JOC Article

Stereoselective Synthesis of Polyhydroxylated Indolizidines Based on Pyridinium Salt Photochemistry and Ring Rearrangement Metathesis

Ling Song, Eileen N. Duesler, and Patrick S. Mariano*

Department of Chemistry, University of New Mexico, Albuquerque, New Mexico 87131

mariano@unm.edu

Received July 1, 2004

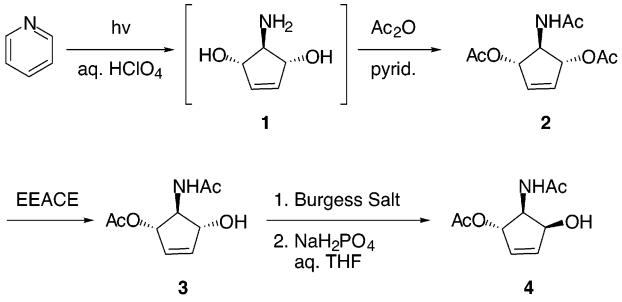
Ruthenium-catalyzed ring rearrangement metathesis (RRM) reactions of stereochemically diverse, differentially protected 4-*N*-allylacetamidocyclopenten-3,5-diols, prepared by using pyridinium salt photochemistry, have been explored as part of a program to develop novel routes for the synthesis of polyhydroxylated indolizidines. The RRM reactions, which produce selectively protected 1-acetyl-2-allyl-3-hydroxy-1,2,3,6-tetrahydropyridines, were found to take in high yields and with high levels of regioselectivity. The significance of RRM reactions of 4-*N*-allylacetamidocyclopenten-3,5-diols in the context of polyhydroxylated indolizidine synthesis is demonstrated by an application to the concise preparation of the potent glycosidase inhibitor, (−)-swainsonine.

Introduction

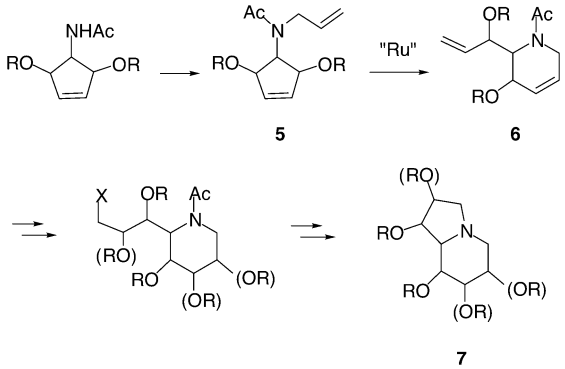
In previous publications, we reported the results of studies aimed at developing the synthetic potential of a novel photochemical reaction of pyridinium salts.[1,2] An example of this excited-state process is found in the photoinduced transformation of in situ generated pyridinium perchlorate to *trans*,*trans*-3,5-dihydroxy-4-aminocyclopentene (**1**), isolated as the triacetyl derivative **2** (Scheme 1).[3] In an early effort, we demonstrated that the meso-diester **2** is enzymatically (EEACE) desymmetrized, producing the monoalcohol **3** in 80% ee.[4] Also, by using an acetamide-directed alcohol inversion protocol, the trans,trans-alcohol **3** can be converted to the cis,trans-analogue **4**.[4] Additional investigations probing the synthetic potential of this chemistry demonstrated that the aminocyclopentendiol derivatives prepared in this fashion serve as ideal starting materials in concise sequences for stereoselective preparation of aminocyclopentitol natural and nonnatural products[5] and selectively protected 3-aminoaldopentoses.[6]

The synthetic power of the pyridinium salt photochemical process is a consequence of the fact that it transforms a simple, inexpensive starting material into a stereochemically defined, structurally complex product, which is endowed with functionality that can be used to guide a wide variety of secondary reactions. In line with this theme, we recognized that aminocyclopentendiol derivatives related to **2**−**4** might serve as starting points in novel sequences for the stereocontrolled synthesis of polyhydroxylated indolizidines. The key step in the proposed routes (Scheme 2) involves the ruthenium-catalyzed tandem ring opening−ring closing metathesis (or ring-rearrangement metathesis, RRM) chemistry

SCHEME 1



SCHEME 2



(1) Kaplan, L.; Pavlik, J. W.; Wilzbach, K. E. *J. Am. Chem. Soc.* **1972**, *94*, 3283.

(2) Yoon, U. C.; Quillen, S. L.; Mariano, P. S.; Swanson, R.; Stavinoha, J. L.; Bay, E. *J. Am. Chem. Soc.* **1983**, *105*, 1204.

(3) Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 4439.

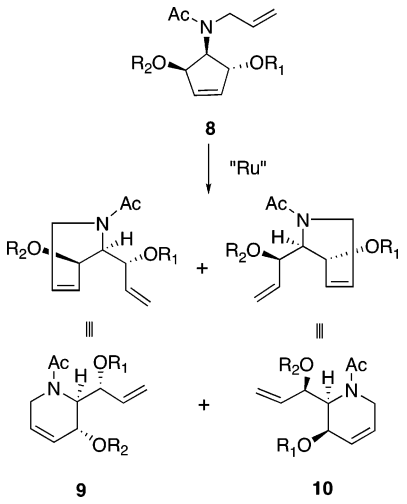
(4) Ling, R.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 6072. A newly developed procedure for hydrolytic ring opening of the oxazoline, formed by treatment of **3** and related substances with the Burgess salt, was used in this case (see the description of the process used to transform **19** to **20**).

(5) (a) Cho, S. J.; Ling, R.; Kim, A.; Mariano, P. S. *J. Org. Chem.* **2000**, *65*, 1574. (b) Lu, H.; Mariano, P. S.; Lam, Y. F. *Tetrahedron Lett.* **2001**, *42*, 4755.

(6) Lu, H.; Su, Z.; Song, L.; Mariano, P. S. *J. Org. Chem.* **2002**, *67*, 3525.

10.1021/jo040226a CCC: $27.50
Published on Web 09/21/2004

SCHEME 3



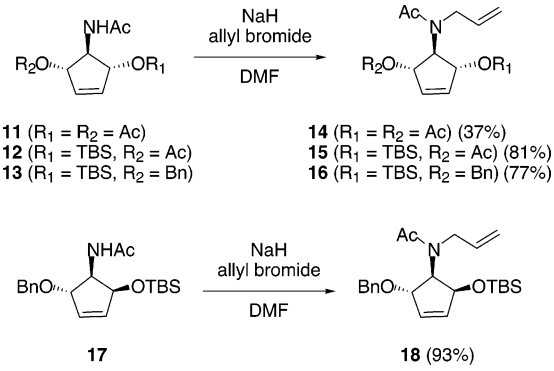
developed by Grubbs[7] and others.[8,9] Accordingly, we envisaged that *N*-allylacetamidocyclopentenes **5** might serve as substrates in RRM-promoted formation of 6-allyl-1,2,3,6-tetrahydropyridines **6**. Relative and absolute stereochemistry at the three chiral centers in **6** would be controlled by the choice of the amidocyclopentene used as starting materials for these reactions. Also, terminal functionalization of the exocyclic allyl moiety in **6** would then set the stage for cyclization to produce the indolizidine skeleton **7**. Finally, the allylic hydroxyl functionality in **6** could be used to control the course of dihydroxylation reactions at either or both of the unsaturated centers either prior to or following indolizidine ring construction.

To explore the feasibility of the chemistry embodied in the synthetic plan outlined in Scheme 2, a number of *N*-allylacetamidocyclopentene derivatives related to **5** were prepared and subjected to RRM reaction conditions. An important question probed in the exploratory phase of this effort concerns the regiochemical course of the RRM process, which has potential relative and absolute stereochemical implications. This issue is exemplified by the tandem metathesis reaction of the *cis*,*trans*-*N*-allylacetamidocyclopentene **8**, which can generate either of the structurally ($R_1 \neq R_2$) or diastereomerically ($R_1 = R_2$) related tetrahydropyridines **9** and **10** depending on its regiochemical course (Scheme 3). Observations made in this effort demonstrate that the RRM reactions of *N*-allylacetamidocyclopentenes take place to generate 6-allyltetrahydropyridines in modest to excellent yields and with high levels of regiochemical/stereochemical control. In a second phase of this study, we have demonstrated that this chemistry can be used as the foundation for concise, stereocontrolled syntheses of biologically significant indolizidines.

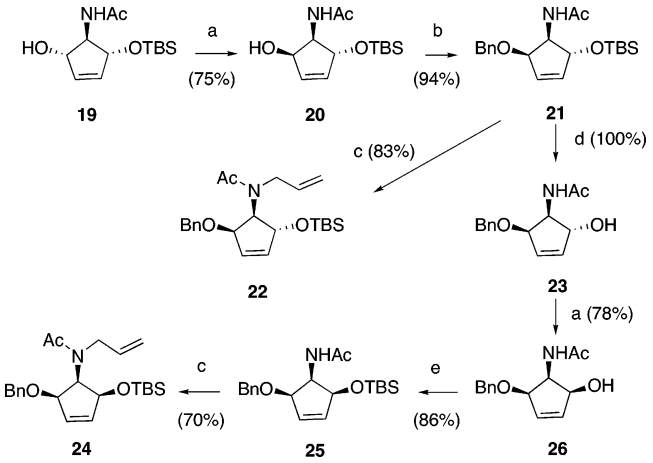
Results and Discussion

Preparation and RRM Reactions of *N*-Allylacetamidocyclopentenes. Several stereochemically diverse

SCHEME 4



SCHEME 5[a]



[a] Reagents and conditions: (a) Burgess salt; NaH_2PO_4, aq THF; (b) NaH, BnBr, DMF; (c) NaH, allyl bromide, DMF; (d) TBAF, THF; (e) TBSCl, imidazole.

enantiomerically enriched (ca. 80% ee) *N*-allylacetamidocyclopentenes were synthesized to probe the efficiency and regiochemical/stereochemical course of the ruthenium-catalyzed RRM process. Included in this series are substrates **14**−**16** and **18** (Scheme 4), which are prepared by *N*-allylation reactions of previously reported[4−6] acetamidocyclopentenes **11**−**13** and **17**. In addition, the *trans*,*cis*- and *cis*,*cis*-amidocyclopentenes, **22** and **24**, are prepared by sequences starting with the known[4,6] mono-TBS blocked cyclopentendiol **19** (Scheme 5).

Tandem metathesis reactions of the *N*-allylacetamidocyclopentenes are conducted by using ethylene-saturated CH_2Cl_2 solutions containing 10−15 mol % of the ruthenium alkylidene **27**[10] at reflux for 2−28 h. Chromatographic separation in each case (except for reaction of **24**) yields a single tetrahydropyridine product along with trace or minor amounts of cross metathesis products (e.g., **29**) (Scheme 6). A ca. 15:1 mixture of tetrahydropyridines **41** and **42** is generated in the tandem metathesis reaction of the *cis*,*cis*-*N*-allyacetamidocyclopentene **24**.

Structural and stereochemical assignments to the tetrahydropyridine products, generated in these reactions, are made by using a combination of NMR spectroscopic methods and chemical transformations. Specifi-

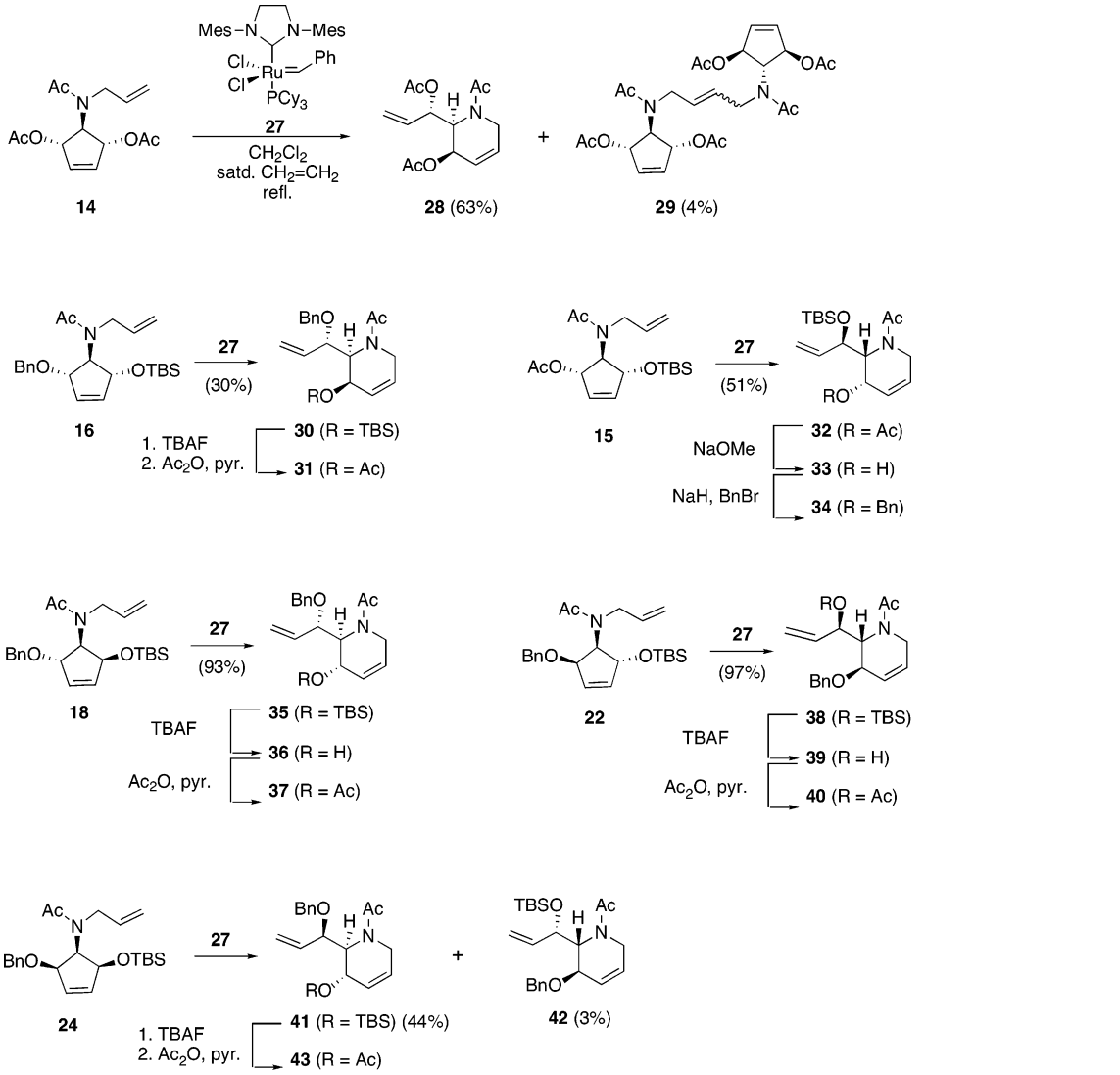
(7) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634.

(8) Stragies, R.; Blechert, S. *Synlett* **1998**, 169. Stragies, R.; Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584.

(9) For a recent review see: Randl, S.; Blechert, S. In *Hanbook of Metathesis. Applications in Organic Synthesis*; Grubbs, R. H., Ed.; Wiley-VCH: Morlenbach, 2003; Vol. 2.

(10) Morgan, J. P.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 3153. Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674.

SCHEME 6



cally, the exocyclic (C-7) vs cyclic (C-5) locations of the OTBS groups in **30**, **35**, **38**, and **41** are assigned by (1) using COSY and HMQC NMR methods to determine the chemical shifts of H-7 and H-5, (2) transforming OTBS to OAc groups, and (3) again using COSY and HMQC methods to assign chemical shifts to H-7 and H-5 in the derived acetates (Table 1). In this manner, locations of the OTBS groups in the tetrahydropyridines are revealed by downfield shifts of either H-7 or H-5 promoted by the OTBS → OAc transformations. A similar method (OAc → OBn) is used to assign the structure of tetrahydropyridine **32** (Table 1).

Additional support for the structural assignments comes from (1) X-ray crystallographic analysis of the monoalcohol **36** derived from tetrahydropyridine **35** (Figure 1) and (2) the observation that the OBn derivative **34**, formed from tetrahydropyridine **32**, is not equivalent to **30**.

Regiochemical/Stereochemical Features of the RRM Reactions. The observations summarized above demonstrate that RRM reactions of the *N*-allylacetamidocyclopentenes take place with modest to high efficiencies. The exceptionally high levels of regiochemical control observed for reactions of the unsymmetrically substituted substrates requires comment. It is generally believed that RRM reactions, like their RCM counterparts, are equilibrium processes occurring between interconvertible alkenylcycloalkene starting materials and products.[11] An

TABLE 1. ^{1}H NMR Chemical Shift Data for the 6-Allyl-1,2,5,6-tetrahydropyridines

	^{1}H NMR chemical shifts (ppm)			
compd	H-4	H-5	H-7	H-8
30	5.60	3.75	4.05	5.85
31	5.55	5.50	3.85	5.70
32	5.60	5.65	5.10	5.90
33	5.65	3.85	4.65	5.90
34	5.71	3.99	4.34	5.82
35	5.65	4.10	3.55	5.75
36	5.80	4.01	3.52	5.68
37	5.80	5.10	3.55	5.80
38	5.85	3.85	3.85	5.65
40	5.90	3.90	5.20	5.70
41	5.60	4.46	3.65	5.70
43	5.90	5.45	3.74	5.70

(11) Miller, S. J.; Kim, S. H.; Chen, Z. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108. Smith, A. B.; Adams, C. M.; Kozmin, S. A. *J. Am. Chem. Soc.* **2001**, *123*, 990.

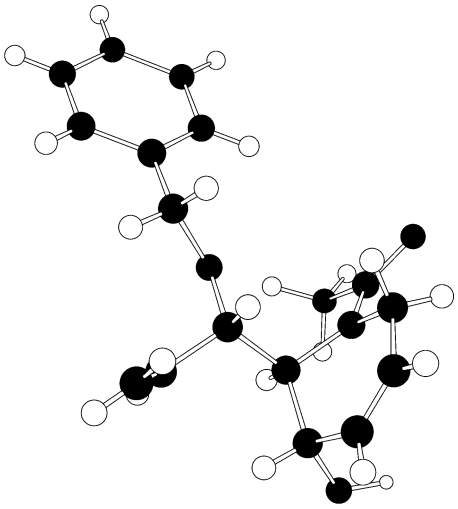
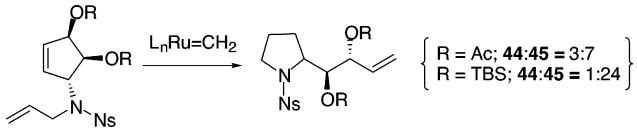


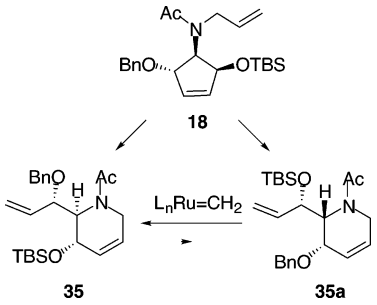
FIGURE 1. Chem-3D plot of the X-ray crystallographically determined atomic coordinates of **36**.

SCHEME 7



44 **45**

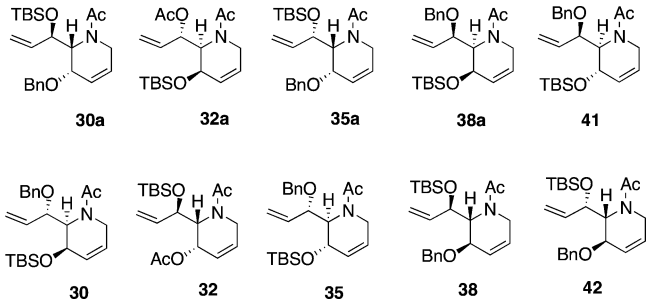
SCHEME 8



example of this is found in studies of RRM reactions of 3-sulfonamidocyclopentenes (Scheme 7) by Blechert.[12] The observed substituent effects on percent conversion of starting materials **44** to products **45** is in accord with thermodynamic arguments based on the influence substituent size on the equilibrium constant for interconversion of **44** to **45**.

Thus, the regioselectivities of RRM reactions of the unsymmetrically substituted 4-*N*-allylacetamidocyclopentenes observed in the current study could be a consequence of energy differences between two equilibrating 2-allyl-1,2,3,6-tetrahydropyridine products. This is depicted in Scheme 8 for reaction of cyclopentene **18**, which could generate either the observed tetrahydropyridine **35** or the unobserved regioisomer **35a**. To evaluate whether the observed results are consistent with thermodynamic expectations, molecular mechanics calculations (Macromodel) were performed on all possible tetrahydropyridine regioisomers that could have been produced in RRM reactions of substrates **15**, **16**, **18**, **22**, and **24**. The results, compiled in Table 2, demonstrate that in most, but not all, cases the exclusive or major tetrahydropyridine product is calculated to have the lowest energy. Importantly, in some instances, the energetic preferences are only marginal (e.g., **35** vs **35a**) and in one case (**41** vs **42**) the regioisomer formed in a minor amount is lower in energy than the major product. Finally, in several cases (**30** vs **30a** and **41** vs **42**) the relative energies of the regioisomeric tetrahydropyridines are dependent on the choice of force constant parameters used (MM2 vs MM3).

TABLE 2. Macromodel (MM2 and MM3) Globally Minimized Energies of Possible Products of RRM Reactions of *N*-Allylacetamidocyclopentenes



N-allylacetamidocyclopentene	minimized energies (macromodel) of tetrahydropyridine products					
	product obsd	energy[a]		product not obsd	energy[a]	
		MM2	MM3		MM2	MM3
15	**32**	+31	122	**32a**	+68	167
16	**30**	−46	182	**30a**	−21	158
18	**35**	−46	178	**35a**	−43	181
22	**38**	−48	180	**38a**	−41	181
24	**41** (major)	−50	174	**42** (minor)	−53	178

[a] Energy in kJ/mol.

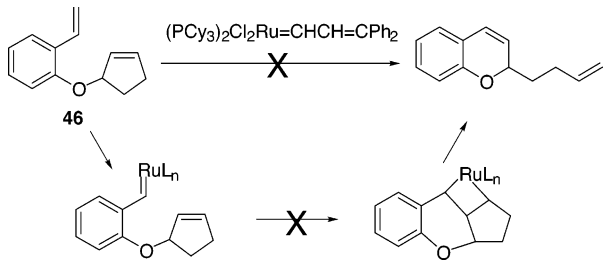
It is clear that the high degrees of regiochemical control observed in RRM reactions of the 4-*N*-allylacetamidocyclopentenes are not well correlated with the calculated energies of the possible tetrahydropyridine products. Although the cause of this might be due to the calculation method, an additional observation suggests that the RRM reactions are not controlled by thermodynamics. Specifically, the major and minor tetrahydropyridines **41** and **42**, formed from acetamidocyclopentene **24**, do not interconvert when they are independently subjected to the RRM reaction conditions under which they are produced.

Several observation made in earlier studies of Ru-catalyzed metathesis reactions suggest that kinetics can govern features of the process. For example, a kinetic argument was offered by Hoveyda and co-workers[13] to explain the surprising lack of reactivity of the cyclopentenylstyrenyl ether **46** (Scheme 9) under RRM reaction conditions. Ring strain associated with transformation of an initially formed, exocyclic ruthenium-alkylidene intermediate to a ruthenacyclobutane is believed to block reaction of this substrate (Scheme 9). In a similar fashion, the regiochemical course of RRM reactions of the unsymmetrically substituted acetamidocyclopentenes might be governed by the relative rates of formation of the regio-

(12) Ovaa, H.; Stapper, C.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H.; Blechert, S. *Tetrahedron* **2002**, *58*, 7503.

(13) Harrity, J. P. A.; Visser, M. S.; Gleason, J. D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 1488. Harrity, J. P. A.; La, D. S.; Cefalo, D. R.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 2343.

SCHEME 9

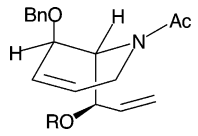


isomeric tetrahydropyridine products. In these processes, internal cross-metathesis reactions of an exocyclic Ru-alkylidene,[14] formed initially from the cyclopentene substrates, can occur in two regiochemically different directions to competitively generate two polycyclic ruthenacyclobutanes. This is shown in Scheme 10 for reaction of exocyclic ruthenium-alkylidene derived from **18**, which generates ruthenacyclobutanes **47** or **48**, and for reaction of the exocyclic ruthenium-alkylidene derived from **22**, which forms **49** and **50**. Steric interactions between the large group ligated, ruthenium ,and endo-positioned OTBS and OBn groups in **48** and **50**, respectively, would make production of the polycyclic ruthenacyclobutanes **47** and **49** preferred. Thus, selective formation of the respective tetrahydropyridines **35** and **38** in RRM reactions of **18** and **22** could be the result of steric effects governing competitive rates of formation of ruthenacyclobutane intermediates.[13,15] A thermodynamic argument, based on energetically biased (**47** favored over **48**) equilibration of the tricyclic ruthenacyclobutane intermediates, could also be used to explain these results. Interestingly, a similar analysis can be applied to the RRM reaction of *cis*,*cis*-acetamidocyclopentene **24** (Scheme 11). Here, the preference for metallacyclobutane **51** over **52**, resulting from the size difference between the OBn and OTBS groups, leads to selective formation of **41** as the major tetrahydropyridine product.

Despite these successes, the kinetic/thermodynamic argument presented above cannot be used to explain the high degrees of regioselectivity attending RRM reactions of the *trans*,*trans*-4-*N*-allylacetamidocyclopentenes **15** and **16**. In each of these systems, the ruthenacyclobutane intermediates (**53** and **54**, Scheme 12), derived from initially formed exocyclic alkylidenes, are expected to have nearly equal energies. Thus, kinetic considerations suggest that, in opposition to the experimental findings, these processes should be nonselective. However, it is interesting to note that RRM reactions of **15** and **16** occur with much lower yields than those of the corresponding amidocyclopentenes **18**, **22**, and **24**. At the current time, we are unable to offer an explanation for these differences.

Synthesis of Polyhydroxylated Indolizidines. The RRM processes described above appear to be ideally suited for applications to concise, stereocontrolled routes for the synthesis of naturally occurring and nonnatural polyhydroxylated indolizidines.[16] As shown in Scheme 2, the endocyclic and exocyclic alkene moieties in 2-allyl-1,2,3,6-tetrahydropyridines, generated by RRM reaction of 4-*N*-allylacetamidocyclopentenes, can serve as sites for installation of hydroxyl functionality present in the targets and required for key C−N bond forming cyclizations to construct the indolizidine ring system. Clearly, a critical feature of this general strategy is the control of stereochemistry and regiochemistry in reactions used to selectively introduce the hydroxyl groups. For example, application of this methodology to the synthesis of the potent glycosidase inhibitor, (−)-swainsonine (**59**),[17] or its analogues (Scheme 13) requires the execution of a selective dihyroxylation and reduction of the respective exocyclic and endocyclic alkene moieties in 2-allyltetrahydropyridines **56** generated by the RRM process. On the other hand, selective dihydroxylation and hydroboration−oxidation is required in sequences used for the conversion of tetrahydropyridines **56** to (+)-castanospermine (**60**) or its analogues**.**

(−)-Swainsonine. Issues associated with selective ring versus side chain olefin hydroxylation/dihydroxylation were addressed in a preliminary manner in a route developed for synthesis of (−)-swainsonine starting with tetrahydropyridine **38**. This substance is efficiently formed by RRM reaction of the acetamidocyclopentene **22** (Scheme 6). The challenge here resides in the requirement for regioselective and stereoselective dihydroxylation of the exocyclic olefin group in **38**. Molecular modeling of **38** as well as its alcohol and acetate derivatives, **39** and **40**, confirms the prediction (based on $A^{1,3}$-strain considerations) that there is a strong preference for these substances to exist in 5,6-diaxial conformations. Consequently, approach to either face of the endocyclic π-moieties in **38**−**40** by hydroxylation reagents would be



38 (R = TBS)
39 (R = H)
40 (R = Ac)

sterically blocked. Thus, mono dihydroxylation of these substrates should occur at the exocyclic double bond, preferentially. Moreover, substrate[18] and/or catalyst[19] control should serve to guide the stereochemical course of the dihydroxylation process in order to derive exocyclic erythro diol derivatives required for a (−)-swainsonine synthesis.

Observations made in studies of the dihydroxylation reactions of **38**−**40** indicate that these expectations are only partially fulfilled. For example, treatment of **38** under the Sharpless AD-mix-α conditions[19] or with the catalytic OsO_4/NMO reagent pair leads to predominant formation of the ring-hydroxylated product **60** along with

(14) Observation suggesting that RRM reactions of terminal-alkenyl-substituted cycloalkenes are intiated by metathesis at the terminal olefinic center is found in refs 7 and 13.

(15) Steric arguments such as the one presented here have been used by Snapper (Snapper, M. L.; Tallarico, J. A.; Randall, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1478) to explain the regiochemical course of cross metathesis reactions of fused cyclobutenes.

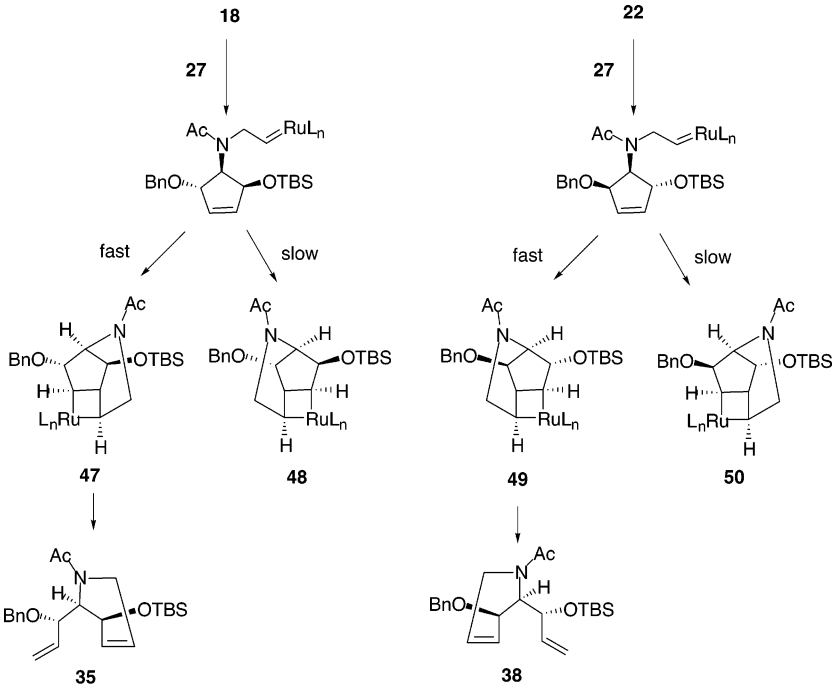
(16) For other recent approaches to the synthesis of *N*-heterocycles relying on RRM reactions, see: Stragies, R.; Blechert, S. *Tetrahedron* **1999**, *55*, 8179. Voigtmann, U.; Blechert, S. *Org. Lett.* **2000**, *2*, 3971. Buschmann, N.; Ruckert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325.

(17) For a description of a recent synthesis of (−)-swainsonine as well as references to earlier work, see: Pearson, W. H.; Ren, Y.; Powers, J. D. *Heterocycles* **2002**, *58*, 421.

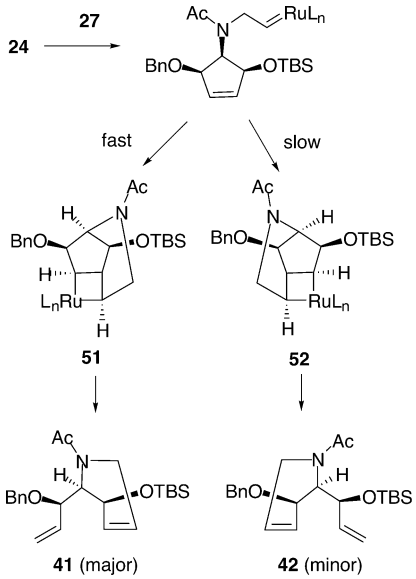
(18) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943. Cha, J. K.; Kim, N. S. *Chem. Rev.* **1995**, *95*, 1761.

(19) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768.

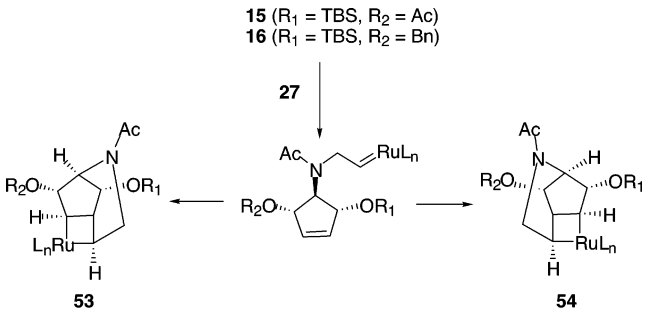
SCHEME 10



SCHEME 11

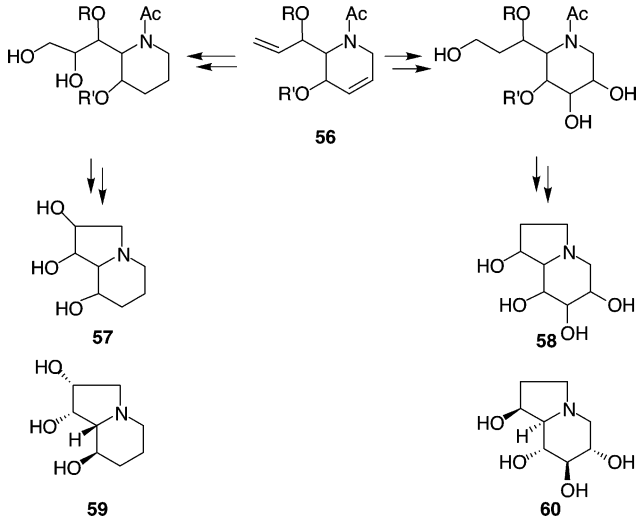


SCHEME 12

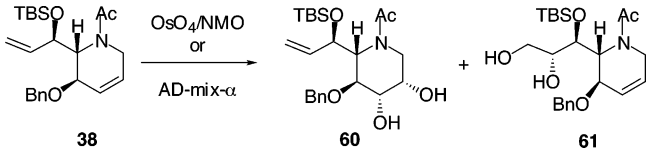


a minor amount of the desired exocyclic erythro diol derivative **61** (Scheme 14). Reduction in the size of the exocyclic allylic substituent has a pronounced effect on

SCHEME 13



SCHEME 14

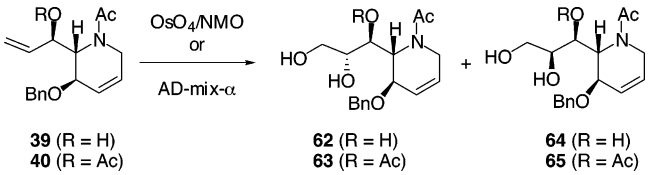


the regiochemical course of this process. Thus, reaction of alcohol **39** with catalytic OsO_4/NMO gives an ca. 1:1 mixture of the erythro and threo triols, **62** and **64** (Scheme 15). Similarly, AD-mix-α treatment of acetate **40** leads to production of a ca. 1:1 mixture of exocyclic diols **63** and **65** (Scheme 15).

Fortunately, in accord with earlier observations,[20] catalytic OsO_4/NMO dihydroxylation of acetate **40** efficiently (81%) generates a mixture of exocyclic diols **63**

(20) Marshall, J. A.; Tang, Y. *J. Org. Chem.* **1994**, *59*, 1457.

SCHEME 15

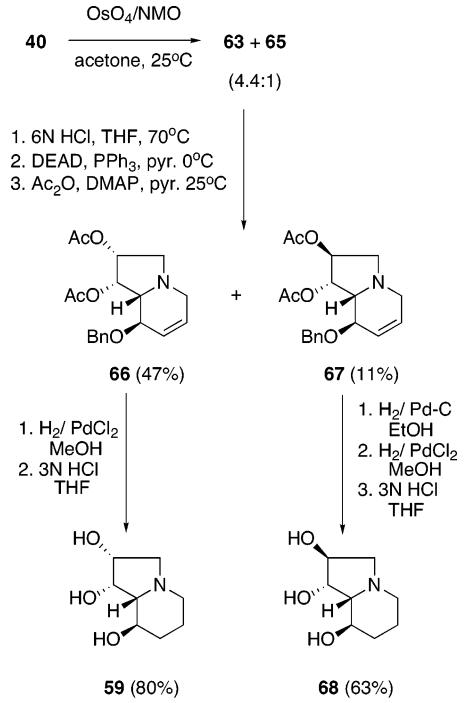


39 (R = H)
40 (R = Ac)

62 (R = H)
63 (R = Ac)

64 (R = H)
65 (R = Ac)

SCHEME 16



and **65**, in which the erythro isomer **63** dominates by 4.4:1 (Scheme 15). Without separation, **63** and **65** are converted to the separable indolizidine diacetates **66** (47%) and **67** (11%) by sequential treatment with 6 N HCl, DEAD/Ph_3P, and Ac_2O/DMAP (Scheme 16). Although hydrogenation and hydrogenolysis at the benzyloxy-allyl moiety in **66** can be performed in a stepwise manner, it is more convenient to carry out the two operations simultaneously. Accordingly, reaction of **66** with $H_2/PdCl_2$ in MeOH, followed by acid-promoted ester hydrolysis and ion exchange chromatography leads to the formation of (−)-swainsonine (**59**) (80%, ca. 80% ee). The physical[21] (mp 139−140 °C [lit.[22] mp 141−143 °C]; $[\alpha]^{25}_D$ −60 (*c* 0.84, MeOH) [lit.[21] $[\alpha]^{25}_D$ −71 (*c* 0.56, MeOH)]) and spectroscopic properties of the synthetic material matched those previously reported for the natural product.

In a similar fashion, the indolizidine diacetate **67** is converted to (−)-2-*epi*-swainsonine (**68**) (63%; mp 168−169 °C [lit.[23] mp 169.5−172 °C]; $[\alpha]^{25}_D$ −35 (*c* 0.61, MeOH) [lit.[23] $[\alpha]^{25}_D$ −61 (*c* 0.12, EtOH)]) by sequential hydrogenation, hydrogenolysis, and ester hydrolysis (Scheme 16).

Experimental Section

***trans,trans*-4-[*N*-Allylacetamido]-3,5-diacetoxycyclopentene (14): A Representative *N*-Allylation Procedure.** A solution of the known[4] 4-acetamido-3,5-diacetoxycyclopentene **11** (750 mg, 3.1 mmol) in 4 mL of DMF at 0 °C containing NaH (94 mg, 3.7 mmol, 95%) was stirred for 20 min at 0 °C. Allyl bromide (1.3 mL, 15.5 mmol) was added and the mixture was stirred at 0°C for 1 h, diluted with water, and extracted with EtOAc. The EtOAc extracts were washed with water and then brine and concentrated in vacuo giving a residue, which was subjected to column chromatography (silica gel, 3:1 hexane−acetone) to afford **14** (320 mg, 37%). ^{1}H NMR δ 6.05−5.65 (m, 5H), 5.20−5.01 (m, 2H), 3.93 (t, J = 4.9 Hz, 1H), 3.86−3.84 (m, 2H), 2.00 (s, 3H), 1.96 (s, 6H); ^{13}C NMR δ 171.4, 170.4, 133.4, 132.8, 116.9, 78.5, 70.1, 52.6, 22.0, 20.8; HRMS (FAB) *m*/*z* 282.1354 (M + 1) (calcd for $C_{14}H_{20}NO_5$ 282.1341).

***N*-Allylacetamidocyclopentenes 15, 16, 18, 22, and 24.** By using the *N*-allylation procedure described above, the acetamidocyclopentenes **12**[5a] (370 mg, 1.2 mmol), **13**[6] (40 mg, 0.11 mmol), **17**[6] (169 mg, 0.47 mmol), **21** (100 mg, 0.28 mmol), and **25** (199 mg, 0.55 mmol) were transformed into the respective *N*-allylacetamidocyclopentenes 1**5** (338 mg, 81%), **16** (34 mg, 77%), **18** (175 mg, 93%), **22** (92 mg, 83%), and **24** (160 mg, 72%).

15: ^{1}H NMR (mixture of rotamers) δ 5.83 (d, J = 5.5 Hz, 0.6H), 5.82−5.62 (m, 3H), 5.35 (d, J = 6.4 Hz, 0.2H), 5.04−4.91 (m, 2.7H), 4.51 (d, J = 5.5 Hz, 0.3H), 4.16 (t, J = 6.3 Hz, 0.3H), 3.95−3.82 (m, 1.2H), 3.70−3.65 (m, 0.7H), 3.58−3.62 (m, 0.3H), 3.36 (t, J = 5.5 Hz, 0.7H), 2.04 (s, 0.9H), 1.91 (s, 2.1H), 1.88 (s, 0.9H), 1.83 (s, 2.1H), 0.71 (s, 9H), −0.13 (s, 6H); ^{13}C NMR, rotamer A δ 170.9, 170.2, 136.8, 133.4, 130.0, 117.0, 77.4, 75.9, 75.4, 54.4, 25.5, 22.2, 20.8, 17.7, −4.9, −5.1, rotamer B δ 170.6, 170.0, 136.5, 133.6, 130.2, 115.6, 76.1, 75.2, 72.8, 45.3, 25.5, 21.6, 20.5, 17.7−4.9, −5.1; HRMS (FAB) *m*/*z* 354.2096 (M + 1) (calcd for $C_{18}H_{32}NO_4Si$ 354.2101).

16: ^{1}H NMR (mixture of rotamers) δ 7.33−7.25 (m, 5H), 5.92−5.78 (m, 3H), 5.25 (s, 0.5H), 5.19−5.10 (m, 2H), 4.95−4.90 (m, 0.5H), 4.61−4.58 (m, 0.5H), 4.57−4.54 (m, 2H), 4.45−4.40 (m, 0.5H), 4.35−4.25 (m, 0.5H), 4.20−4.05 (m, 0.5H), 4.0−3.85 (m, 1H), 3.65−3.50 (m, 0.5H), 3.48 (t, J = 11.2 Hz, 0.5H), 2.23 (s, 1.5H), 2.07 (s, 1.5H), 0.874 (s, 9H), 0.053−0.025 (m, 6H); ^{13}C NMR, rotamer A δ 171.1, 138.8, 135.7, 134.3, 131.3, 128.2, 127.6, 127.5, 117.2, 82.6, 77.1, 75.7, 71.3, 55.1, 25.7, 22.7, 22.0, −4.7, −4.8, rotamer B δ 171.1, 138.5, 135.3, 133.6, 131.2, 128.4, 127.8, 126.8, 115.9, 81.1, 75.6, 75.1, 71.6, 45.7, 25.6, 22.7, 22.0, 18.2, −4.7, −4.8; HRMS (FAB) *m*/*z* 402.2448 (M + 1) (calcd for $C_{23}H_{36}NO_3Si$ 402.2464).

18: ^{1}H NMR (mixture of rotamers) δ 7.32−7.24 (m, 5H), 6.03−6.01 (m, 1H), 5.95−5.93 (m, 1H), 5.93−5.75 (m, 1H), 5.30−5.20 (m, 1H), 5.15−5.0 (m, 2H), 4.95−4.85 (m, 1H), 4.85−4.75 (m, 0.3H), 4.75−4.65 (m, 0.7H), 4.55−4.45 (m, 2H), 4.15−4.10 (m, 0.3H), 4.10−3.95 (m, 1.7H), 2.11 (s, 1H), 2.09 (s, 1H), 0.85 (s, 9H), 0.07−0.01 (m, 6H); ^{13}C NMR (mixture of rotamers) δ 171.9, 171.1, 138.2, 137.9, 135.8, 135.3, 134.7, 133.7, 133.5, 128.4, 128.2, 127.7, 127.6, 127.5, 115.7, 114.8, 84.2, 83.8, 74.8, 74.3, 71.9, 71.0, 60.9, 50.0, 25.7, 21.8, 17.9, −4.9, −5.0; HRMS (FAB) *m*/*z* 402.2468 (M + 1) (calcd for $C_{23}H_{36}NO_3Si$ 402.2464).

22: ^{1}H NMR (mixture of rotamers) δ 7.29−7.24 (m, 5H), 6.01−5.90 (m, 3H), 5.24−4.93 (m, 3.5H), 4.68−4.66 (m, 0.5H), 4.48−4.43 (m, 3H), 4.15−4.05 (m, 0.25H), 3.94−3.92 (m, 1.5H), 3.85−3.75 (m, 0.25H), 2.11 (s, 1H), 2.05 (s, 2H), 0.83 (s, 9H), 0.03−0.02 (m, 6H); ^{13}C NMR (mixture of rotamers) δ 171.7, 170.5, 137.9, 137.3, 137.1, 135.2, 134.6, 132.2, 131.5, 127.8, 127.2, 127.0, 126.9, 126.8, 115.4, 114.8, 80.6, 80.3, 77.2, 77.0, 71.8, 67.9, 63.0, 49.3, 25.1, 21.6, 21.5, 17.3, −4.6, −4.7, −5.0, −5.2; HRMS (FAB) *m*/*z* 402.2470 (M + 1) (calcd for $C_{23}H_{36}NO_3Si$ 402.2464).

24: ^{1}H NMR δ 7.31−7.24 (m, 5H), 6.05−5.95 (m, 1H), 5.94−5.93 (m, 1H), 5.88−5.85 (m,2H), 5.01−4.96 (m, 2H), 4.66−4.64 (m, 1H), 4.60−4.40 (ABq, J = 11.8 Hz, 2H), 4.40−4.38 (m, 1H), 3.91−3.89 (m, 1H), 3.85−3.84 (m, 1H), 2.07 (s, 3H), 0.87 (s, 9H), 0.077 (d, J = 3.3 Hz, 3H), 0.04 (s, 3H); ^{13}C NMR δ 173.2, 137.9, 136.6, 135.7, 132.8, 128.2, 127.7, 127.5, 115.3, 80.3, 74.3, 71.9, 57.6, 51.2, 25.7, 22.8, 18.0, −5.0, −5.3.; HRMS (FAB) *m*/*z* 402.2456 (M + 1) (calcd for $C_{23}H_{36}NO_3Si$ 402.2464).

(21) Lindsay, K. B.; Pyne, S. G. *J. Org. Chem.* **2002**, *67*, 7774.
(22) Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1994**, *59*, 1358.
(23) Elbein, A. D.; Szumilo, T.; Sanford, B. A.; Sharpless, K. B.; Adams, C. *Biochemistry* **1987**, *26*, 2502.

***trans,cis*-3-*tert*-Butyldimethylsilyloxy-4-acetamidocyclopenten-5-ol (20).** To a solution of the known[6] alcohol **19** (55 mg, 0.20 mmol) in 5 mL of THF at 70 °C was added a solution of the Burgess reagent (58 mg, 0.24 mmol) in 5 mL of THF. The resulting solution was stirred for 3 h at 70 °C and 10 mL of aqueous NaH_2PO_4 (pH 5.2) was added. The mixture was stirred at 25 °C for 3 d, concentrated in vacuo, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were concentrated in vacuo to give a residue that was subjected to column chromatography (silica gel, 2:1 hexane−acetone) to afford **20** (42 mg, 76%) as a solid, mp 111−112 °C. ^{1}H NMR δ 6.29 (d, J = 7.5 Hz, 1H), 5.86−5.92 (m, 2H), 4.76−4.78 (m, 1H), 4.69 (s, 1H), 4.05−4.18 (m, 1H), 3.31 (s, 1H), 1.99 (s, 3H), 0.85 (s, 9H), 0.04 (s, 6H); ^{13}C NMR δ 170.9, 138.4, 133.2, 80.3, 73.4, 60.3, 25.7, 23.3, 18.1, −4.7, −4.9; HRMS (FAB) m/z 272.1684 (M + 1) (calcd for $C_{13}H_{26}NO_3Si$ 272.1682).

***trans,cis*-3-*tert*-Butyldimethylsilyloxy-4-acetamido-5-benzyloxycyclopentene (21).** A solution of alcohol **20** (168 mg, 0.62 mmol) and NaH (19 mg, 0.74 mmol, 95%) in 3 mL of DMF was stirred at 0 °C for 20 min. Benzyl bromide (30 μL, 0.25 mmol) was added and the solution was stirred for 2 h at 25 °C, diluted with water, and extracted with EtOAc. The EtOAc extracts were washed with water and brine and concentrated in vacuo providing a residue, which was subjected to column chromatography (silica gel, 2:1 hexanes−ethyl acetate) to afford the **21** (210 mg, 94%). Mp 77−78 °C; ^{1}H NMR δ 7.34−7.26 (m, 5H), 6.04 (d, J = 8.2 Hz, 1H), 5.97−5.92 (m, 2H), 4.68 (s, 1H), 4.51 (d, J = 5.7 Hz, 1H), 4.51−4.43 (ABq, J = 11.6 Hz, 2H), 4.37−4.32 (m, 1H), 1.94 (s, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR δ 169.8, 138.8, 137.9, 131.7, 128.4, 127.9, 127.7, 80.7, 80.6, 72.0, 58.6, 25.7, 23.3, 18.0, −4.8, −5.0; HRMS (FAB) m/z 362.2166 (M + 1) (calcd for $C_{20}H_{32}NO_3Si$ 362.2151).

***trans,cis*-4-Acetamido-5-benzyloxycyclopenten-3-ol (23).** A solution of **21** (19 mg, 0.052 mmol) and TBAF (16 mg, 0.062 mmol) in 3 mL of THF was stirred at 25 °C for 3 h and concentrated in vacuo to provide a residue, which was subjected to column chromatography (silica gel, 1:2 hexane−acetone) to afford **23** (12 mg, 100%). Mp. 130−131°C; ^{1}H NMR δ 7.32−7.25 (m, 5H), 6.54 (br s, 1H), 6.04−6.02 (m, 1H), 5.96−5.94 (m, 1H), 4.71 (s, 1H), 4.69 (s, 1H), 4.50 (m, 2H), 4.43−4.41 (m, 1H), 3.92−3.90 (m, 1H), 1.93 (s, 3H); ^{13}C NMR δ 171.9, 138.9, 137.5, 130.2, 128.3, 127.7, 127.6, 81.5, 80.1, 71.2, 60.6, 22.6; HRMS (FAB) m/z 248.1296 (M + 1) (calcd for $C_{14}H_{18}NO_3$ 248.1287).

***cis,cis*-4-Acetamido-5-benzyloxycyclopenten-3-ol (26).** To a solution of **23** (310 mg, 1.3 mmol) in 20 mL of THF at 70 °C was added a solution of the Burgess reagent (58 mg, 0.24 mmol) in 10 mL of THF. The resulting solution was stirred for 3 h at 70 °C. An aqueous NaH_2PO_4 solution (30 mL, pH 5.2) was added and the mixture was stirred at 25 °C for12 h, concentrated in vacuo, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were concentrated in vacuo to give a residue that was subjected to column chromatography (silica gel, 1:2 hexane−acetone) to afford **26** (240 mg, 77%). ^{1}H NMR δ 7.34−7.28 (m, 5H), 6.39 (d, J = 6.3 Hz, 1H), 6.07−6.00 (m, 2H), 4.49 (s, 2H), 4.41−4.38 (m, 1H), 4.34−4.27 (m, 2H), 3.19 (br s, 1H), 2.02 (s, 3H); ^{13}C NMR δ 170.6, 137.8, 136.5, 133.7, 128.2, 127.6, 127.6, 79.5, 72.9, 72.0, 52.9, 22.9; HRMS (FAB) m/z 248.1290 (M + 1) (calcd for $C_{14}H_{18}NO_3$ 248.1287).

***cis,cis*-3-*tert*-Butyldimethylsiloxy-4-acetamido-5-benzyloxycyclopentene (25).** A solution of **26** (229 mg, 0.99 mmol), imidazole (162 mg, 2.4 mmol), and TBSCl (179 mg, 1.2 mmol) in 10 mL of CH_2Cl_2 was stirred at 25 °C for 12 h, diluted with water, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were concentrated in vacuo to provide a residue, which was subjected to column chromatography (silica gel, 2:1 hexane−acetone) to afford **25** (304 mg, 85%). ^{1}H NMR δ 7.30−7.24 (m, 5H), 6.0−5.9 (m, 3H), 4.6−4.5 (m, 4H), 4.33−4.32 (m, 1H), 1.94 (s, 3H), 0.88 (9H), 0.068 (d, J = 5.4 Hz, 6H); ^{13}C NMR δ 169.7, 138.6, 136.2, 133.2, 128.3, 127.4, 127.3, 79.2, 73.2, 71.6, 52.3, 25.7, 23.2, 18.1, −4.7, −4.9; HRMS (FAB) m/z 362.2168 (M + 1) (calcd for $C_{20}H_{32}NO_3Si$ 362.2151).

Ruthenium-Catalyzed Tandem Metathesis Reaction of *N*-Allylacetamidocyclopentene 14 Forming 2-Allyltetrahydropyridine 28: A Representative RRM Procedure. A solution of *N*-allylacetamidocyclopentene **14** (72 mg, 0.25 mmol) and ruthenium catalyst **27** (21 mg, 0.025 mmol) in 13 mL of CH_2Cl_2 was stirred at reflux for 16 h while being purged with C_2H_4. Concentration in vacuo provided a residue, which was subjected to column chromatography (silica gel, 2:1 hexane−acetone) to afford the 2-allyltetrahydropyridine **28** (50 mg, 69%) and dimer **29** (6 mg, 4%).

28: ^{1}H NMR (rotamer mixture) δ 5.90−5.70 (m, 2H), 5.65−5.56 (m, 1.5H), 5.50−5.30 (m, 1.7H), 5.30−5.20 (m, 0.8H), 5.20−5.15 (m, 0.6H), 5.12−5.05 (m, 0.8H), 4.45−4.42 (m, 1H), 3.92−2.89 (m, 0.5H), 3.83−3.79 (m, 0.5H), 3.30−3.26 (m, 0.6H), 2.09 (s, 2.2H), 2.02(s, 1.3H), 1.98 (s, 2.8H), 1.93−1.91 (m, 2.7H); ^{13}C NMR, rotamer A δ 170.9, 169.1, 133.5, 126.2, 123.2, 118.6, 71.1, 67.6, 55.3, 39.6, 21.7, 21.0, rotamer B δ 170.3, 169.8, 133.8, 125.0, 124.6, 115.9, 72.2, 66.0, 48.4, 43.7, 21.9, 20.9; HRMS (FAB) m/z 282.1354 (M + 1) (calcd for $C_{14}H_{20}NO_5$ 282.1341).

29: ^{1}H NMR δ 5.97−5.91 (m, 4H), 5.79−5.74 (m, 3H), 5.60−5.58 (m, 3H), 4.20−4.15 (m, 2H), 3.88 (s, 2H), 3.82 (d, J = 3.5 Hz, 2H), 2.15−2.14 (m, 4H), 2.06−2.00 (m, 14H); ^{13}C NMR δ 171.4, 170.3, 170.2, 132.8, 127.7, 127.3, 78.4, 76.6, 69.4, 69.1, 50.5, 44.4, 21.9, 21.6, 20.8, 20.6; HRMS (FAB) m/z 535.2305 (M + 1) (calcd for $C_{26}H_{35}N_2O_{10}$ 535.2292).

Formation of 2-Allyltetrahydropyridines 30, 32, 35, 38, 40, and 41 by Tandem Metathesis. By using the general procedure described above, *N*-allylacetamidocyclopentene **16** (34 mg, 0.085 mmol) was converted to tetrahydropyridine **30** (10 mg, 30%) and a dimer (9 mg, 14%); **15** (37 mg, 0.1 mmol) was converted to tetrahydropyridine **32** (19 mg, 51%) and dimer (10 mg, 14%), **18** (25 mg, 0.062 mmol) was converted to tetrahydropyridine **35** (18 mg, 72%), **22** (64 mg. 0.16 mmol) was converted to tetrahydropyridine **38** (58 mg, 90%), and **24** (46 mg, 0.11 mmol) was converted to tetrahydropyridines **41** (20 mg, 44%) and **42** (1 mg, 3%).

30: ^{1}H NMR (mixture of rotamers) δ 7.30−7.21 (m, 5H), 5.95−5.75 (m, 1H), 5.75−5.45 (m, 2H), 5.4−5.1 (m, 2H), 5.05−4.95 (m, 0.5H), 4.6−4.55 (m, 0.5H), 4.55−4.5 (m, 0.5H), 4.5−4.35 (m, 1H), 4.4−4.35 (m, 0.5H), 4.3−4.25 (m, 0.5H), 4.25−4.2 (m, 0.5H), 4.05−4.0 (m, 0.5H), 4.00−3.95 (m, 0.5H), 3.8−3.75 (m, 0.5H), 3.3−3.2 (m, 0.5H), 2.12 (s, 1.5H), 2.04 (s, 1.5H), 0.90 (s, 9H), 0.1(m, 6H); ^{13}C NMR, rotamer A δ 170.5, 136.9, 128.7, 128.2, 127.4, 127.1, 123.9, 116.4, 77.0, 70.4, 67.5, 61.1, 40.4, 25.9, 22.1, 18.2, −4.76, rotamer B δ 171.5, 136.8, 129.7, 128.0, 127.7, 127.1, 122.9, 115.6, 78.7, 71.2, 65.9, 52.9, 44.6, 25.9, 22.1, −4.8; HRMS (FAB) m/z 408.2541 (M + 7) (calcd for $C_{23}H_{35}NO_3SiLi$ 408.2546).

32: ^{1}H NMR, rotamer A δ 5.89−5.93 (m, 1H), 5.73−5.59 (m, 3H), 5.19 (d, J = 17.3 Hz, 1H), 5.12−5.08 (m, 3H), 4.44−4.41 (m, 2H), 3.33 (d, J = 19.5 Hz, 1H), 2.06 (s, 3H), 1.95 (s, 3H), 0.89 (s, 9H), 0.067 (s, 6H), rotamer B δ 6.02−5.98 (m, 1H), 5.73−5.59 (m, 3H), 5.12−5.08 (m, 2H), 4.57 (s, 1H), 4.00 (t, J = 6.6 Hz, 1H), 3.82−3.89 (m, 2H), 2.12 (s, 3H), 1.97 (s, 3H), 0.87 (s, 9H), 0.052 (s, 6H); ^{13}C NMR, rotamer A δ 170.3, 169.0, 134.8, 129.9, 122.1, 115.9, 72.7, 65.1, 59.8, 44.0, 25.7, 22.0, 21.0, 17.9, −4.9, rotamer B δ 170.7, 169.2, 135.2, 128.3, 123.8, 114.8, 71.2, 66.8, 51.2, 40.1, 25.6, 21.9, 20.9, 18.0, −4.9; HRMS (FAB) m/z 354.2101 (M + 1) (calcd for $C_{18}H_{32}NO_4Si$ 354.2101).

35: ^{1}H NMR δ 7.32−7.19 (m, 5H), 5.80−5.65 (m, 3H), 5.43−5.40 (m, 1H), 5.35−5.32 (m, 1H), 4.66−4.6 0(m, 1H), 4.58−4.51 (m, 1H), 4.24−4.18 (m, 1H), 4.19−4.10 (m, 1H), 4.12−4.10 (m, 1H), 3.57−3.52 (m, 1H), 3.08 (d, J = 20 Hz, 1H), 2.15 (s, 3H), 0.86 (s, 9H), 0.02 (d, J = 14.6 Hz, 6H); ^{13}C NMR δ 171.8, 137.4, 135.6, 128.4, 127.9, 126.2, 124.1, 120.9, 77.7, 70.0, 64.0, 63.8, 56.7, 38.9, 25.8, 21.6, 19.2, 18.1, −4.2, −4.6; HRMS (FAB) m/z 402.2466 (M + 1) (calcd for $C_{23}H_{36}NO_3Si$ 402.2464).

38: ^{1}H NMR δ 7.24−7.31 (m, 5H), 6.15−6.05 (m, 1H), 5.95−5.80 (m, 1H), 5.75−5.60 (m, 1H), 5.20−5.05 (m, 2H), 4.80−4.75 (m, 1H), 4.75−4.35 (m, 2H), 4.15−4.00 (m, 1H), 4.00−3.80 (m, 2H), 3.45−3.35 (m, 1H), 2.12 (s, 2.4H), 2.10 (s, 0.6H), 0.84 (s, 3.6H), 0.81 (s, 5.4H), −0.02−0.04 (m, 6H); ^{13}C NMR δ 171.4, 138.7, 138.2, 129.9, 128.3, 128.0, 127.6, 127.4, 124.2, 121.9, 118.3, 116.7, 73.4, 72.9, 70.2, 69.5, 69.1, 61.7, 54.2, 43.5, 39.1, 25.7, 25.5, 22.3, 21.7, 17.7, −4.0, −4.3, −5.0; HRMS (FAB) *m/z* 402.2461 (M + 1) (calcd for $C_{23}H_{36}NO_3Si$ 402.2464).

41: ^{1}H NMR δ 7.34−7.25 (m, 5H), 5.78−5.76 (m, 1H), 5.76−5.72 (m, 1H), 5.70−5.69 (m, 1H), 5.33−5.2 8 (m, 2H), 4.75−4.70 (m, 1H), 4.58 (ABq, J = 12 Hz, 1H), 4.42 (Abq, J = 12 Hz, 1H), 4.46 (d, J = 5.4 Hz, 1H), 3.86 (d, J = 9.8 Hz, 1H), 3.67(t, J = 6.01 Hz, 1H), 3.15 (d, J = 19.7 Hz, 1H), 2.11 (s, 3H), 0.85 (s, 9H), 0.07 (d, J = 2.75 Hz, 3H), 0.03 (s, 3H); ^{13}C NMR δ 170.6, 137.6, 135.5, 128.3, 127.8, 127.7, 127.3, 124.5, 120.1, 78.7, 70.6, 64.0, 63.1, 38.8, 25.9, 25.7, 21.6, 18.0, −4.4, −4.7; HRMS (FAB) *m/z* 402.2456 (M + 1) (calcd for $C_{23}H_{36}NO_3Si$ 402.2464).

42: ^{1}H NMR δ 6.02−5.98 (m, 0.6H), 5.92−5.84 (m, 1.4H), 5.79−5.71 (m, 1H), 5.23−5.06 (m, 2H), 4.80−4.69 (m, 1.2H), 4.62−4.55 (m, 1.4H), 4.50−4.44 (m, 0.4H), 4.20 (d, J = 5.4 Hz, 1H), 4.07−4.03 (m, 0.4H), 3.98−3.93 (m, 0.7H), 3.91−3.87 (m, 0.9H), 3.75−3.70 (m, 0.4H), 3.29 (d, 19.7 Hz, 0.6H), 2.08 (s, 2H), 2.05 (s, 1H), 0.82 (s, 6H), 0.79 (s, 3H), −0.04 to −0.05 (m, 3H), −0.08 to −0.10 (m, 3H); ^{13}C NMR δ 170.6, 140.3, 138.4, 129.3, 128.3, 127.9, 127.6, 127.4, 127.1, 123.8, 122.1, 117.4, 116.3, 73.9, 72.3, 70.5, 69.5, 69.1, 61.3, 53.3, 43.1, 39.3, 25.6, 22.3, 21.8, 17.9, −4.21, −5.13; HRMS (FAB) *m/z* 402.2480 (M + 1) (calcd for $C_{23}H_{36}NO_3Si$ 402.2464).

Tetrahydropyridine 31. A solution of **30** (10 mg, 0.025 mmol) in 5 mL of THF and TBAF (6.8 mg, 0.027 mmol) was stirred at 25 °C for 2 h. The reaction mixture was concentrated, CH_2Cl_2 (5 mL), pyridine (0.05 mL), DMAP (1 mg, 0.013 mmol), and acetic anhydride (0.08 mL) were added, and stirring was continued overnight at 25 °C. The solvent was removed in vacuo to provide a residue, which was subjected to column chromatography (silica gel,2:1 hexane−acetone) to afford **31** (7 mg, 88%). ^{1}H NMR δ 7.31−7.20 (m, 5H), 5.80−5.65 (m, 2.3H), 5.65−5.55 (m, 0.7H), 5.45 (m, 1H), 5.35−5.25 (m, 2H), 4.54−4.50 (m, 1.4H), 4.47 (d, J = 2.8 Hz, 0.4H), 4.42 (t, J = 6.9 Hz, 0.6H), 4.30−4.20 (m, 1.4H), 4.10−4.00 (m, 0.3H), 3.86 (t, J = 7.8 Hz, 1H), 3.85−3.60 (m, 0.2H), 3.26−3.20 (m, 0.7H), 2.14 (s, 2H), 2.06 (s, 1H), 1.99 (s, 2H), 1.98 (s, 1H); ^{13}C NMR δ 170.9, 170.4, 137.8, 136.1, 135.7, 128.3, 128.1, 127.7, 127.6, 127.3, 126.3, 125.4, 124.9, 123.7, 118.8, 117.1, 78.5, 76.6, 70.4, 69.7, 68.4, 67.0, 56.6, 49.7, 44.2, 39.9, 22.0, 21.2, 21.0; HRMS (FAB) *m/z* 330.1715 (M + 1) (calcd for $C_{19}H_{24}NO_4$ 330.1705).

Tetrahydropyridine 33. A solution of **32** (74 mg, 0.21 mmol) and NaOMe (3 mg, 0.04 mmol) in 10 mL of MeOH was stirred at 25 °C for 12 h, diluted with water, and extracted with CH_2Cl_2. Concentration in vacuo of the CH_2Cl_2 extracts gave a residue, which was subjected to column chromatography (silica gel, 2:1 hexane−acetone) to afford the product **33** (51 mg, 78%). ^{1}H NMR (mixture of rotamers) 6.0−5.85 (m, 1H), 5.7−5.5 (m, 2H), 5.4−5.3 (m, 1H), 5.1−5.05 (m, 1H), 5.02−5.01 (m, 0.6H), 4.7−4.5 (m, 2.4H), 3.94−3.90 (m, 1H), 3.86−3.82 (m, 0.6H), 3.51 (d, J = 18.9 Hz, 0.4H), 2.08 (s, 1.2H), 2.05 (s, 1.8H), 0.90 (s, 4.5H), 0.88 (s, 4.5H), 0.09 (s, 6H); ^{13}C NMR, rotamer A δ 170.5, 137.1, 129.3, 124.3, 113.9, 72.1, 65.4, 52.7, 44.0, 25.7, 22.0, 17.9, −4.87, −4.92, rotamer B δ 170.4, 137.7, 128.1, 125.4, 115.6, 71.9, 66.8, 60.3, 40.2, 25.7, 21.9, 17.9, −4.9, −4.9; HRMS (FAB) *m/z* 312.1998 (M + 1) (calcd for $C_{16}H_{30}NO_3Si$ 312.1995).

Tetrahydropyridine 34. To a solution of **33** (31 mg, 0.1 mmol) in 2 mL of DMF at 0 °C was added NaH (5 mg, 0.2 mmol, 95%). After 10 min of stirring at 0 °C, benzyl bromide (30 uL,0.25 mmol) was added and the mixture was stirred for 12 h at 25 °C, diluted with water, and extracted with EtOAc. The EtOAc extracts were dried and concentrated in vacuo to provide a residue, which was subjected to column chromatography (silica gel, 2:1 hexanes−ethyl acetate) to afford **34** (36 mg, 90%). ^{1}H NMR (mixture of rotamers) δ 7.34−7.26 (m, 5H), 6.05−5.9 (m, 0.6H), 5.9−5.75 (m, 1.2H), 5.75−5.65 (m, 0.4H), 5.6−5.55 (m, 0.4H), 5.30−5.09 (m, 2.4H), 4.67−4.63 (m, 0.6H), 4.58 (s, 1.8H), 4.50−4.46 (m, 0.6H), 4.25−4.24 (m, 0.6H), 4.35−4.25 (m, 0.6H), 4.20−4.15 (m, 0.4H), 4.1−3.98 (m, 1H), 3.85−3.75 (m, 0.4H), 3.6−3.54 (m, 1H), 2.07 (s, 3H), 0.83 (s, 9H), −0.023 to −0.0881 (m, 6H); ^{13}C NMR, rotamer A δ 171.0, 139.8, 137.8, 128.4, 127.6, 125.8, 115.5, 73.5, 71.3, 71.3, 59.2, 41.1, 25.7, 22.1, 17.9, −4.0, −4.8, rotamer B δ 170.2, 139.7, 137.9, 128.3, 127.7, 124.5, 114.6, 71.6, 71.6, 71.3, 50.9, 44.9, 25.9, 22.2, 17.8, −4.4, −4.5; HRMS (FAB) *m/z* 402.2468 (M + 1) (calcd for $C_{23}H_{36}NO_3Si$ 402.2464).

Tetrahydropyridine 36. A solution of **35** (129 mg, 0.32 mmol) and TBAF (101 mg, 0.38 mmol) in 10 mL of THF was stirred at 25 °C for 2 h and concentrated in vacuo giving a residue that was subjected to column chromatography (silica gel, 1:1 acetone−hexane) to afford **36** (90 mg, 98%). Mp 127−128 °C; ^{1}H NMR δ 5.90−5.80 (m, 1H), 5.80−5.70 (m, 1H), 5.70−5.60 (m, 1H), 5.37 (d, J = 10.2 Hz, 1H), 5.22 (d, J = 17.1 Hz, 1H), 4.54−4.48 (m, 2H), 4.19 (d, J = 11.6 Hz, 1H), 4.01−3.96 (m, 2H), 3.52 (t, J = 9.0 Hz, 1H), 3.03 (d, J = 20 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR δ 172.6, 137.6, 135.2, 128.3, 127.8, 127.6, 127.4, 124.4, 121.0, 77.5, 69.8, 63.4, 63.2, 39.0, 21.6; HRMS (ES) *m/z* 310.1418 (M + Na) (calcd for $C_{17}H_{21}NO_3Na$ 310.1414).

Tetrahydropyridine 37. To a solution of **35** (10 mg, 0.024 mmol) in 5 mL of THF was added TBAF (7 mg, 0.027 mmol), and the reaction mixture was stirred [at] 25 °C for 2 h and concentrated. To the residue was added CH_2Cl_2 (5 mL), pyridine (0.05 mL), DMAP (1 mg, 0.013 mmol), and acetic anhydride (0.0 8 mL) and the resulting mixture was stirred at 25 °C for 12 h and concentrated in vacuo to provide a residue, which was subjected to column chromatography (silica gel, 2:1 hexane−acetone) to afford the product **37** (5 mg, 66%). ^{1}H NMR (mixture of rotamers) δ 7.33−7.18 (m, 5H), 5.97−5.94 (m, 1H), 5.94−5.76 (m, 2H), 5.46−5.43 (m, 0.8H), 5.40−5.30 (m, 0.2H), 5.30−5.26 (m, 0.8H), 5.24−5.28 (m, 0.2H), 5.11−5.09 (m, 0.8H), 5.05−5.00 (m, 0.2H), 4.66−4.61 (m, 0.8H), 4.56−4.53 (m, 0.8H), 4.10−4.05 (m, 0.4H), 4.04−4.02 (m, 0.8H), 3.95−3.90 (m, 0.2H), 3.7−3.65 (m, 0.2H), 3.59(t, J = 9.4 Hz, 0.8H), 3.4−3.3 (d, J = 20 Hz, 0.2H), 3.09 (d, J = 20 Hz, 0.8H), 2.13 (s, 2.5H), 2.10 (s, 0.5H), 2.0 1(s, 2.5H), 1.98 (s, 0.5H); ^{13}C NMR (mixture of rotamers) δ 171.6, 170.5, 137.5, 135.3, 134.8, 131.6, 129.6, 128.4, 128.3, 127.9, 127.8, 127.6, 122.1, 121.7, 120.3, 120.1, 78.1, 77.4, 70.0, 69.7, 66.1, 59.9, 53.5, 43.0, 39.0, 21.7, 21.0; HRMS (FAB) *m/z* 330.1711 (M + 1) (calcd for $C_{19}H_{24}NO_4$ 330.1705).

Tetrahydropyridine 40. A solution of **38** (220 mg, 0.55 mmol) in 5 mL of THF and TBAF (172 mg, 0.66 mmol) was stirred at 25 °C for 2 h and concentrated in vacuo giving a residue, which was subjected to column chromatography to yield 154 mg (94%) of alcohol **39**. ^{1}H NMR δ 7.30−7.23 (m, 5H), 6.0−5.76 (m, 3H), 5.25−5.15 (m, 2H), 5.01 (d, J = 11.0 Hz, 0.3 H), 4.9−4.2 (m, 2.5H), 4.11 (d, J = 16.5 Hz, 0.5H), 4.0−3.7 (m, 2H), 3.54 (d, J = 19.9 Hz, 0.7H), 2.12 (s, 3H); ^{13}C NMR δ 172.3, 138.1, 138.0, 137.4, 128.4, 128.3, 128.0, 127.8, 127.7, 127.5, 121.9, 118.5, 72.1, 70.6, 70.4, 69.7, 69.1, 62.1, 54.4, 43.0, 39.1, 22.1, 21.6; HRMS (FAB) *m/z* 288.1608 (M + 1) (calcd for $C_{17}H_{22}NO_3$ 288.1600).

A solution of alcohol **39** (52 mg, 0,13 mmol) in THF (5 mL) containing acetyl chloride (22 μL, 0.3 mmoL) and Et_3N (32uL, 0.23 mmol) was stirred for 12 h at 25 °C. Concentration in vacuo gave a residue that was subjected to column chromatography (silica gel, 1:1 hexane−acetone) to afford the product acetate **40** (34 mg, 58%). ^{1}H NMR δ 7.34−7.24 (m, 5H), 6.15−6.05 (m, 1H), 6.0−5.8 (m, 1H), 5.8−5.6 (m, 1H), 5.35−5.15 (m, 3H), 4.72−4.63 (m, 1H), 4.60−4.40 (m, 2H), 4.09−4.06 (m, 1H), 4.0−3.8 (m, 1H), 3.39−3.34 (m, 1H), 2.12 (s, 2H), 2.10 (s, 1H), 1.99 (s, 1.5H), 1.98 (s, 1.5H); ^{13}C NMR δ 171.1, 170.5, 169.9, 169.3, 137.9, 137.8, 132.8, 132.9, 130.4, 128.4, 128.3, 128.1, 127.8, 127.5, 123.5, 121.3, 121.2, 120.1, 72.9, 72.0, 70.5, 70.4, 69.2, 59.5, 51.5, 43.2, 39.2, 22.0, 21.3, 21.0, 20.8; HRMS (FAB) *m/z* 330.1715 (M + 1) (calcd for $C_{19}H_{24}NO_4$ 330.1705).

Tetrahydropyridine 43. To a solution of **41** (20 mg, 0.05 mmol) in 5 mL of THF was added TBAF (14 mg, 0.06 mmol), and the reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated, CH_2Cl_2 (5 mL), pyridine (0.05 mL), DMAP (2 mg), and acetic anhydride (0.08 mL) were added, and stirring was continued for 12 h at 25 °C. Concentration in vacuo provided a residue, which was subjected to column chromatography (silica gel, 2:1 hexane−acetone) to afford product **43** (10 mg, 50%). ^{1}H NMR (mixture of rotamers) 7.35−7.24 (m, 5H), 5.96−5.92 (m, 1H), 5.87−5.85 (m, 1H), 5.85−5.67 (m, 1H), 5.56−5.55 (m, 0.35H), 5.50−5.48 (d, J = 5.6 Hz, 0.65H), 5.5−5.3 (m, 1.3H), 5.3−5.25 (m, 0.35H), 5.19 (d, J = 17.1 Hz, 0.35H), 5.04 (d, J = 9.4 Hz, 0.35H), 4.78−4.72 (m, 0.65H), 4.61−4.58 (m, 1H), 4.28−4.22 (m, 1H), 4.04−3.99 (m, 1H), 3.76−3.62 (m, 1.35H), 3.22 (d, J = 20 Hz, 0.65H), 2.10 (s, 2H), 2.05 (s, 1H), 2.00 (s, 2H), 1.98 (s, 1H); ^{13}C NMR (mixture of rotamers) δ 170.5, 170.4, 170.3, 170.2, 137.8, 137.2, 136.2, 134.9, 130.4, 128.4, 128.3, 127.9, 127.8, 127.7, 122.3, 120.9, 120.7, 119.8, 79.3, 78.1, 70.7, 70.1, 66.3, 65.5, 59.6, 53.2, 43.0, 39.0, 22.2, 21.7, 21.0, 20.9; HRMS (FAB) m/z 330.1696 (M + 1) (calcd for $C_{19}H_{24}NO_4$ 330.1705).

Conversion of 40 to Indolizidines 66 and 67. To a solution of **40** (425 mg, 1.33 mmol) in 16 mL of acetone was added NMO (148 mg, 1.26 mmol), with stirring for 10 min. Then a solution of OsO_4 (17 mg, 0.07 mmol) in 1:1 acetone/H_2O was added and the resulting mixture was stirred at 25 °C for 3 h and diluted with 3 mL of saturated aqueous $Na_2S_2O_3$, and then mixture was stirred at 25 °C for 1 h. $MgSO_4$ was added and the mixture was filtered. The filtrate was concentrated in vacuo to provide a residue, which was subjected to column chromatography (silica gel, 1:1 hexane−acetone) to afford erythro and threo diols **63** and **65** (389 mg, 81%) as a 4.4:1 mixture. A solution of this mixture (99 mg, 0.27 mmol) in 8 mL of 6 N HCl/THF (1:1) was stirred at 70 °C for 4 h and concentrated in vacuo to give a residue that was dissolved in 2 mL of pyridine-containing Ph_3P (89 mg, 0.34 mmol), 4A molecular sieves, and DEAD (57 μl, 0.34 mmol). This solution was stirred at 0 °C for 3 h and diluted with 3 mL of CH_2Cl_2 before adding 0.5 mL of Ac_2O and DMAP with stirring for an additional 12 h at 25 °C. Concentration of the mixture in vacuo gave a residue that was partitioned between aq $NaHCO_3$ and CH_2Cl_2. Concentration of the CH_2Cl_2 layer in vacuo provided a residue that was subjected to column chromatography (silica gel, 8:1 hexane−acetone) to yield **66** (44 mg, 47%, 79% ee by (chiral HPLC)) and **67** (11 mg, 11%, 78% ee (chiral HPLC)).

66: $[\alpha]^{25}_D$ −85 (c 0.51, $CHCl_3$); ^{1}H NMR δ 7.32−7.24 (m, 5H), 5.93−5.88 (m, 1H), 5.83−5.80 (m, 1H), 5.57−5.52 (m, 1H), 5.37−5.30 (m, 1H), 4.59 (ABq, J = 28 Hz, 1H), 4.49 (Abq, J = 28 Hz, 1H), 4.32−4.28 (m, 1H), 3.48−3.39 (m, 1H), 3.15−3.08 (m, 1H), 2.82−2.66 (m, 2H), 2.52−2.46 (m, 1H), 1.99 (s, 3H), 1.93 (s, 3H); ^{13}C NMR δ 170.0, 169.9, 137.9, 128.4, 127.8, 127.7, 126.4, 126.1, 70.9, 70.8, 70.7, 69.9, 65.4, 58.3, 51.9, 20.6, 20.4; HRMS (FAB) m/z 346.1641 (M + 1) (calcd for $C_{19}H_{24}NO_5$ 346.1654).

67: $[\alpha]^{25}_D$ −57 (c 0.13, $CHCl_3$); ^{1}H NMR δ 7.32−7.28 (m, 5H), 5.91 (ABq, J = 12 Hz, 1H), 5.81 (ABq, J = 12 Hz, 1H), 5.36 (d, J = 4.5 Hz, 1H), 4.95 (t, J = 5.9 Hz, 1H), 4.59 (ABq, J = 14 Hz, 1H), 4.44 (Abq, J = 14 Hz, 1H), 4.22 (d, J = 8.0 Hz, 1H), 3.73−3.69 (m, 1H), 3.42 (d, J = 15.9 Hz, 1H), 2.82 (d, J = 16.3 Hz, 1H), 2.63 (t, J = 4.7 Hz, 1H), 2.22−2.18 (m, 1H), 2.04 (s, 3H), 1.91 (s, 3H); ^{13}C NMR δ 169.9, 169.7, 138.0, 128.4, 127.9, 127.7, 126.5, 125.8, 77.5, 77.0, 76.6, 76.4, 76.1, 71.0, 70.7, 64.9, 59.3, 51.9, 20.7; HRMS (FAB) m/z 346.1650 (M + 1) (calcd for $C_{19}H_{24}NO_5$ 346.1654).

Conversion of 66 to (−)-Swainsonine (59). A solution of **66** (25 mg, 0.072 mmol) in 2 mL of CH_3OH containing $PdCl_2$ (9.7 mg, 0.055 mmol) was stirred under a H_2 atmosphere for 1 h, filtered through Celite, and concentrated in vacuo. A solution of the residue in 6 mL of 3 N HCl/THF (1:1) was stirred at 25 °C for 24 h and extracted with ether. Concentration of the ether extracts provided a residue that was subjected to ion-exchange chromatography (Dowex 1-X8, OH^- form, 100−200 mesh, eluting with water) to yield 10 mg (80%) of (−)-swainsonine (**59**) as a solid; mp 139−140 °C [lit.[22] mp 141−143 °C]; $[\alpha]^{25}_D$ −60 (c 0.84, MeOH) [lit.[21] $[\alpha]^{25}_D$ −71 (c 0.56, MeOH)]; HRMS (FAB) m/z 174.1128 (M + 1) (calcd for $C_8H_{16}NO_3$ 174.1130). The ^{1}H NMR and ^{13}C NMR spectra of the synthetic material matched those reported earlier.[21]

Conversion of 67 to (−)-2-Episwainsonine (68). A solution of **67** (26 mg, 0.074 mmol) in 2 mL of ethanol containing 10% Pd/C (12 mg, 0.011 mmol) was stirred under a H_2 atmosphere at 25 °C for 2 h, filtered through Celite, and concentrated in vacuo to provide 24 mg (93%) of the reduced product, which was used in the next step without further purification; $[\alpha]^{25}_D$ −27 (c 0.48, $CHCl_3$); ^{1}H NMR δ 7.31−7.24 (m, 5H), 5.36 (d, J = 4.2 Hz, 1H), 4.89 (t, J = 6.3 Hz, 1H), 4.5 (ABq, J = 14 Hz, 1H), 4.37 (Abq, J = 14 Hz, 1H), 3.67 (t, J = 9.4 Hz, 1H), 3.54−3.51 (m, 1H), 3.0 (d, J = 10.3 Hz, 1H), 2.3−2.1 (m, 2H), 2.07 (s, 3H), 1.95 (s, 3H), 1.76−1.72 (m, 1H), 1.58−1.54 (m, 1H), 1.23−1.18 (m, 1H); ^{13}C NMR δ 169.9, 169.7, 138.1, 128.3, 127.7, 127.6, 76.7, 76.6, 73.1, 70.5, 69.1, 59.9, 52.0, 29.4, 23.5, 20.8, 20.7; HRMS (FAB) m/z 348.1813 (M + 1) (calcd for $C_{19}H_{26}NO_5$ 348.1811).

A solution of the reduction product (20 mg, 0.057 mmol) in 2 mL of CH_3OH containing $PdCl_2$ (8 mg, 0.045 mmol) was stirred under a H_2 atmosphere at 25 °C for 1 h, filtered through Celite, and concentrated in vacuo. A solution of the residue in 6 mL of 3 N HCl/THF (1:1) was stirred at 25 °C for 48 h and washed with ether. Concentration of the aqueous layer provided a residue that was subjected to ion-exchange chromatography (Dowex 1-X8, OH form, 100−200 mesh, eluting with water) to yield 7 mg (68%) of (−)-2-episwainsonine (**68**) as a solid; mp 168−169 °C [lit.[23] mp 169.5−172 °C], $[\alpha]^{25}_D$ −35 (c 0.61, MeOH) [lit.[23] $[\alpha]^{25}_D$ −61 (c 0.12, absolute EtOH)]; HRMS (FAB) m/z 174.1130 (M + 1) (calcd for $C_8H_{16}NO_3$ 174.1130). ^{1}H NMR spectroscopic data for this substance matches those previously reported.[24] ^{13}C NMR data not previously reported are as follows: δ 78.0, 77.5, 72.5, 66.9, 61.4, 52.6, 33.3, 24.1.

Acknowledgment. These studies were conducted with financial support provided by the National Institutes of Health (GM-27251). We thank Professor Robert Grubbs for providing us with information about possible factors governing the regiochemical course of RRM reactions.

Supporting Information Available: General experimental information, ^{1}H and ^{13}C NMR spectra for **14**−**16**, **18**, **20**−**26**, **28**−**43**, and **66**−**68**, and a summary of crystallographic parameters for **36**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO040226A

(24) The ^{1}H NMR spectrum of **68** was kindly provided by C. Adams.