attached to the ruthenium center.

experiment where the TMS ether **12** was found to cyclize smoothly in the presence of **10** to give **13** (Scheme 3). It is perhaps instructive to consider a possible cause for the lack of the observed reactivity of **9** toward **10**, even though such reasoning is presently speculative. On the basis of steric considerations, **10** would likely react preferentially with the less hindered allylic carbon–carbon double bond of **9**. If the proximal hydroxy group then coordinated with the ruthenium ion as in **14**, the complex could then be locked in a conformation that would be unreactive toward further metathesis because of the relative orientation of the carbene and the pendant vinyl group.

Although this synthesis of **13** provided an effective solution to the problem associated with the lack of reactivity

Scheme 3

12

10, 40 °C

63%

13

14

of **9** toward **10**, the requirement to protect the hydroxyl group on **9** added steps and hence was not appealing. We then turned to the second generation Grubbs' catalyst **11**, which is substantially more reactive and less Lewis acidic than **10**.¹³ In the event, we discovered that reaction of **9** with **11** delivered (–)-**2** in nearly quantitative yield (Scheme 2). This material exhibited ¹H and ¹³C NMR spectral, MS, and TLC properties virtually identical to those obtained for a sample of racemic **2**.¹⁴ The [α]_D of our synthetic (–)-**2** was –79.5° (c 0.6, CHCl₃), whereas the literature value was –126° (c 1.02, CHCl₃).³ However, Mosher ester analysis using racemic **2** confirmed that our (–)-**2** was >98% enantiomerically pure.

We have thus completed a concise formal synthesis of (–)-peduncularine (**1**) by preparing the key intermediate (–)-**2**

in only four operations and 36% overall yield from the known aminal **6**. This synthesis of **2** illustrates the potential of RCM for the facile synthesis of alkaloids containing bridged azabicyclic rings. Further applications of RCM to alkaloid synthesis are the subjects of current investigations, the results of which will be disclosed in due course.

Acknowledgment. We thank the National Institutes of Health, the Robert A. Welch Foundation, Pfizer, Inc., and Merck Research Laboratories for their generous support of this research. D.G.W. is also grateful to the American Cancer Society for a Postdoctoral Fellowship. We also thank Mr. Christopher L. Franklin for technical assistance.

Supporting Information Available: Copies of ¹H NMR spectra of **2**, **7–9**, and the Mosher esters of (–)-**2** and racemic **2**, as well as experimental procedures and analytical data for compounds **2**, **7–9**, and the Mosher esters of **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL0354066

(11) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110.

(12) (a) Maughon, B. R.; Grubbs, R. H. *Macromolecules* **1997**, *30*, 3459–3469. (b) Ackermann, L.; Tom, D. E.; Fürstner, A. *Tetrahedron* **2000**, *56*, 2195–2202. (c) Rodriguez, J. R.; Castedo, L.; Mascarenas, J. L. *Org. Lett.* **2000**, *2*, 3209–3212.

(13) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956. (b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554.

(14) We thank Professor Steven M. Weinreb (The Pennsylvania State University) for an authentic sample of racemic **2**.