JOC Article
pubs.acs.org/joc

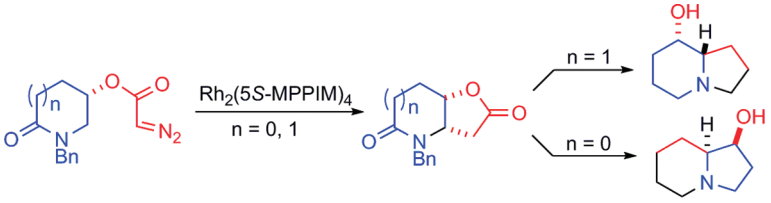
Nonracemic Bicyclic Lactam Lactones via Regio- and *cis*-Diastereocontrolled C−H Insertion. Asymmetric Synthesis of (8*S*,8a*S*)-Octahydroindolizidin-8-ol and (1*S*,8a*S*)-Octahydroindolizidin-1-ol

Andrew G. H. Wee,* Gao-Jun Fan, and Hypolite M. Bayirinoba

Department of Chemistry and Biochemistry, University of Regina, Regina Saskatchewan, S4S 0A2, Canada

andrew.wee@uregina.ca

Received August 18, 2009



The Rh_2(MPPIM)$_4$-catalyzed intramolecular C−H insertion reaction of (*S*)- and (*R*)-1-benzyl-5-(α-diazoacetoxy)piperidin-2-one and (*S*)-1-benzyl-4-(α-diazoacetoxy)pyrrolidin-2-one proceeds with high regioselectivity and *cis*-diastereoselectivity to give good yields of chiral nonracemic bicyclic lactam lactones (BLLs). For (*S*)- and (*R*)-1-benzyl-5-(α-diazoacetoxy)piperidin-2-one, the regio selectivity of the C−H insertion is catalyst-dependent; for example, (*S*)-1-benzyl-5-(α-diazoacetoxy)piperidin-2-one undergoes C−H insertion at C-6 preferentially when Rh_2(5*S*-MPPIM)$_4$ is used, but with Rh_2(5*R*-MPPIM)$_4$, C−H insertion occurs preferentially at C-4. This effect is not observed in the reaction of (*S*)-1-benzyl-4-(α-diazoacetoxy)pyrrolidin-2-one. The utility of the BLLs as chiral building blocks in alkaloid synthesis is exemplified by the synthesis of (8*S*,8a*S*)-octahydroindolizidin-8-ol and (1*S*,8a*S*)-octahydroindolizidin-1-ol.

Introduction

The piperidine and pyrrolidine moieties are found as core structures or as subfeatures in many structurally diverse and stereochemically interesting alkaloids isolated from marine and terrestrial plants and animals.[1] Many of the alkaloids also possess potent and therapeutically interesting biological activities, which has led to their use as drug candidates or as lead compounds in new drug designs.[2] A wide range of synthetic methods for the stereoselective construction of functionalized piperidine and pyrrolidine derivatives have been developed.[1a,b,3] Among these, methods based on *N*-acyliminium ion cyclization,[4] intramolecular cyclization reactions (S_N2,[5] reductive amination,[1b,3] carboamination[6]), imino Diels−Alder[7] and 1,3-dipolar nitrone[8] cycloaddition, ring closing metathesis,[9] and the use of N-heterocyclic intermediates[10] are the most widely studied. In spite of the

(1) (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139. (b) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773. (c) Garraffo, H. M.; Caceres, J.; Daly, J. W.; Spande, T. F.; Andriamaharavo, N. R.; Andriantsiferana, M. *J. Nat. Prod.* **1993**, *56*, 1016. (d) Attygalle, A. B.; Morgan, E. D. *Chem. Soc. Rev.* **1984**, *13*, 245.

(2) (a) Kishore, N.; Mishra, B. B.; Tripathi, V.; Tiwari, V. K. *Fitoterapia* **2009**, *80*, 149. (b) Pearson, M. S. M.; Mathe-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, 2159. (c) Vilsmaier, E. *J. Prakt. Chem.* **2000**, *342*, 218.

(3) (a) Vanecko, J. A.; West, F. G. *Heterocycles* **2007**, *74*, 125. (b) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (c) Yoda, H. *Curr. Org. Chem.* **2002**, *6*, 223. (d) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633.

(4) (a) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339. (b) Maryanoff, B. E.; Zhang, H. C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431. (c) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311. (d) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

(5) Cai, G. R.; Zhu, W.; Ma, D. W. *Tetrahedron* **2006**, *62*, 5697.

(6) (a) Aillaud, I.; Collin, J.; Hannedouche, J.; Schulz, E. *Dalton Trans.* **2007**, 5105. (b) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367.

(7) (a) Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721. (b) Caballero, E.; Figueroa, J.; Puebla, P.; Pelaez, R.; Tome, F.; Medarde, M. *Eur. J. Org. Chem.* **2008**, 4004.

(8) (a) Holmes, A. B.; Bourdin, B.; Collins, I.; Davison, E. C.; Rudge, A. J.; Stork, T. C.; Warner, J. A. *Pure Appl. Chem.* **1997**, *69*, 531. (b) Li, X. L.; Zhu, Z. G.; Duan, K. F.; Chen, H.; Li, Z. W.; Li, Z.; Zhang, P. Z. *Tetrahedron* **2009**, *65*, 2322. (c) Stecko, S.; Solecka, J.; Chmielewski, M. *Carbohydr. Res.* **2009**, *344*, 167.

(9) (a) Felpin, F. X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693. (b) Pavlyuk, O.; Teller, H.; McMills, M. C. *Tetrahedron Lett.* **2009**, *50*, 2716. (c) Muroni, D.; Mucedda, M.; Saba, A. *Tetrahedron Lett.* **2008**, *49*, 2373.

(10) (a) Toyooka, N.; Nemoto, H. *Studies in Natural Products Chemistry: Bioactive Natural Products* (*Part J*); Atta-ur-Rahman, Ed.; Elsevier: New York, 2003; Vol. 29, p 419. (b) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843. (c) Husson, H. P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383.

DOI: 10.1021/jo901790g Published on Web 10/07/2009

progress achieved to date, versatile and stereoselective routes are still highly desired.

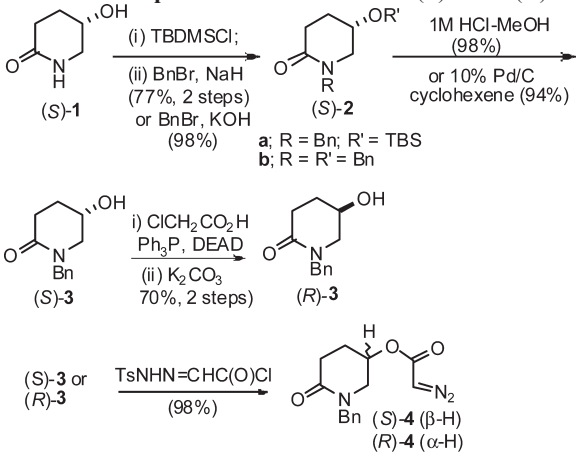
The Rh(II)-catalyzed intramolecular carbon−hydrogen insertion reaction continues to attract considerable attention due to the high levels of regio-, chemo-, and diastereoselectivity that can be achieved.[11] Over a decade ago, Doyle and co-workers reported[12] the intramolecular C−H insertion reactions of chiral nonracemic alkyl-substituted cyclohexyl diazoacetates catalyzed by chiral dirhodium(II) carboxamidates. The catalysts showed matched/mismatched relationship to the diazo substrates; $Rh_2(MEPY)_4$ and $Rh_2(MEOX)_4$ emerged as effective catalysts, which promoted highly regioselective C−H insertion into equatorial secondary and tertiary C−H bonds to give lactone products. The regioselectivity in $Rh_2(MPPIM)_4$-catalyzed reactions, however, was found to be substrate-dependent.[12] On the other hand, the regio- and diastereoselectivities of C−H insertion in equivalent heterocyclic diazoacetates have not been extensively examined. Previously, we showed[13] that the Rh(II)-carboxamidate-catalyzed C−H insertion of 3-(*N*-Cbz-pyrrolidinyl)diazoacetate did not exhibit a matched/mismatched relationship and also demonstrated the use of the method in the synthesis of the necine base, (−)-turneforcidine.

In keeping with our ongoing interest in the asymmetric synthesis of piperidine and pyrrolidine-containing alkaloids,[14] we needed access to functionalized, nonracemic building blocks that would permit the facile assembly of the wide variety of substituents and stereochemical diversity around the pyrrolidine and piperidine framework. We have investigated the rhodium(II)-catalyzed diazo decomposition of γ- and δ-lactam diazoacetates as a method for accessing functionalized nonracemic compounds and, herein, report the details of our study.[14a] We found that the C−H insertion reactions in both the γ- and δ-lactam diazoacetates were efficiently catalyzed by $Rh_2(MPPIM)_4$ catalysts to give bicyclic lactam lactones (BLLs) with high regioselectivity and excellent *cis*-diastereoselectivity. For the δ-lactam diazoacetate system, the regioselectivity of the C−H insertion exhibited a unique matched/mismatched relationship with $Rh_2(MPPIM)_4$, which was not observed for the γ-lactam diazoacetate system. We have demonstrated the synthetic utility of the functionalized BLLs in the synthesis of select alkaloids, and in this report, we also detail the synthesis of two indolizidine alkaloids, (8*S*,8a*S*)-octahydroindolizidin-8-ol and (1*S*,8a*S*)-octahydroindolizidin-1-ol.

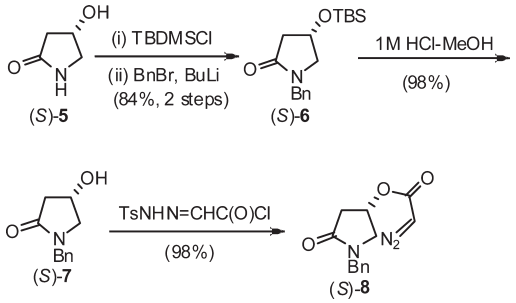
Results and Discussion

Preparation of δ- and γ-Lactam Diazoacetates: (*S*)-4, (*R*)-4, and (*S*)-8. The known[15a] lactam alcohol (*S*)-**1** was converted to (*S*)-**3** using two different routes. The first, higher yielding route involved silylation (TBSCl) and N-benzylation to give (*S*)-**2a** followed by acid-mediated desilylation to obtain (*S*)-**3** in 77% yield over two steps (Scheme 1). The second route involved N,O-dibenzylation[15b] of (*S*)-**1** to provide (*S*)-**2b**, which was then selectively O-debenzylated under catalytic transfer hydrogenation conditions[16] to give (*S*)-**3** in 67% overall yield. Inversion of configuration at C-5 in (*S*)-**3** via Mitsunobu reaction[17] ($ClCH_2CO_2H$, DEAD, Ph_3P) gave the corresponding chloroacetate, which was hydrolyzed to afford the enantiomeric alcohol (*R*)-**3**. Treatment of (*S*)-**3** and (*R*)-**3** with the House−Blankley reagent [TsNHN=CHC(O)Cl][18] provided the diazoacetates (*S*)-**4** and (*R*)-**4**.

SCHEME 1. Preparation of Diazoacetates (*S*)-4 and (*R*)-4



SCHEME 2. Preparation of Diazoacetate (*S*)-8

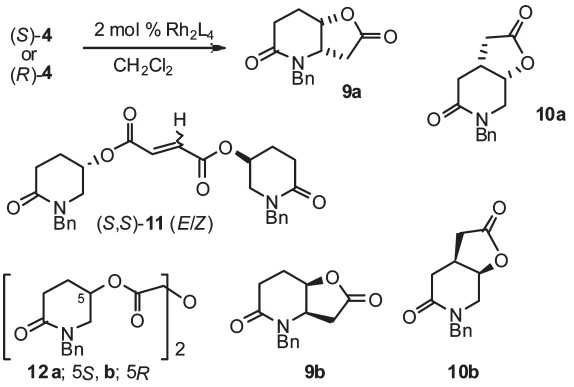


Informed by the preparation of (*S*)-**4**, we prepared γ-lactam diazoacetate (*S*)-**8** starting from commercially available (*S*)-**5**[19a] (Scheme 2) via O-silylation and N-benzylation to obtain (*S*)-**6**[19b] followed by O-desilylation under acidic conditions to afford the alcohol (*S*)-**7**[19b−d] in 82% overall yield. Subsequent treatment with House−Blankley reagent[18] proceeded efficiently to give the diazoacetate (*S*)-**8**.

Rh(II)-Catalyzed C−H Insertion Studies. The diazoacetate, (*S*)-**4**, was used to delineate optimal reaction conditions for C−H insertion reaction and to determine product distribution. In (*S*)-**4**, there are two likely sites, C-**4** and C-**6**, at which Rh(II)-carbenoid C−H insertion can occur. It was reasoned that the C-**4** methylene hydrogens would be electronically deactivated toward Rh(II)-carbenoid insertion

(11) Wee, A. G. H. *Curr. Org. Synth.* **2006**, *3*, 499.
(12) (a) Doyle, M. P.; Dyatkin, A. B.; Autry, C. I. *J. Chem. Soc., Perkin Trans. 1* **1995**, 619. (b) Doyle, M. P.; Dyatkin, A. B.; Roos, G. H. P.; Canas, F.; Pierson, D. A.; Vanbasten, A.; Muller, P.; Polleux, P. *J. Am. Chem. Soc.* **1994**, *116*, 4507.
(13) (a) Wee, A. G. H. *Tetrahedron Lett.* **2000**, *41*, 9025. (b) Wee, A. G. H. *J. Org. Chem.* **2001**, *66*, 8513.
(14) (a) Fan, G. J.; Wang, Z. Y.; Wee, A. G. H. *Chem. Commun.* **2006**, 3732. (b) Wee, A. G. H.; Fan, G. J. *Org. Lett.* **2008**, *10*, 3869.
(15) (a) Olsen, R. K.; Bhat, K. L.; Wardle, R. B.; Hennen, W. J.; Kini, G. D. *J. Org. Chem.* **1985**, *50*, 896. (b) N,O-Dibenzylation of rac-1, see: Herdeis, C. *Arch. Pharm.* **1983**, *316*, 719.
(16) Hanessian, S.; Liak, T. J.; Vanasse, B. *Synthesis* **1981**, 396.
(17) (a) But, T. Y. S.; Toy, P. H. *Chem. Asian J.* **2007**, *2*, 1340. (b) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127.
(18) (a) House, H. O.; Blankley, C. J. *J. Org. Chem.* **1968**, *33*, 53. (b) Corey, E. J.; Myers, A. G. *Tetrahedron Lett.* **1984**, *25*, 3559.
(19) (a) Purchased from Sigma Aldrich Chemical Co., USA. (b) Chang, D. L.; Witholt, B.; Li, Z. *Org. Lett.* **2000**, *2*, 3949. (c) Huang, P. Q.; Zheng, X. A.; Wang, S. L.; Ye, J. L.; Jin, L. R.; Chen, Z. *Tetrahedron: Asymmetry* **1999**, *10*, 3309. (d) Inagaki, S.; Shitara, H.; Hirose, T.; Nohira, H. *Enantiomer* **1998**, *3*, 187.

TABLE 1. Rh(II)-Catalyzed Reaction of Diazoacetates (*S*)-4 and (*R*)-4



entry	diazo	Rh_2L_4[a]	yield (%)[c]	relative yield (%) **9a**/**b**:**10a**/**b**	% **11**[d] (*E*:*Z*)[e]	% **12a**/**b**[d]
1	(*S*)-**4**	$Rh_2(OAc)_4$[b]	0	0	20 (1:2.5)	0
2	(*S*)-**4**	$Rh_2(OAc)_4$	6	100:0	14 (1:1)	21
3	(*S*)-**4**	Rh_2(*S*-PTTL)$_4$	28	100:0	11 (1:3)	0
4	(*S*)-**4**	$Rh_2(cap)_4$[b]	5	100:0	50 (1:2.4)	21
5	(*S*)-**4**	$Rh_2(cap)_4$	11	100:0	64 (1:3)	23
6	(*S*)-**4**	Rh_2(5*S*-MEPY)$_4$	45	100:0	28 (1:3.1)	13
7	(*S*)-**4**	Rh_2(5*R*-MEPY)$_4$	14	100:0	12 (1:3)	3
8	(*S*)-**4**	Rh_2(4*S*-MEOX)$_4$	44	100:0	28 (1:3.1)	9
9	(*S*)-**4**	Rh_2(4*R*-MEOX)$_4$	39	42:58	0	12
10	(*S*)-**4**	Rh_2(4*S*-MPPIM)$_4$	87	100:0	0	3
11	(*S*)-**4**	Rh_2(4*R*-MPPIM)$_4$	86	17:83	0	10
12	(*R*)-**4**	Rh_2(4*S*-MPPIM)$_4$	84	20:80	0	14
13	(*R*)-**4**	Rh_2(4*R*-MPPIM)$_4$	85	100:0	0	4

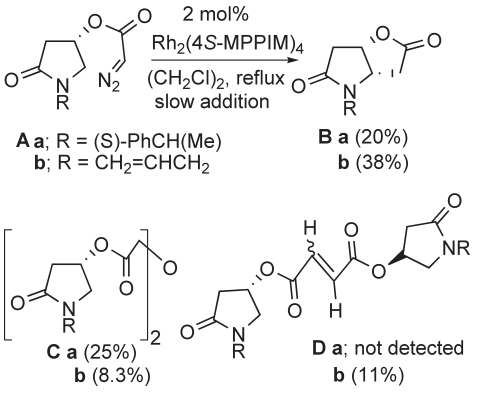
[a]Reaction conducted under argon in refluxing CH_2Cl_2, unless otherwise stated, using 2 mol % of Rh(II) catalyst. [b]Reaction conducted at 25 °C. [c]Combined isolated yields of **9a**; **10a** or **9b**; **10b**. [d]Based on isolated yields of (*S*,*S*)-**11** or **12a**,**b**. [e]Ratio of *Z*:*E* isomers was based on the integration of the singlets due to the olefinic hydrogens centered at δ 6.12 (*Z*) and δ 6.64 (*E*).

because they are located β to the amide carbonyl group,[20] whereas the C-6 methylene hydrogens are activated by the amide nitrogen[21] and metallocarbenoid insertion at C-6 to give **9a** should be favored. Another potential Rh(II)-carbenoid insertion site is at the C-5-methine to give a β-lactone product; however, we considered this would represent a very minor pathway, if it were to occur, because of ring strain. We examined the reaction of (*S*)-**4** with both achiral and chiral Rh(II) carboxylate and carboxamidate catalysts,[22a] and the results are collected in Table 1.

In general, it was found that chiral Rh(II) catalysts were better than achiral ones at promoting C−H insertion reaction. Carbon−hydrogen insertion was inefficient with $Rh_2(OAc)_4$ as catalyst; at rt, neither **9a** nor **10a** was detected. When the reaction was conducted at reflux, a very low yield (6%) of **9a** was obtained. The main products formed were the olefin dimers **11** and the ether product **12a**, arising from interception of the Rh(II)-carbenoid by adventitious water (entries 1 and 2). The use of the chiral Rh(II) carboxylate, Rh_2(*S*-PTTL)$_4$, gave a 28% yield of **9a**, which was an improvement over that achieved with $Rh_2(OAc)_4$. The dimers **11** were still formed, but ether **12a** was not detected (entry 3). In all of the cases examined, the regioisomeric C−H insertion product **10a** and the β-lactone product were not detected.

The use of the less electrophilic $Rh_2(cap)_4$ either at rt or reflux did not favor the C−H insertion pathway, and low yields of **9a** were obtained (entries 5 and 6). The preferred reaction pathway was dimerization of the Rh(II)-carbenoid to form **11**, and this was also accompanied by the formation of **12a**. We next evaluated the effectiveness of three enantiomeric pairs of Rh(II) carboxamidates to catalyze the C−H insertion of (*S*)-**4**. With Rh_2(5*S*-MEPY)$_4$, a modest but

(20) Stork, G.; Nakatani, K. *Tetrahedron Lett*. **1988**, *29*, 2283.
(21) Wee, A. G. H.; Duncan, S. C. *J. Org. Chem*. **2005**, *70*, 8372.
(22) (a) Rh_2(*S*-PTTL)$_4$: Dirhodium(II) tetrakis[(S)-N-phthaloyl-tert-leucinate]; for the full names of the Rh(II) carboxamidates, see ref 13b. (b) At this time, it appears that the N-benzyl protecting group is optimal for efficient C−H insertion. We have examined the C−H insertion of the N-(α-methyl)benzyl and N-allyl lactams **Aa,b** catalyzed by Rh_2(5*S*-MPPIM)$_4$ under identical conditions (slow addition, refluxing $(CH_2Cl)_2$) to that used for (*S*)-8. We found that the yields of the C−H insertion products **Ba,b** are markedly lower, and ether products **Ca,b** were also obtained. The dimer **Db** was also formed in the reaction of **Ab** but was not detected in the reaction of **Aa**.



Other effects of the influence of azacyclic N-protecting group on the efficiency of reactions have been noted. See for example: Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J.; Pflum, D. A.; Petsch, D. T. *J. Am. Chem. Soc*. **1997**, *119*, 9641.

encouraging 45% yield of only **9a** was obtained, although the dimers **11** were still formed in appreciable amounts along with **12a** (entry 6). The enantiomeric Rh_2(5*R*-MEPY)$_4$ gave a significantly lower yield of **9a** (14%), and again, **10a** was not detected (entry 7). The yield of **9a** was comparable to that achieved using Rh_2(cap)$_4$ (compare entries 5 and 7), but the yields of the dimer and ether products were substantially lower.

The results from the reactions catalyzed by the enantiomeric sets of Rh_2(MEOX)$_4$ and Rh_2(MPPIM)$_4$ were especially interesting and displayed important differences from those obtained from the previous two chiral catalysts, Rh_2(*S*-PTTL)$_4$ and Rh_2(5*R* or 5*S*-MEPY)$_4$. Although the results obtained for Rh_2(4*S*-MEOX)$_4$ mirrored that of Rh_2(5*S*-MEPY)$_4$ (compare entries 6 and 8), the reaction catalyzed by Rh_2(4*R*-MEOX)$_4$ gave a 1:1.1 ratio of **9a**/**10a** (entry 9) and in a combined yield of 39%. Further, olefin dimers **11** were not observed.

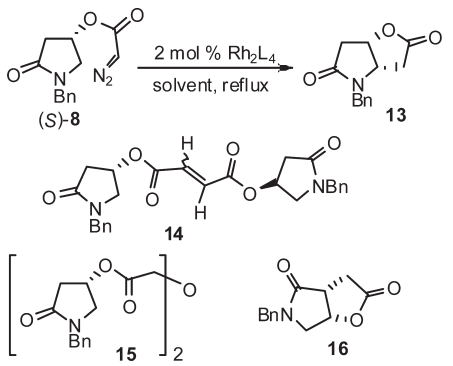
The use of the hindered Rh_2(4*S*-MPPIM)$_4$ resulted in a high yield (87%) of **9a**, without dimer formation (entry 10). More importantly, the regioisomer **10a** was not detected. With Rh_2(4*R*-MPPIM)$_4$, the yield of **9a** depreciated significantly (entry 11), and the regioisomeric **10a** was now obtained as the major product in synthetically good yield (71%). This outcome was confirmed by the Rh_2(MPPIM)$_4$-catalyzed reaction of (*R*)-**4**. Thus, Rh_2(4*R*-MPPIM)$_4$ gave a high yield (85%) of only **9b** (entry 13), whereas with Rh_2(4*S*-MPPIM)$_4$, a 17% yield of **9b** was realized and the yield of the regioisomer **10b** was 68% (entry 12). In these reactions, dimer formation was not observed and formation of the ethers **12a**,**b** was a minor pathway.

The overall results show that the optimal catalyst for achieving high regioselectivity in the formation of bicyclic lactam lactones **9** is the use of Rh_2(MPPIM)$_4$; (*S*)-**4**/Rh_2(4*S*-MPPIM)$_4$ and (*R*)-**4**/Rh_2(4*R*-MPPIM)$_4$ represent the matched pairs for regioselective C−H insertion reaction. It is also interesting to note that the regioisomeric **10a**,**b** are also useful chiral nonracemic synthetic intermediates and are readily accessible via the use of the mismatched sets, that is, (*S*)-**4**/Rh_2(4*R*-MPPIM)$_4$ and (*R*)-**4**/Rh_2(4*S*-MPPIM)$_4$.

It is also evident from the results above that dimer formation is very competitive with C−H insertion. There is also a preference for the formation of the (*Z*)-**11** over the (*E*)-**11** (entries 1, 3−8). The interception of the metallocarbenoid by adventitious water is a minor pathway, and interestingly, the yields of ether **12a** (or **12b**) obtained for each of the enantiomeric sets of chiral Rh(II) carboxamidates were found to be invariable between sets. Also, in the *matched* reactions, the yields of ether **12a**,**b** were lower than those in the mismatched reactions (compare entries 10 and 13 with 11 and 12, respectively).

Next, the effect of a smaller ring size on the efficiency and regioselectivity of C−H insertion reaction (Table 2) was investigated using the γ-lactam diazoacetate, (*S*)-**8**,[22b] and the enantiomeric sets of Rh_2(MEOX)$_4$ and Rh_2(MPPIM)$_4$. It is clear from Table 2 that the C−H insertion reaction also proceeded with excellent *cis*-diastereoselectivity and high regioselectivity. Further, reaction temperature has a definite influence on the efficiency of the reaction; in refluxing CH_2Cl_2, which was found to be effective in the δ-lactam case (vide supra), poor to moderate yields of the C−H insertion product **13** were obtained. For the *S*-configurated

TABLE 2. Rh(II)-Catalyzed Reaction of (*S*)-8



entry	Rh_2L_4	solvent, temp °C	% **13**[a]	% **14**[a] (*E*:*Z*)[b]	% **15**[a]
1	Rh_2(4*S*-MEOX)$_4$	CH_2Cl_2, 45	17	20 (1:11)	21
2	Rh_2(4*R*-MEOX)$_4$	CH_2Cl_2, 45	6	11 (1:33)	13
3	Rh_2(4*S*-MPPIM)$_4$	CH_2Cl_2, 45	51	20 (2.4:1)	28
4	Rh_2(4*R*-MPPIM)$_4$	CH_2Cl_2, 45	0	30 (1.5:1)	37
5	Rh_2(4*S*-MPPIM)$_4$	$(CH_2Cl)_2$, 83	70	7 (*E* only)	11
6	Rh_2(4*R*-MPPIM)$_4$	$(CH_2Cl)_2$, 83	0	0	19

[a]Isolated yields of **13**, **14**, and **15**. For entry 6, the remaining material balance consisted of intractable polar mixtures. [b]Ratio of *Z*:*E* isomers was based on the integration of the singlets for the olefinic hydrogens centered at δ 6.23 (*Z*) and δ 6.78 (*E*).

catalysts, Rh_2(4*S*-MEOX)$_4$ and especially Rh_2(4*S*-MPPIM)$_4$ (entries 1 and 3), better yields of **13** were obtained, whereas the corresponding *R*-catalysts (entries 2 and 4) led either to a poor yield of **13** or no formation of product. A significantly higher yield (70%) of **13** was realized when the Rh_2(4*S*-MPPIM)$_4$-catalyzed reaction of (*S*)-**8** was conducted in refluxing dichloroethane (compare entries 3 and 5). Unlike the δ-lactam system, (*S*)-**4** (vide supra), the Rh_2(4*R*-MPPIM)$_4$-catalyzed reaction of (*S*)-**8** did not give the regioisomer **16**; a modest yield of the ether **15** was formed along with major amounts of uncharacterizable mixture of products.

The data from entries 1−5 (Table 2) indicated that the formation of dimer **14** and ether **15** was very competitive with the desired C−H insertion to form **13**. Moreover, it is interesting to note that, with Rh_2(MEOX)$_4$, there was a strong preference for (*Z*)-**14** over (*E*)-**14** (entries 1 and 2), whereas for the Rh_2(MPPIM)$_4$ catalysts, (*E*)-**14** was preferred over (*Z*)-**14** (entries 3 and 4).

Reaction Conformers and Product Formation. To understand the formation of the BLL-**9** and its regioisomer **10**, we will use the Rh_2(4*S* and 4*R*-MPPIM)$_4$-catalyzed reaction of (*S*)-**4** as an example. We envisioned the formation of the bicyclic δ-lactam lactones **9a** and **10a** to proceed via the rapidly interconverting reaction conformers,[23] **A**, **A′** and **B**, **B′**, depicted in Figure 1. In the half-chair conformers **A** and **B′**, the Rh(II)-carbenoid moiety is oreinted in the pseudoaxial position, and in **B** and **A′**, the Rh(II)-carbenoid unit is pseudoequatorial.

The generally accepted view for C−H insertion reaction is that the Rh(II)-carbenoid intermediate has to adopt an

(23) The minimum energy conformation about the Rh(II)-carbene carbon bond is based on: Doyle, M. P.; Winchester, W. R.; Hoorn, J. A. A.; Lynch, V.; Simonsen, S. H.; Ghosh, R. *J. Am. Chem. Soc.* **1993**, *115*, 9968. (b) AM1 calculations (PC Spartan Pro, v.6.0.6) were performed on the δ-lactams with a pseudoaxial and pseudoequatorial diazoacetyl unit: ΔH_f (axial)=−31.822 kcal/mol, ΔH_f (equatorial)=−32.164 kcal/mol.

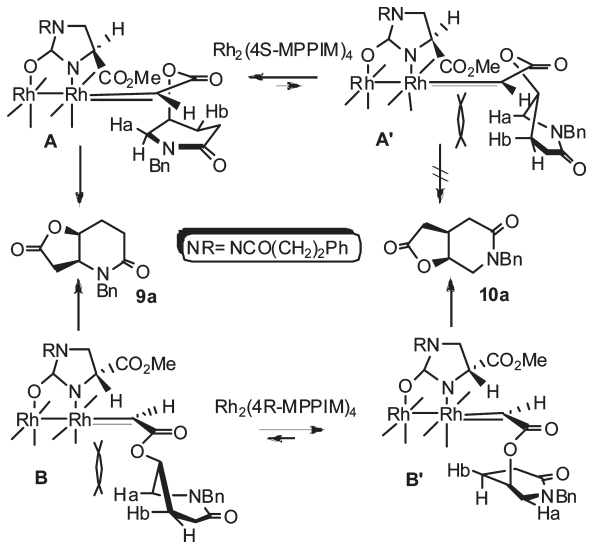


FIGURE 1. C−H insertion reaction conformers of $Rh_2(MPPIM)_4$-carbenoid derived from (*S*)-**4**.

arrangement wherein the Rh(II)-carbenoid bond and the target C−H σ-bond are aligned parallel to each other.[24] This would allow for the proper trajectory required for the interaction of the vacant p-orbital of the carbenoid carbon with the σ-orbital of the C−H bond. Further, the degree of interaction depends on the "electron-richness" of the C−H bond. For a less electron-rich C−H bond, the interaction occurs farther along the reaction coordinate, which would involve a more compact transition state (TS). On the other hand, for a more electron-rich C−H bond, the interaction occurs earlier along the reaction coordinate, which would involve in a less compact (open) TS.[21]

For the *matched* $Rh_2(4S\text{-MPPIM})_4$-catalyzed reaction, the two reactive conformers, **A** and **A′**, are involved. In **A**, metallocarbenoid insertion into C−Ha is geometrically favored and is also facilitated by the greater nucleophilicity of the σ-bond (early TS) due to the activating influence of the amide nitrogen atom. However, insertion of the metallocarbenoid into C−Hb is prevented from occurring because the C−Hb σ-bond and the Rh(II)-carbenoid bond cannot adopt the proper alignment. Reactive conformer **A′** is destabilized by the close interaction of the pseudoaxial C−Ha and C−Hb σ-bonds with the ligand wall of the Rh(II) catalyst and especially between C−Hb and the NR moiety [NR=NC(O)$(CH_2)_2$Ph)] of the ligand. Therefore, preferential C−H insertion occurs via **A** to give the observed **9a**.

In the *mismatched* $Rh_2(4R\text{-MPPIM})_4$-catalyzed reaction, reactive conformer **B** is destabilized by the interaction of the pseudoaxial C−Ha and C−Hb with the ligand wall and especially between C−Ha and the NR unit. However, because C−Ha is activated by the amide nitrogen, its interaction with the vacant p-orbital of the Rh(II)-carbenoid carbon can occur at a greater distance (early TS), resulting in the formation of the minor product, **9a**. On the other hand, in **B′**, the metallocarbenoid bond and the C−Hb bond are

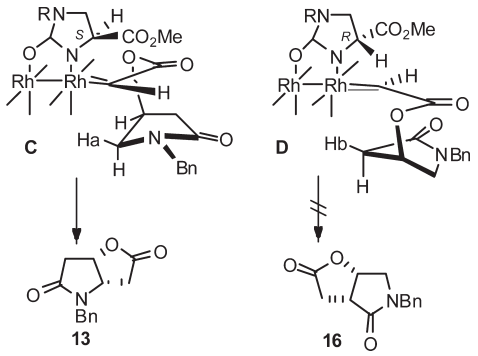


FIGURE 2. C−H insertion reaction conformers of $Rh_2(MPPIM)_4$-carbenoid derived from (*S*)-**8**.

properly aligned for insertion reaction to occur to provide **10a** as the major product; insertion into C−Ha, as was with C−Hb in **A**, is geometrically disfavored.

In the reaction of (*S*)-**8**, catalyzed by $Rh_2(4S\text{-MPPIM})_4$, C−H insertion is envisaged to occur via an envelope-like reaction conformer, **C** (Figure 2). The amide N-activated C−Ha bond has the correct alignment to the Rh(II)-carbenoid bond, and C−H insertion results in the formation of the BLL-**13**. With $Rh_2(4R\text{-MPPIM})_4$, the reaction conformer **D** is envisioned. Although C−Hb and the Rh(II)-carbenoid bond in **D** have the proper alignment for insertion, the C−Hb bond is deactivated toward metallocarbenoid C−H insertion by the amide carbonyl group. Consequently, the regiosiomer **16** was not formed. This outcome taken in context with the result from the $Rh_2(4R\text{-MPPIM})_4$-catalyzed reaction of (*S*)-**4** to form **10a** indicated that C−H bonds located α to an amide carbonyl group are more deactivated compared to those that are located β to the amide carbonyl unit. This observation is in accord with those made by Stork regarding the deactivating influence of the ester group on C−H bonds located α and β to the ester group.[20] It is also clear that, in the reaction of the γ-lactam diazoacetate (*S*)-**8**, the matched/mismatched relationship that was observed in the δ-lactam diazoacetate (*S*)-**4** [or (*R*)-**4**] does not apply.

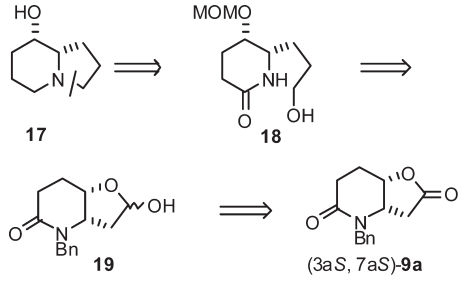
Synthesis of (8*S*,8a*S*)-Octahydroindolizidin-8-ol (17) and (1*S*,8a*S*)-Octahydroindolizidin-1-ol (22). The nonracemic BLLs have several attributes that are particularly advantageous for their application in alkaloid synthesis. The inherent functionalities of the BLLs facilitate the ready modification of their carbon framework and for the installation of additional substituents. Further, their *cis*-fused bicyclic structures afford practical stereocontrol over reactions conducted on the BLLs. To demonstrate the utility of BLLs, **9a** and **13**, we detail below the syntheses of (8*S*,8a*S*)-octahydroindolizidin-8-ol (**17**) and (1*S*,8a*S*)-octahydroindolizidin-1-ol (**22**). The successful syntheses of alkaloids **17** and **22** also serves to confirm the absolute configuration of C-3a, C-7a in **9a** and of C-3a, C-6a in **13**.

Indolizidine (17). Several reports have described the synthesis of (±)-**17**,[25a−d] and to date, only one[25e] asymmetric synthesis of (8*S*,8a*S*)-**17** has been reported. Our retrosynthetic

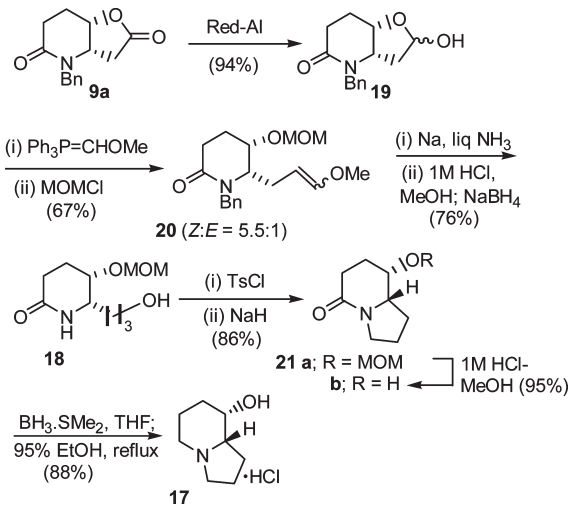
(24) Trajectory for C−H insertion: (a) Taber, D. F.; You, K. K.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547. (b) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958. (c) Yoshikai, N.; Nakamura, E. *Adv. Synth. Catal.* **2003**, *345*, 1159. (d) Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 7181.

(25) (a) Barton, D. H. R.; Pereira, M.; Taylor, D. K. *Tetrahedron Lett.* **1994**, *35*, 9157. (b) Bond, T. J.; Jenkins, R.; Ridley, A. C.; Taylor, P. C. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2241. (c) Shono, T.; Matsumura, Y.; Tsubata, K.; Inoue, K.; Nishida, R. *Chem. Lett.* **1983**, 21. (d) Rader, C. P.; Young, R. L.; Aaron, H. S. *J. Org. Chem.* **1965**, *30*, 1536. (e) Lee, H. K.; Chun, J. S.; Pak, C. S. *J. Org. Chem.* **2003**, *68*, 2471.

SCHEME 3. Retrosynthesis of Indolizidine 17



SCHEME 4. Synthesis of Indolizidine (8*S*,8a*S*)-17

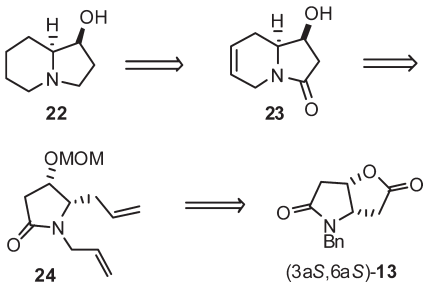


analysis of **17** (Scheme 3) suggested that the indolizidine framework can be formed via the precursor **18**, which in turn can be derived from the bicyclic lactol **19**; compound **19** is to be prepared from BLL-**9a**.

Our synthesis began with the chemoselective reduction of **9a** with Red-Al to provide an excellent yield of the bicyclic lactam lactol **19** (Scheme 4). Wittig olefination using (methoxymethylene)triphenylphosphorane followed by MOM protection of the secondary alcohol gave the ether **20**. N-Debenzylation (Na, NH_3) was followed by selective acid hydrolysis of the enol ether and sodium borohydride reduction to give the primary alcohol **18** in an overall yield of 76%. Tosylation of **18** and subsequent treatment of the primary tosylate with sodium hydride resulted in intramolecular cyclization to afford the bicyclic lactam **21a** in 86% yield. Deprotection of the MOM ether in **21a** followed by reduction of the lactam group using excess $BH_3 \cdot SMe_2$ initially gave a very stable, nonpolar **17**-borane complex as a white solid.[26] The volatile indolizidine **17** was obtained only after refluxing the **17**-borane complex in 95% ethanol for 24 h. Compound (8*S*,8a*S*)-**17** was purified (Dowex 50x2-400, H^+ form) and characterized as its hydrochloride salt ($[\alpha]^{22}_D$ +12.5 (*c* 0.60, CH_3OH).

Indolizidine (22). Interest in the synthesis of compound **22** stems from it being one of the intermediates that is involved in the biosynthesis of hydroxylated indolizidines such as swainsonine and slaframine.[27] Four asymmetric syntheses[28] and one involving resolution of racemic **22**[27] have been reported. The retrosynthetic analysis of the indolizidine **22** (Scheme 5) suggested the unsaturated bicycle **23** as the precursor, which can be assembled via a ring closing metathesis (RCM) reaction of the diallyl γ-lactam **24** that can be obtained from BLL-**13**.

SCHEME 5. Retrosynthesis of Indolizidine 22



An obvious starting point is to use the γ-lactone moiety in **13** to install the C-4 hydroxy and C-5 allyl units, which is modeled along the chemistry that we have developed for the conversion of **9a** to **20** (Scheme 4). We found, however, that although reduction of BLL-**13** with Red-Al proceeded to give a good yield (70%) of the corresponding lactol the subsequent Wittig olefination using methylenetriphenylphosphorane was unsuccessful under a variety of reaction conditions examined. To circumvent this unexpected difficulty, an alternative approach based on Julia–Lythgoe-type[29] chemistry was investigated.

BLL-**13** was treated with methyl phenyl sulfone anion (Scheme 6) to afford an 80% yield of an inseparable mixture of diastereomeric lactols, which was reduced with $NaBH_4$ to the corresponding diol followed by diacetylation (Ac_2O, DMAP) to obtain **25**. The conversion of the β-acetoxy sulfone **25** to alkene **26a** was examined. Attempted reductive elimination using Mg/EtOH[30] in the presence of a catalytic amount of $HgCl_2$ did not yield the desired olefin **26a**, and only starting material was recovered.

With SmI_2 (0.1 M SmI_2/HMPA)[31] as the reductant, a 60% yield of **26a** was obtained as well as a minor amount (10%) of the vinylic sulfone **26b**.[32] It is useful to note that reductive

(26) This white solid product was reported (ref 25e) as the indolizidine **17**. However, the spectral data of the compound we obtained following the literature procedure indicated that this solid was in fact the indolizidine **17**·borane complex; its IR spectrum showed the following characteristic absorptions at ν_{max} (B–H): 2367 and 2320 cm^{-1}. ^1H NMR of this complex is identical to that reported (see Supporting Information).

(27) (a) Harris, C. M.; Harris, T. M. *Tetrahedron Lett*. **1987**, *28*, 2559. (b) Harris, T. M.; Harris, C. M.; Hill, J. E.; Ungemach, F. S.; Broquist, H. P.; Wickwire, B. M. *J. Org. Chem*. **1987**, *52*, 3094.

(28) (a) Pourashraf, M.; Delair, P.; Rasmussen, M. O.; Greene, A. E. *J. Org. Chem*. **2000**, *65*, 6966. (b) Sibi, M. P.; Christensen, J. W. *J. Org. Chem*. **1999**, *64*, 6434. (c) Green, D. L. C.; Kiddle, J. J.; Thompson, C. M. *Tetrahedron* **1995**, *51*, 2865. (d) Takahata, H.; Banba, Y.; Momose, T. *Tetrahedron: Asymmetry* **1990**, *1*, 763.

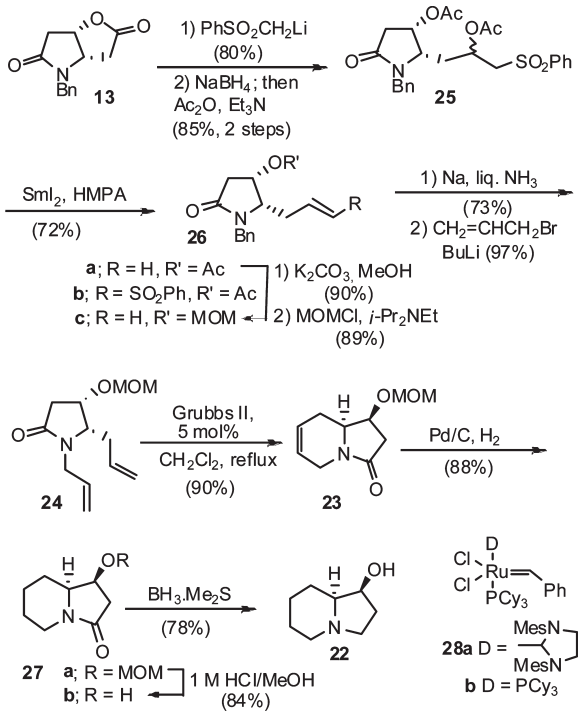
(29) (a) Julia, M.; Paris, J. M. *Tetrahedron Lett*. **1973**, 4833. (b) Kocienski, P. J.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1045.

(30) Lee, G. H.; Lee, H. K.; Choi, E. B.; Kim, B. T.; Pak, C. S. *Tetrahedron Lett*. **1995**, *36*, 5607.

(31) (a) Concellon, J. M.; Rodriguez-Solla, H. *Chem. Soc. Rev*. **2004**, *33*, 599. (b) Ihara, M.; Suzuki, S.; Taniguchi, T.; Tokunaga, Y.; Fukumoto, K. *Tetrahedron* **1995**, *51*, 9873.

(32) Compound **26b** showed the following data: IR ν_{max} 1740, 1695, 1584 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.78–7.90 (m, 2 H), 7.52–7.68 (m, 3 H), 7.15–7.35 (m, 5 H), 6.78 (ddd, *J*=15.1, 7.2, 7.2 Hz, 1 H), 6.25 (d, *J*=15.1 Hz, 1 H), 5.27–5.31 (m, 1 H), 4.88 (d, *J*=15.0 Hz, 1 H), 4.02 (d, *J*=15.2 Hz, 1 H), 3.78–3.86 (m, 1 H), 2.78 (dd, *J*=17.4, 7.5 Hz, 1 H), 2.50 (dd, *J*=17.7, 5.4 Hz, 1 H), 1.95–2.12 (m, 2 H),1.93 (s, 3 H). The characteristic resonances of the hydrogens of the vinylic sulfone occurred at δ 6.25 (d, *J*=15.1 Hz, 1 H) and δ 6.78 (ddd, *J*=15.1, 7.2, 7.2 Hz, 1 H).

SCHEME 6. Synthesis of Indolizidine (1*S*,8a*S*)-22



elimination did not occur when DMPU[33] was used instead of HMPA as the additive. Compounds **26a** and **26b** were readily separated, but vinylic sulfone **26b** was found to be contaminated by an uncharacterizable impurity that was difficult to remove in spite of repeated chromatography.

Next, the plan was to replace the acetyl group in **26a** with the MOM ether group, which would be more stable under the reducing (Na, NH_3) conditions for N-debenzylation. Thus, base hydrolysis of the acetate gave the corresponding secondary alcohol, which was then treated with MOMCl to obtain **26c** (80% over two steps). Birch reduction of **26c** gave the debenzylated γ-lactam, which was N-allylated to obtain the RCM precursor **24** in good overall yield (64% over two steps). Cyclization of **24** catalyzed by Grubbs II[34a−d] (**28a**) proceeded efficiently in refluxing CH_2Cl_2 and was complete within 1 h to give **23** in 90% yield; in comparison, the use of Grubbs I[34e,f] (**28b**) required 6 h for completion, but the yield of **23** was 95%.

The double bond in **23** was then hydrogenated (10% Pd/C, 2 atm H_2) in a Parr apparatus to afford **27a** in 88% yield. Acid hydrolysis of the MOM group in **27a** gave the hydroxy lactam **27b**, whose spectral and physical properties were in agreement with those reported by Greene et al.[28a] The alkaloid **22** was obtained after the reduction of the lactam carbonyl unit in **27b** with $BH_3 \cdot SMe_2$ complex. This compound was identical in all respects to the properties reported for **22** {$[\alpha]^{26}_D$ +19.2 (*c* 0.13, $CHCl_3$); lit.[28a] $[\alpha]^{22}_D$ +17.4 (*c* 0.4, $CHCl_3$)}.

(33) Pospisil, J.; Pospisil, T.; Marko, I. E. *Org. Lett.* **2005**, *7*, 2373.

(34) (a) Morgan, J. P.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 3153. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (c) Weskamp, T.; Kohl, F. J.; Hieringer, W.; Gleich, D.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2416. (d) Huang, J. K.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (e) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *Organometallics* **2001**, *20*, 5314. (f) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974.

Conclusions

$Rh_2(MPPIM)_4$ was found to be the best catalyst for effecting the intramolecular C−H insertion reaction of chiral nonracemic δ-lactam diazoacetate, (*S*)- and (*R*)-**4**, and the γ-lactam diazoacetate (*S*)-**8**. The C−H insertion proceeded efficiently, with excellent regioselectivity and *cis*-diastereoselectivity to give bicyclic lactam lactones (BLLs). The regioselectivity of the reaction in the δ-lactam diazoacetate was also found to be dependent on the chirality of the $Rh_2(MPPIM)_4$ catalyst; however, this effect was not observed in the γ-lactam diazoacetate. Reaction conformer models were proposed to explain the observed regioselectivity of the C−H insertion reaction. The use of BLL-**9a** and BLL-**13** in the synthesis of (8*S*,8a*S*)-octahydroindolizidin-8-ol (**17**, 9 steps, 34% overall yield) and (1*S*,8a*S*)-octahydroindolizidin-1-ol (**22**, 11 steps, 14.4% overall yield) nicely demonstrates the utility of the BLLs as chiral building blocks in alkaloid synthesis. Further studies in this area are in progress.

Experimental Section

General: Only diagnostic absorptions in the infrared spectrum are reported. Reported melting points are uncorrected. ^1H (200 or 300 MHz) and ^{13}C (50 or 75 MHz) NMR spectra were recorded in $CDCl_3$ unless stated otherwise. The residual $CHCl_3$ singlet at $\delta_H = 7.24$ and the $CDCl_3$ triplet centered at $\delta_C = 77.0$ were used as internal references for ^1H and ^{13}C NMR spectra, respectively. Where applicable, the positions of the signals of minor diastereomers are given within square brackets. High-resolution electron impact (70 eV) and chemical ionization mass spectral analyses were performed at the Chemistry Department, University of Saskatchewan, Canada. Optical rotations were recorded at the Na_D line using an Optical Activity (AA5) polarimeter. Reaction progress was monitored by thin-layer chromatography on Merck silica gel 60_{F254} precoated (0.25 mm) on aluminum-backed sheets. Air- and moisture-sensitive reactions were conducted under a static pressure of argon. All organic extracts were dried over anhydrous Na_2SO_4. Chromatographic purification implies flash column chromatography, which was performed on SiliaFlash 60 (230−400 mesh). Dichloromethane, 1,2-dichloroethane, dimethoxy ethane, chloroform, *N*,*N*-(diisopropyl)ethylamine, and acetonitrile were dried by distillation from calcium hydride. THF and diethyl ether were dried by distillation from sodium using sodium benzophenone ketyl as indicator.

General Procedure for Rh(II)-Catalyzed Reaction of (*S*)-4, (*R*)-4, and (*S*)-8. The appropriate Rh(II) catalyst (2 mol %) was dried under vacuum at 80 °C for 1 h and then cooled to rt. Dry CH_2Cl_2 (2 mL) was added, and the mixture was heated (oil bath) to reflux. A solution of the appropriate lactam diazoacetate (0.2 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise, via syringe pump, over a period of 1 h. After addition was complete, the mixture was refluxed for an additional 1 h and then cooled to rt. The solvent was removed under reduced pressure, and the crude product was purified by chromatography: For the δ-lactam diazoacetates, (*S*)-**4** and (*R*)-**4**: EtOAc/MeOH 10:1 and then 5:1 EtOAc/MeOH gave compounds **9a**,**b**, **10a**,**b**, **11**, and **12a**,**b**. For the γ-lactam diazoacetate (*S*)-**8**: 1:1 petroleum ether/EtOAc, EtOAc and then 10:1 EtOAc/MeOH gave subsequently compounds **13**, **14**, and **15**. See Tables 1 and 2 for details.

(3a*S*,7a*S*)-4-Benzyltetrahydrofuro[3,2-*b*]pyridine-2,5(3*H*,6*H*)-dione (9a): light yellow needles; mp 131−132 °C; $[\alpha]^{22}_D$ +50.0 (*c* 1.90, $CHCl_3$); IR ν_{max} 1778, 1642, 1202, 1166 cm^{-1}; ^1H NMR (300 MHz) δ 7.18−7.38 (m, 5 H), 5.28 (d, *J* = 15.0 Hz, 1 H), 4.84 (ddd, *J* = 3.7, 3.7, 7.0 Hz, 1 H), 4.11 (ddd, *J* = 3.4, 7.4, 7.4 Hz, 1 H), 3.97 (d, *J* = 15.0 Hz, 1 H), 2.75 (dd, *J* = 7.7, 18.1 Hz, 1 H),

2.45−2.68 (m, 3 H), 2.32 (ddd, J = 4.6, 9.1, 18.9 Hz, 1 H), 2.00 (dddd, J = 3.2, 5.0, 11.8, 14.8 Hz, 1 H); ^{13}C NMR (50 MHz) δ 173.9, 169.1, 135.9, 128.9, 128.0, 127.9, 75.6, 54.7, 47.5, 35.7, 26.5, 24.0; HRMS calcd for $C_{14}H_{15}NO_3$ 245.1052, found 245.1047.

(3a*R*,7a*R*)-4-Benzyltetrahydrofuro[3,2-*b*]pyridine-2,5(3*H*,6*H*)-dione (9b): light yellow oil, $[\alpha]^{22}_D$ −48.4 (*c* 1.60, $CHCl_3$); IR ν_{max} 1778, 1642, 1449, 1202, 1167 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.18−7.38 (m, 5 H), 5.28 (d, J = 15.0 Hz, 1 H), 4.84 (ddd, J = 3.7, 3.7, 7.0 Hz, 1 H), 4.11 (ddd, J = 3.4, 7.4, 7.4 Hz, 1 H), 3.97 (d, J = 15.0 Hz, 1 H), 2.75 (dd, J = 7.7, 18.1 Hz, 1 H), 2.45−2.68 (m, 3 H), 2.32 (ddd, J = 4.6, 9.1, 18.9 Hz, 1 H), 2.00 (dddd, J = 3.2, 5.0, 11.8, 14.8 Hz, 1 H); ^{13}C NMR (50 MHz) δ 173.9, 169.0, 135.9, 128.9, 128.0, 127.9, 75.5, 54.7, 47.5, 35.6, 26.4, 24.0; HRMS calcd for $C_{14}H_{15}NO_3$ 245.1052, found 245.1059.

(3a*R*,7a*S*)-6-Benzyltetrahydrofuro[2,3-*c*]pyridine-2,5(3*H*,6*H*)-dione (10a): $[\alpha]^{22}_D$ −44.2 (*c* 1.30, $CHCl_3$); IR ν_{max} 1754, 1649, 1472, 1437, 1178 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.19−7.38 (m, 5 H), 4.80−4.86 (m, 1 H), 4.83 (d, J = 14.4 Hz, 1 H), 4.36 (d, J = 14.6 Hz, 1 H), 3.44 (d, J = 3.2 Hz, 2 H), 3.06−3.19 (m, 1 H), 2.83 (dd, J = 10.9, 18.7 Hz, 1 H), 2.54 (dd, J = 5.6, 15.4 Hz, 1 H), 2.47 (dd, J = 4.4, 15.4 Hz, 1 H), 2.36 (dd, J = 6.0, 18.7 Hz, 1 H); ^{13}C NMR (50 MHz) δ 175.0, 169.6, 136.2, 128.7, 128.1, 127.7, 76.6, 50.0, 49.0, 36.0, 33.5, 30.6; HRMS calcd for $C_{14}H_{15}NO_3$ 245.1052, found 245.1060.

(3a*S*,7a*R*)-6-Benzyltetrahydrofuro[2,3-*c*]pyridine-2,5(3*H*,6*H*)-dione (10b): $[\alpha]^{22}_D$ +36.4 (*c* 1.10, $CHCl_3$); IR ν_{max} 1778, 1654, 1178 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.19−7.38 (m, 5 H), 4.80−4.86 (m, 1 H), 4.83 (d, J = 14.4 Hz, 1 H), 4.36 (d, J = 14.6 Hz, 1 H), 3.44 (d, J = 3.2 Hz, 2 H), 3.06−3.19 (m, 1 H), 2.83 (dd, J = 10.9, 18.7 Hz, 1 H), 2.54 (dd, J = 5.6, 15.4 Hz, 1 H), 2.47 (dd, J = 4.4, 15.4 Hz, 1 H), 2.36 (dd, J = 6.0, 18.7 Hz, 1 H); ^{13}C NMR (50 MHz) δ 174.9, 169.7, 136.2, 128.7, 128.0, 127.7, 76.6, 50.1, 49.0, 36.0, 33.5, 30.6; HRMS calcd for $C_{14}H_{15}NO_3$ 245.1052, found 245.1058.

(3a*S*,6a*S*)-4-Benzyltetrahydro-2*H*-furo[3,2-*b*]pyrrole-2,5(3*H*)-dione (13): light yellow powder; mp 114−116 °C; $[\alpha]^{22}_D$ −38.9 (*c* 0.90, $CHCl_3$); IR ν_{max} 1782, 1692, 1399, 1159 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.17−7.38 (m, 5 H), 5.03 (ddd, J = 3.9, 3.9, 5.6 Hz, 1 H), 4.97 (d, J = 15.0 Hz, 1 H), 4.19 (ddd, J = 2.0, 5.9, 5.9 Hz, 1 H), 4.02 (d, J = 15.0 Hz, 1 H), 2.81 (d, J = 3.9 Hz, 2 H), 2.69 (dd, J = 2.0, 18.4 Hz, 1 H), 2.60 (dd, J = 6.0, 18.4 Hz, 1 H); ^{13}C NMR (50 MHz) δ 173.7, 171.2, 135.0, 129.0, 128.1, 128.0, 75.5, 57.3, 44.6, 37.1, 32.6; HRMS calcd for $C_{13}H_{13}NO_3$ 231.0895, found 231.0895.

(3a*S*,7a*S*)-4-Benzyl-2-hydroxyhexahydrofuro[3,2-*b*]pyridin-5(6*H*)-one (19): Red-Al (0.25 mL, 65 wt % in toluene) was dissolved in dry toluene (5 mL). This solution (4.3 mL, 0.68 mmol) was added, dropwise, to a solution of lactone **9a** (240 mg, 0.98 mmol) in dry THF (20 mL) at −78 °C under argon. The mixture was stirred at −78 °C for 4 h, at which time methanol (1.0 mL) and then saturated aqueous NH_4Cl (8 mL) were added. The reaction mixture was allowed to warm slowly to rt. The organic layer was separated, and the aqueous layer was back-extracted with ethyl acetate. The combined organic layers were dried, filtered, and evaporated. The residue was purified by chromatography (2:1 CH_2Cl_2/acetone) to give unreacted **9a** (19 mg) and a diastereomeric mixture of lactol **17** (209 mg, 86%; 94% based on recovered starting material) as a colorless oil: IR ν_{max} 3354 (br), 2931, 1625 cm^{-1}; ^{1}H NMR (300 MHz) δ (major diastereomer) 7.12−7.30 (m, 5 H), 5.50 (d, J = 4.8 Hz, 1 H), 5.08 (d, J = 14.8 Hz, 1 H), 4.40−4.48 (m, 1 H), 3.98 (q, J = 7.6 Hz, 1 H), 3.94 (d, J = 15.0 Hz, 1 H), 1.60−2.45 (m, 6 H); δ (minor diastereomer) 7.12−7.30 (m, 5 H), 5.44 (t, J = 3.6, 3.4 Hz, 1 H), 5.34 (d, J = 15.0 Hz, 1 H), 4.22−4.30 (m, 1 H), 3.80 (d, J = 15.0 Hz, 1 H), 3.71 (q, J = 5.3 Hz, 1H), 2.62−2.76 (m, 1 H), 1.60−2.45 (m, 5 H); ^{13}C NMR (50 MHz) δ (major diastereomer) 171.2, 136.8, 128.6, 128.1, 127.5, 97.0, 72.5, 57.6, 48.1, 41.6, 27.5, 24.8; δ (minor diastereomer) 171.1, 136.7, 128.3, 128.0, 127.4, 97.6, 75.3, 57.5, 47.3, 39.0, 27.1, 24.5; HRMS calcd for $C_{14}H_{17}NO_3$ 247.1208, found 247.1208.

(5*S*,6*S*)-1-Benzyl-6-(3-methoxyallyl)-5-(methoxymethoxy)-piperidin-2-one (20):. $Ph_3P^+CH_2OMeCl^-$ (1.67 g, 4.86 mmol) was suspended in dry THF (20 mL) and cooled to −60 °C. BuLi (2.2 mL, 4.45 mmol, 2 M in hexane) was added, dropwise, to the suspension. After addition was complete, the resulting red solution was gradually warmed (∼40 min) to −20 °C and then recooled to −40 °C. A solution of **19** (500 mg, 2.0 mmol) in dry THF (4 mL) was added via cannula, and after addition was complete, the reaction temperature was gradually increased to rt (2 h). Saturated aqueous NH_4Cl (10 mL) was added, and the organic layer separated, and the aqueous layer back-extracted with EtOAc. The combined organic layers were dried, filtered, and concentrated. The crude product was purified by chromatography (1:1 then 1:3 petroleum ether/EtOAc and finally EtOAc) to afford a 5.5:1 ratio of *Z*:*E* diastereomeric mixture of the enol ether (407 mg, 74%): IR ν_{max} 3366 (br), 2931, 1613 cm^{-1}; ^{1}H NMR (200 MHz) δ (*E*-diastereomer) 7.10−7.30 (m, 5 H), 6.22 (d, J = 12.6 Hz, 1 H), 5.20 (d, J = 15.1 Hz, 1 H), 4.62 (dt, J = 8.0, 15.1 Hz, 1 H), 3.70−4.10 (m, 2 H), 3.40 (s, 3 H), 3.12−3.30 (m, 1 H), 1.50−2.60 (m, 6 H); δ (*Z*-diastereomer) 7.10−7.30 (m, 5 H), 5.88 (d, J = 6.2 Hz, 1 H), 5.16 (d, J = 15.3 Hz, 1 H), 4.30 (dd, J = 7.8, 14.2 Hz, 1 H), 3.70−4.10 (m, 2 H), 3.50 (s, 3 H), 3.12−3.30 (m, 1 H), 1.50−2.60 (m, 6 H); ^{13}C NMR (50 MHz) δ (*E*-diastereomer) 169.9, 148.4, 136.8, 128.2, 127.2, 126.9, 99.0, 66.0, 59.4, 55.6, 48.4, 28.3, 27.0, 25.0; δ (*Z*-diastereomer) 170.1, 147.7, 137.0, 128.1, 127.1, 126.8, 102.2, 65.8, 60.1, 55.6, 47.4, 28.0, 25.1, 23.2; HRMS calcd for $C_{16}H_{21}NO_3$ 275.1521, found 275.1526.

A solution of the secondary alcohol (370 mg, 1.34 mmol) in dry 1,2-dichloroethane (20 mL) containing Bu_4NI (5 mg) was cooled to 0 °C, and *i*-Pr_2NEt (0.94 mL, 5.36 mmol) and MOMCl (0.2 mL, 2.7 mmol) were added. Then the solution was refluxed overnight. The reaction mixture was cooled to rt and then at 0 °C. Saturated aqueous Na_2CO_3 (1 mL) and brine (5 mL) were added to the reaction mixture, and the organic layer was separated and dried. After the solvent was removed, the resulting oil was purified by chromatography (1:1 and then 1:2 petroleum ether/EtOAc) to give a *Z*:*E* mixture (3:1 based on the integration of the methyl group of the enol ether unit) of the MOM ether **20** as a colorless oil (381 mg, 89%): $[\alpha]^{23}_D$ −36.9 (*c* 1.10, CH_2Cl_2); IR ν_{max} 2931, 1637 cm^{-1}; ^{1}H NMR (200 MHz) δ (*Z*-diastereomer) 7.16−7.38 (m, 5 H), 5.97 (d, J = 6.2 Hz, 1 H), 5.46 (d, J = 14.7 Hz, 1 H), 4.48−4.64 (m, 2 H), 4.32−4.48 (m, 1 H), 4.00 (d, J = 15.0 Hz, 1 H), 3.72−3.88 (m, 1 H), 3.61 (s, 3 H), 3.30−3.48 (m, 1 H), 3.32 (s, 3 H), 1.85−2.75 (m, 6 H); δ (*E*-diastereomer) 7.16−7.38 (m, 5 H), 6.31 (d, J = 12.6 Hz, 1 H), 5.40 (d, J = 14.3 Hz, 1 H), 4.66−4.80 (m, 1 H), 4.48−4.64 (m, 2 H), 4.02 (d, J = 15.0 Hz, 1 H), 3.72−3.88 (m, 1 H), 3.53 (s, 3 H), 3.30−3.48 (m, 1 H), 3.32 (s, 3 H), 1.85−2.75 (m, 6 H); ^{13}C NMR (75 MHz) δ (*Z*-diastereomer) 168.8, 147.3, 137.0, 127.8, 127.2, 126.5, 102.0, 94.8, 72.1, 58.8, 57.4, 54.8, 47.6, 28.2, 23.0, 22.8; δ (*E*-diastereomer) 168.7, 148.3, 136.8, 127.9, 127.1, 126.6, 98.4, 94.9, 72.1, 58.5, 55.2, 54.9, 48.2, 28.1, 27.0, 22.7; HRMS calcd for $C_{18}H_{26}NO_4$ (M + 1) 320.1862, found 320.1864.

(5*S*,6*S*-6-(3-Hydroxypropyl)-5-(methoxymethoxy)piperidine-2-one (18): Sodium metal (166 mg, 7.2 mmol) was added to liquid NH_3 (20 mL) at −78 °C under argon. The mixture was stirred for 10 min, and a solution of the diastereomeric mixture of *N*-benzyl lactam **20** (380 mg, 1.2 mmol) in THF (2 mL) was added, dropwise, via cannula. The solution was stirred at −78 °C for 3 h, and then solid NH_4Cl (250 mg) was added. The solution was gradually warmed to rt, and the residue was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated. The crude product was purified by chromatography (2:1 CH_2Cl_2/acetone) to give the

debenzylated lactam (272 mg, 100%) as a colorless oil: $[\alpha]^{22}_D$ +11.1 (*c* 0.50, $CHCl_3$); IR ν_{max} 3200, 2931, 1660 cm^{-1}; ^1H NMR (200 MHz) δ (*E*-diastereomer) 6.58 (s, 1H), 6.16 (d, *J* = 12.6 Hz, 1H), 4.50 (d, *J* = 7.3 Hz, 1H), 4.40 (d, *J* = 7.3 Hz, 1H), 4.30−4.50 (m, 1H), 3.60−3.70 (m, 1H), 3.29 (s, 3H), 3.16 (s, 3H), 3.05−3.25 (m, 1H), 1.70−2.40 (m, 5H), 1.40−1.60 (m, 1H); δ (*Z*-diastereomer) 6.35 (s, 1 H), 5.80 (d, *J* = 6.2 Hz, 1 H), 4.49 (d, *J* = 7.3 Hz, 1H), 4.40 (d, *J* = 7.3 Hz, 1H), 4.08 (q, *J* = 7.3 Hz, 1H), 3.60−3.70 (m, 1H), 3.36 (s, 3H), 3.16 (s, 3H), 3.05−3.25 (m, 1H), 1.70−2.40 (m, 5H), 1.40−1.60 (m, 1H); ^{13}C NMR (75 MHz) δ (*E*-diastereomer) 171.2, 149.6, 96.8, 95.0, 69.5, 56.4, 55.5, 55.4, 26.3, 26.2, 24.3; δ (*Z*-diastereomer) 171.1, 148.6, 100.1, 95.1, 69.7, 59.2, 56.1, 55.3, 29.8, 26.1, 24.4; HRMS calcd for $C_{11}H_{20}NO_4$ (MH^+) 230.1392, found 230.1401.

The debenzylated lactam (270 mg, 1.18 mmol) was dissolved in THF (8 mL), and aqueous 1 M HCl (4 mL) was added. The mixture was stirred at rt for 3 h, and then solid Na_2CO_3 was added. The organic layer was separated, and aqueous layer was back-extracted with CH_2Cl_2. The combined organic layers were dried, filtered, and concentrated. The crude product was dissolved in 95% EtOH (10 mL) and treated with $NaBH_4$ (90 mg, 2.38 mmol). After 3 h, the mixture was quenched with saturated aqueous NH_4Cl (1 mL). The mixture was evaporated and then extracted with CH_2Cl_2. The combined organic layers were dried, filtered, and concentrated. The residue was purified by chromatography (5:1 EtOAc/MeOH) to give recovered debenzylated lactam (10 mg) and primary alcohol **18** (188 mg, 76%): $[\alpha]^{23}_D$ +23.0 (*c* 0.65, $CHCl_3$); IR ν_{max} 3284 (br), 2930, 1651 cm^{-1}; ^1H NMR (200 MHz) δ 6.97 (br s, 1 H), 4.73 (d, *J* = 7.0 Hz, 1 H), 4.62 (d, *J* = 7.0 Hz, 1 H), 3.84−3.94 (m, 1 H), 3.68−3.76 (m, 2 H), 3.40−3.50 (m, 1 H), 3.39 (s, 3 H), 2.50−2.00 (m, 3 H), 1.80−1.60 (m, 5 H); ^{13}C NMR (50 MHz) δ 172.1, 95.2, 70.2, 62.1, 56.4, 56.0, 28.6, 28.5, 26.7, 24.4; HRMS calcd for $C_{10}H_{19}NO_4$ 217.1314, found 217.1323.

(8*S*,8a*S*)-8-(Methoxymethoxy)hexahydroindolizin-5(1*H*)-one (21a): A solution of **18** (185 mg, 0.85 mmol), tosyl chloride (243 mg, 1.3 mmol), Et_3N (0.23 mL, 1.7 mmol), and DMAP (10 mg) in dry CH_2Cl_2 (10 mL) was stirred at rt for 20 h under argon. The reaction mixture was washed with saturated aqueous NH_4Cl, and the organic layer was separated and dried, filtered, and concentrated. The residue was purified by chromatography (2:3 CH_2Cl_2/acetone) to give the corresponding tosylate (286 mg, 91%) as a colorless oil: $[\alpha]^{23}_D$ +18.8 (*c* 0.80, $CHCl_3$); IR ν_{max} 1658 cm^{-1}; ^1H NMR (200 MHz) δ 7.77 (d, *J* = 8.3 Hz, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 6.26 (br s, 1 H), 4.70 (d, *J* = 7.0 Hz, 1 H), 4.58 (d, *J* = 7.0 Hz, 1 H), 4.04 (t, *J* = 6.0 Hz, 2 H), 3.78−3.90 (m, 1 H), 3.30−3.38 (m, 1H), 3.35 (s, 3 H), 2.44 (s, 3 H), 2.05−2.60 (m, 3 H), 1.64−1.88 (m, 4 H), 1.38−1.56 (m, 1 H); ^{13}C NMR (50 MHz) δ 171.6, 144.8, 132.8, 129.8, 127.8, 95.2, 69.8, 69.5, 56.0, 55.9, 27.8, 26.8, 24.9, 24.2, 21.6; HRMS calcd for $C_{17}H_{26}NO_6S$ (M + 1) 372.1481, found 372.1491.

Hexane-washed NaH (56 mg, 60% dispersion in oil) was suspended in dry THF (7 mL), and a solution of the above tosylate (263 mg, 0.70 mmol) in dry THF (3 mL) was added via cannula. The mixture was stirred at rt, and the reaction was monitored by TLC. After the starting material was consumed, the mixture was cooled in ice−water bath and saturated aqueous NH_4Cl (5 mL) was carefully added. The organic layer was separated, and aqueous layer was back-extracted with CH_2Cl_2. The combined organic layers were dried, filtered, and concentrated. The crude residue was purified by chromatography (2:3 CH_2Cl_2/acetone) to give the indolizidinone **21a** (134 mg, 95%) as a colorless oil: $[\alpha]^{22}_D$ +1.88 (*c* 4.0, $CHCl_3$); IR ν_{max} 1631, 1455 cm^{-1}; ^1H NMR (300 MHz) δ 4.73 (d, *J* = 6.9 Hz, 1 H), 4.62 (d, *J* = 6.9 Hz, 1 H), 4.01 (ddd, *J* = 2.1, 2.1, 4.0 Hz, 1 H), 3.40−3.62 (m, 3 H), 3.39 (s, 3 H), 2.28−2.52 (m, 2 H), 2.20 (dddd, *J* = 2.2, 4.0, 8.7, 14.2 Hz, 1 H), 1.64−2.02 (m, 5 H); ^{13}C NMR (75 MHz) δ 168.7, 95.0, 68.6, 62.1, 55.8, 45.1, 27.5, 26.6, 25.5, 22.0; HRMS calcd for $C_{10}H_{17}NO_3$ 199.1208, found 199.1207.

(8*S*,8a*S*)-Octahydroindolizidin-8-ol (17): MOM ether **21a** (80 mg, 0.40 mmol) was dissolved in 1 M methanolic HCl (5 mL), and the mixture was heated at 60−65 °C (oil bath) for 100 min. The reaction mixture was cooled to rt, solid Na_2CO_3 was added, and the reaction mixture was concentrated. The residue was extracted with MeOH, and the methanol extract was filtered through a pad of Celite. The filtrate was concentrated, and the crude alcohol was purified by chromatography (10:1 EtOAc/MeOH) to afford the bicyclic lactam alcohol **21b** (59 mg, 95%) as a white solid: mp 104−105 °C, lit.[25e] mp 98−100 °C; $[\alpha]^{22}_D$ −44.4 (*c* 2.70, $CHCl_3$), lit.[25e] $[\alpha]^{22}_D$ −30.6 (*c* 2.0, $CHCl_3$); IR ν_{max} 3378 (br), 1601, 1478 cm^{-1}; ^1H NMR (300 MHz) δ 4.13 (ddd, *J* = 2.2, 2.2, 4.1 Hz, 1 H), 3.40−3.58 (m, 3 H), 2.91 (s, 1 H), 2.51 (ddd, *J* = 7.4, 11.8, 18.5 Hz, 1 H), 2.33 (br dd, *J* = 7.4, 17.9 Hz, 1 H), 2.08 (dddd, *J* = 1.7, 3.9, 7.3, 14.1 Hz, 1 H), 1.64−2.02 (m, 5 H); ^{13}C NMR (75 MHz) δ 169.3, 63.2, 62.6, 45.2, 28.3, 27.5, 26.1, 22.0; HRMS calcd for $C_8H_{13}NO_2$ 155.0946, found 155.0946.

The alcohol **21b** (17 mg, 0.11 mmol) was dissolved in dry THF (2 mL) and cooled to 0 °C. $BH_3 \cdot SMe_2$ in ether (0.35 mL, 5 M) was added dropwise to the solution, and the mixture was stirred at 0 °C for 30 min and then at rt for 22 h. The reaction mixture was cooled to 0 °C, and then EtOH (4 mL) was carefully added. The reaction mixture was concentrated, and the resulting white solid was redissolved in EtOH (8 mL) and refluxed for 24 h. The mixture was cooled to rt, and five drops of concentrated HCl was added. EtOH was removed under reduced pressure, and the resulting white solid was dissolved in distilled water (5 mL) and washed with CH_2Cl_2. The aqueous solution was concentrated, and the residue was purified using ion exchange chromatography (Dowex 50x2-400 ion-exchange resin, 200−400 mesh, eluent: water and then 5% NH_4OH solution). The combined fractions containing **17** were concentrated by fractional distillation using a vigreux column. The remaining aqueous mixture was treated with three drops of concentrated HCl and then evaporated under reduced pressure to afford **17**·HCl (20 mg, 88%) as a white solid: mp 128−130 °C; $[\alpha]^{22}_D$ +12.5 (*c* 0.60, CH_3OH); IR ν_{max} 3354 (br) cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 4.30 (s, 1 H), 3.540−3.70 (m, 2 H), 3.22−3.36 (m, 1 H), 2.90−3.12 (m, 2 H), 1.66−2.24 (m, 8 H); ^{13}C NMR (CD_3OD, 75 MHz) δ 70.5, 64.0, 54.1, 53.0, 30.8, 24.8, 20.4, 19.1; HRMS calcd for $C_8H_{16}NO$ (MH^+) 142.1232, found 142.1229.

(4*S*,5*S*)-4-Acetoxy-5-(2-acetoxy-3-phenylsulfonylpropyl)-1-benzylpyrrolidin-2-one (25): A solution of methyl phenyl sulfone (70.8 mg, 0.453 mmol) in dry THF (1 mL) was cooled to −78 °C, and *n*-BuLi (0.25 mL of 1.79 M in hexanes, 0.450 mmol) was added dropwise, resulting in a clear, bright yellow solution, which was stirred for 2 h, and then warmed to −40 °C. The bicyclic γ-lactam lactone **13** (80.5 mg, 0.350 mmol) in dry THF (1 mL) was added dropwise via cannula, and then the cannula was rinsed with 0.5 mL of dry THF. The mixture was stirred at −40 °C for 1.5 h and at 0 °C for 1.5 h, by which time reaction was judged to be complete by TLC. The reaction mixture was cooled to −40 °C, quenched with saturated NH_4Cl (2 mL), and then diluted with CH_2Cl_2 (2 mL). The aqueous layer was saturated with NaCl and brine; the resulting mixture was stirred for 30 min and then extracted with CH_2Cl_2. The combined organic extracts were dried, concentrated, and the crude product was purified by chromatography (5:1 CH_2Cl_2/acetone) to give an inseparable mixture of lactols (107 mg, 80%) as a colorless oil: $[\alpha]^{26}_D$ +6.6 (*c* 0.38, $CHCl_3$); IR ν_{max} 3500−3125, 3050, 1687, 1667, 1600, 1512 cm^{-1}. ^1H NMR (300 MHz) (major diastereomer) δ 7.85−7.92 (m, 2 H), 7.59−7.68 (m, 1 H), 7.47−7.57 (m, 2 H), 7.12−7.35 (m, 5 H), 4.78 (d, *J* = 14.7 Hz, 1 H), 4.61−4.71 (m, 1 H), 3.99−4.08 (m, 1 H), 3.90 (d, *J* = 14.7 Hz, 1 H), 3.48 (d, *J* = 14.8 Hz, 1 H), 3.41 (d, *J* = 14.6 Hz, 1 H), 2.52 (dd, *J* = 6.9,

18.1 Hz, 1 H), 2.25 (dd, $J = 7.3$, 13.7 Hz, 1 H), 2.04 (d, $J = 18.1$ Hz, 1 H), 1.83 (dd, $J = 3.5$, 13.7 Hz, 1 H); discernible signals of minor diastereomer δ 5.05 (d, $J = 15$ Hz, 1 H), 4.61−4.67 (m, 1 H), 3.91 (d, $J = 15$ Hz, 1H), 3.54 (d, $J = 14.9$ Hz, 1 H), 2.70 (dd, $J = 6.2$, 18.2 Hz, 1 H), 2.63 (dd, $J = 9.2$, 18.2 Hz, 1 H), 2.46 (d, $J = 13.9$ Hz, 1 H), 1.85 (dd, $J = 3.5$, 13.7 Hz, 1 H); ^{13}C NMR (75 MHz) δ 172.2, 172.0, 140.2, 140.0, 135.6, 133.9, 133.7, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 127.8, 127.6, 103.6, 103.2, 74.6, 63.0, 62.7, 61.3, 61.0, 44.7, 42.9, 40.2, 39.6, 36.8. HRMS calcd for $C_{20}H_{21}NO_5S$ for 387.1140, found 387.1143.

The ratio of the diastereomeric lactols was 1:2 and was based on the integration of the one of the benzylic methylene protons at δ 4.78 and 5.05.

$NaBH_4$ (192 mg, 5.09 mmol) was added to a solution of bicyclic phenylsulfone lactol (148 mg, 0.380 mmol) in ethanol (5 mL) at 0 °C. The mixture was stirred at rt for 1 h and then quenched with three drops of acetic acid at 0 °C, after which the EtOH was removed under reduced pressure to give a white slurry residue. CH_2Cl_2 (15 mL) was added to the residue, and the resulting suspension was suction filtered through a pad of Celite washing the residue with CH_2Cl_2 (40 mL) in the process. The filtrate was concentrated, and the residual thick oil was dried under high vacuum. The dihydroxy sulfone was used in the next step without further purification.

To a mixture of dihydroxy sulfone (124 mg, 0.320 mmol) and DMAP (3.90 mg, 0.0320 mmol) was added dry CH_2Cl_2 (5 mL). After cooling the resulting solution to 0 °C, Ac_2O (0.12 mL, 1.27 mmol) was added and the mixture was stirred at the same temperature for 15 min before Et_3N (0.18 mL, 1.27 mmol) was added dropwise to the mixture. The reaction was stirred at rt for 5 h, by which time reaction was complete as indicated by TLC analysis. The reaction mixture was washed with 0.5 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and finally with water. The organic extract was dried, filtered, and concentrated. The crude product was purified by chromatography (4:1 CH_2Cl_2/acetone) to afford inseparable, diastereomeric diacetates **25** (136 mg, 85% over 2 steps) as a white foam. The diastereomeric ratio was 1:2 and is based on the integration of the signals of the methyl protons of the acetate at δ 1.63 and 1.77: $[\alpha]^{25}_D$ −7.4 (*c* 1.01, $CHCl_3$); IR ν_{max} 3075, 3050, 1736, 1689, 1625, 1500 cm^{-1}. ^{1}H NMR (300 MHz) (major diastereomer) δ 7.77−7.87 (m, 2 H), 7.61−7.69 (m, 1 H), 7.50−7.59 (m, 2 H), 7.14−7.36 (m, 5 H), 5.14−5.27 (m, 1 H), 5.04−5.27 (m, 1 H), 5.04 (d, $J = 15.3$ Hz, 1 H), 3.99 (d, $J = 15.4$ Hz, 1 H), 3.51−3.60 (m, 1 H), 3.27 (dd, $J = 8.9$, 14.6 Hz, 1 H), 3.04 (dd, $J = 9.0$, 14.5 Hz, 1 H), 2.74 (dd, $J = 6.7$, 17.5 Hz, 1 H), 2.51 (dd, $J = 3.2$, 17.5 Hz, 1 H), 1.97−2.21 (m, 2 H), 2.09 (s, 3 H), 1.77 (s, 3 H, Me); discernible signals of minor diastereomer δ 5.27−5.35 (m, 1 H), 5.01 (d, $J = 15.5$ Hz, 1 H), 3.91 (d, $J = 15.4$ Hz, 1 H), 3.41−3.46 (m, 1 H), 3.35 (dd, $J = 8.9$, 14.6 Hz, 1 H), 3.11 (dd, $J = 9.0$, 14.9 Hz, 1 H), 2.80 (dd, $J = 6.7$, 17.5 Hz, 1 H), 1.63 (s, 3 H), 2.01 (s, 3 H); ^{13}C NMR (75 MHz) δ 171.9, 170.1, 169.6, 139.1, 135.5, 134.0, 133.9, 129.3, 129.0, 128.8, 128.7, 128.6, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 67.8, 67.6, 66.0, 64.7, 59.4, 58.7, 56.9, 55.5, 43.9, 43.8, 43.5, 37.7, 31.4, 30.4, 20.8, 20.7, 20.5, 20.3. HRMS calcd for $C_{24}H_{27}NO_7S$ for 473.1508, found 473.1502.

(4*S*,5*S*)-4-Acetoxy-5-allyl-1-benzylpyrrolidin-2-one (26a): To a stirred mixture of SmI_2 (3.5 mL, 0.350 mmol, 0.1 M in THF) and HMPA (0.18 mL, 1.06 mmol) was added a solution of lactam diacetate **25** (33.4 mg, 0.070 mmol) in THF (1 mL) via cannula transfer at rt. The reaction mixture was stirred at the same temperature for 10 min, by which time the deep purple color of the reaction mixture had discharged and the reaction was judged to be complete by TLC analysis. The reaction mixture was cooled to 0 °C and then quenched with three drops of saturated NH_4Cl solution. THF was removed, and then brine and 0.5 M aqueous NaOH (1 mL) were added to the residue. The mixture was stirred at rt for 5 min and then extracted with EtOAc and CH_2Cl_2. The organic extracts were combined, dried, filtered, and concentrated under reduced pressure. Purification by means of flash column chromatography (8:1 CH_2Cl_2/acetone) afforded the desired **26a** (11.8 mg, 61%; 72% based on recovered starting material) as a colorless oil, unreacted **25** (5.1 mg) and a small amount of impure **26b** (2.1 mg, 7%). Further attempts to purify **26b** were unsuccessful. Compound **26a**: $[\alpha]^{23}_D$ −19.5 (*c* 0.77, $CHCl_3$); IR ν_{max} 3050, 3025, 3000, 1738, 1694 1687, 1612, 1512 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.09−7.39 (m, 5 H), 5.55−5.72 (m, 1 H), 5.26−5.34 (m, 1 H), 5.04−5.13 (m, 2 H), 5.04 (d, $J = 15.3$ Hz, 1 H), 4.02 (d, $J = 15.2$ Hz, 1 H), 3.66−3.76 (m, 1 H), 2.75 (dd, $J = 7.0$, 17.3 Hz, 1H), 2.53 (dd, $J = 4.2$, 17.4 Hz, 1 H), 2.38 (t, $J = 6.7$ Hz, 2 H), 2.06 (s, 3 H); ^{13}C NMR (75 MHz) δ 171.9, 170.1, 135.9, 132.6, 128.6, 127.7, 127.6, 118.5, 68.1, 58.9, 44.0, 37.4, 31.7, 20.7; (CI-NH_3)-HRMS calcd for $C_{16}H_{20}NO_3$ (M + 1) 274.1443, found 274.1434.

(4*S*,5*S*)-5-Allyl-1-benzyl-4-(methoxymethoxy)pyrrolidin-2-one (26c): K_2CO_3 (477 mg, 3.46 mmol) was added to a solution of **26a** (282 mg, 1.03 mmol) in methanol (10 mL), and the mixture was stirred at rt for 1 h. Methanol was removed under reduced pressure, and to the resulting residue was added CH_2Cl_2 (20 mL), and then the solution was filtered through a pad of Celite. The filtrate was concentrated, and the residue was purified by chromatography (1:1 petroleum ether/EtOAc) to afford the secondary alcohol (214 mg, 90%) as white crystals: mp 64−65 °C; $[\alpha]^{23}_D$ −47.9 (*c* 0.365, $CHCl_3$); IR ν_{max} 3500−3175, 3050, 1670, 1500 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.13−7.35 (m, 5H), 5.68−5.86 (m, 1 H), 5.06−5.20 (m, 2 H), 4.96 (d, $J = 15.2$ Hz, 1 H), 4.39 (ddd, $J = 3.4$, 5.3, 6.5 Hz, 1 H), 4.07 (d, $J = 15.2$ Hz, 1 H), 3.51 (ddd, $J = 5.4$, 5.4, 8.4 Hz, 1 H), 2.67 (dd, $J = 6.6$, 17.2 Hz, 1 H), 2.48 (dd, $J = 1.3$, 16.5 Hz, 1 H), 2.35−2.48 (m, 2 H), 2.18 (br s, 1 H); ^{13}C NMR (75 MHz) δ 173.1, 136.3, 133.7, 128.6, 127.6, 127.4, 118.3, 66.3, 60.9, 43.9, 40.1, 31.5; HRMS calcd for $C_{14}H_{17}NO_2$ 231.1259, found 231.1256.

To a solution of the above-described secondary alcohol (214 mg, 0.93 mmol) in dry CH_2Cl_2 (10 mL) was added MOMCl (1.86 mmol, 0.14 mL), under Ar, at 0 °C. The mixture was stirred, ^{i}Pr$_2$NEt (1.86 mmol, 0.32 mL) was added, and the reaction mixture was stirred at rt overnight. The solvents were removed in vacuo, the residue was taken into EtOAc, and the organic phase was washed with water, dried, filtered, and concentrated. The residue was purified by chromatography (1:1 petroleum ether/EtOAc) to afford **26c** (227 mg, 89%) as a pale yellow oil: $[\alpha]^{26}_D$ −50 (*c* 0.35, $CHCl_3$); IR ν_{max} 3050, 3025, 1694, 1662, 1600, 1512 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.16−7.39 (m, 5 H), 5.69−5.86 (m, 1 H), 5.06−5.15 (m, 2 H), 5.06 (d, $J = 15.4$ Hz, 1 H), 4.65 (d, $J = 6.9$ Hz, 1 H), 4.61 (d, $J = 6.9$ Hz, 1 H), 4.22−4.32 (m, 1 H), 3.98 (d, $J = 15.2$ Hz, 1 H), 3.39 (ddd, $J = 3.2$, 4.7, 6.3 Hz, 1 H), 3.36 (s, 3 H), 2.64 (dd, $J = 6.9$, 16.8 Hz, 1 H), 2.56 (dd, $J = 5.6$, 16.8 Hz, 1 H), 2.47 (dd, $J = 7.1$, 14.9 Hz, 1 H), 2.37 (dd, $J = 6.0$, 14.1 Hz, 1 H); ^{13}C NMR (75 MHz) δ 172.2, 136.1,133.5, 128.3, 127.5, 127.2, 117.9, 95.8, 71.4, 59.6, 55.6, 43.7, 37.4, 31.4; (CI-NH_3)-HRMS calcd for $C_{16}H_{22}NO_3$ (M + 1) 276.1599, found 276.1598.

(4*S*,5*S*)-1,5-Diallyl-4-(methoxymethoxy)pyrrolidin-2-one (24): To liquid NH_3 (50 mL) at −78 °C was added sodium metal (41.1 mg, 1.80 mmol). The resulting deep blue-black solution was stirred at the same temperature for 30 min, after which a solution of the *N*-benzyl amide **26c** (33.0 mg, 0.120 mmol) in dry THF (3 mL) was transferred via cannula (rinsed with with 1 mL of dry THF). The reaction mixture was allowed to stir at −78 °C for 3 h . The reaction mixture was quenched at −78 °C with excess solid NH_4Cl and then allowed to warm slowly to rt, by which time all the NH_3 had evaporated. The residue was extracted with CH_2Cl_2, the combined extracts were

concentrated under reduced pressure, and the residue was purified by chromatography (2:1 CH_2Cl_2/acetone) to afford the N-debenzylated γ-lactam (16 mg, 73%) as a colorless oil: IR ν_{max} 3231, 3075, 1698, 1650 cm^{-1}; ^1H NMR (300 MHz) δ 5.60−5.84 (m, 2 H), 5.09−5.19 (m, 2 H), 4.65 (d, J = 6.9 Hz, 1 H), 4.60 (d, J = 6.9 Hz, 1 H), 4.31−4.40 (m, 1 H), 3.76 (ddd, J = 5.8, 5.8, 10.2 Hz, 1 H), 3.35 (s, 3 H), 2.55 (dd, J = 6.4, 16.5 Hz, 1 H), 2.39 (dd, J = 4.3, 16.5 Hz, 1 H), 2.37−2.47 (m, 1 H), 2.27 (ddd, J = 9.2, 9.2, 14.2 Hz, 1 H); ^{13}C NMR (75 MHz) δ 175.0, 134.4, 118.7, 96.1, 73.7, 57.6, 56.1, 38.0, 34.4; (CI-NH_3)-HRMS calcd for $C_9H_{16}NO_3$ (M + 1) 186.1130, found 186.1126.

The N-debenzylated γ-lactam (14.0 mg, 0.080 mmol) together with a few crystals of 2,2′-bipyridine was dissolved in dry THF (3 mL), and the solution was cooled to −15 °C. BuLi (0.07 mL, 0.080 mmol, 1.15 M) was then added to the cooled solution dropwise, resulting in a deep red colored solution which was stirred for 10 min before dry DMF (0.5 mL) was added. After stirring the mixture for another 10 min, allylbromide (0.01 mL, 0.120 mmol) was added to the reaction mixture, resulting in an instant discharge of the red color to yellow. The reaction mixture was stirred at −15 °C for 20 min and then allowed to warm gradually to rt, by which time the reaction was complete as indicated on TLC analysis. The reaction mixture was diluted with EtOAc (10 mL) and then washed with brine. The organic layer was dried, filtered, and concentrated. The crude product was purified by chromatography (8:1 CH_2Cl_2/acetone) to afford the diallyl product **24** (16.5 mg, 97% yield) as a pale yellow nonviscous oil: $[\alpha]^{26}_D$ −41.7 (c 0.24, $CHCl_3$); IR ν_{max} 3060, 1689, 1650, 1587, 1550 cm^{-1}; ^1H NMR (300 MHz) δ 5.60−5.88 (m, 2 H), 5.04−5.21 (m, 4 H), 4.64 (d, J = 6.9 Hz, 1 H), 4.60 (d, J = 6.9 Hz, 1 H), 4.33 (dd, J = 4.5, 15.3 Hz, 1 H), 4.28 (dd, J = 6.3, 12.8 Hz, 1 H), 3.69−3.77 (m, 1 H), 3.50 (dd, J = 7.2, 15.7 Hz, 1 H), 3.35 (s, 3 H), 2.56 (dd, J = 6.8, 16.1 Hz, 1 H), 2.47 (dd, J = 2.3, 16.1 Hz, 1 H), 2.32−2.46 (m, 2 H); ^{13}C NMR (75 MHz) δ 172.4, 134.1, 132.6, 118.4, 117.9, 96.3, 71.9, 60.6, 56.1, 43.1, 37.9, 31.9; (CI-NH_3)-HRMS calcd for $C_{12}H_{20}NO_3$ (M + 1) 226.1443, found 226.1440.

(1*S*,8a*S*)-1-(Methoxymethoxy)-1,2,8,8a-tetrahydroindolizin-3(5*H*)-one (23): To a solution of diallyl γ-lactam **24** (25.0 mg, 0.11 mmol) in dry CH_2Cl_2 (3 mL) at reflux was added via cannula transfer a solution of Grubbs (II) catalyst (4.7 mg, 6.0×10^{-3} mmol) in dry CH_2Cl_2 (2 mL). The reaction was refluxed for 1 h, by which time the reaction was judged to be complete by TLC analysis. The reaction was cooled to rt, and the solvent was evaporated and the crude oil purified by chromatography (8:1 CH_2Cl_2/acetone) to give **23** (18.5 mg, 90%) as an amber colored oil: $[\alpha]^{26}_D$ −72.9 (c 0.24, $CHCl_3$); IR ν_{max} 3025, 1689, 1648 cm^{-1}; ^1H NMR (300 MHz) δ 5.79−5.88 (m, 1 H), 5.62−5.71 (m, 1 H), 4.65 (d, J = 6.8 Hz, 1 H), 4.59 (d, J = 6.8 Hz, 1 H), 4.41 (ddd, J = 4.4, 6.7, 6.7 Hz, 1 H), 4.25 (dddd, J = 3.9, 3.9, 3.9, 17.5 Hz, 1 H), 3.72 (ddd, J = 4.8, 5.9, 10.7 Hz, 1 H), 3.51 (br d, J = 17.5 Hz, 1 H), 3.34 (s, 3 H), 2.63 (dd, J = 7.2, 17.3 Hz, 1 H), 2.42−2.54 (m, 1 H), 2.42 (dd, J = 4.2, 17.5 Hz, 1 H), 2.00−2.13 (m, 1 H); ^{13}C NMR (75 MHz) δ 171.8, 124.2, 122.7, 95.8, 70.8, 56.2, 55.6, 40.1, 37.5, 24.2.

(1*S*,8a*S*)-1-Hydroxyhexahydroindolizin-3(5*H*)-one (27b): To a solution of alkene **23** (30 mg, 0.15 mmol) in methanol (4 mL) was added 10 wt % Pd−C (3 mg). The mixture was then subjected to hydrogen pressure of 2 atm on a Parr hydrogenator for 1 h. The methanol was removed under reduced pressure, and the residue was filtered through a short pad of silica gel (2:1 CH_2Cl_2/acetone) to afford indolizidinone **27a** (26 mg, 88%) as a colorless oil: $[\alpha]^{26}_D$ +37.9 (c 0.33, $CHCl_3$); IR ν_{max} 1766, 1684 cm^{-1}; ^1H NMR (300 MHz) δ 4.63 (d, J = 6.8 Hz, 1 H), 4.57 (d, J = 6.8 Hz, 1 H), 4.28 (ddd, J = 2.9, 3.6, 9.7 Hz, 1 H), 4.09 (br d, J = 13.2 Hz, 1 H), 3.43−3.53 (m, 1 H), 3.32 (s, 3 H), 2.50−2.64 (m, 2 H), 2.38 (dd, J = 2.8, 17.2 Hz, 1 H), 1.88−1.97 (m, 1 H), 1.51−1.72 (m, 3 H), 1.28−1.46 (m, 2 H).

Indolizidinone **27a** (20 mg, 0.10 mmol) was dissolved in a mixture of aqueous 1 M HCl and MeOH (1:1 v/v, 5 mL), and the mixture was heated at 60−65 °C with stirring for 100 min. The mixture was cooled to rt, and the reaction was quenched with solid Na_2CO_3. The solvent was removed under reduced pressure, and the residual solid was extracted with MeOH. To the residual solid were added brine and solid NaCl, and the mixture was stirred vigorously and then was extracted thoroughly with CH_2Cl_2. The combined MeOH and CH_2Cl_2 phases were dried, filtered, concentrated, and then purified by chromatography (15:1 EtOAc/MeOH) to afford the lactam alcohol **27b** (13 mg, 84%) as colorless crystals: mp 147−150 °C, lit.[28a] 149−157 °C; $[\alpha]^{26}_D$ +27.8 (c 0.18, acetone); lit.[28a] $[\alpha]^{20}_D$ +26.9 (c 1.5, acetone); IR ν_{max} 3500−3125, 3001, 2390, 1688 1557 cm^{-1}; ^1H NMR (300 MHz) δ 4.30−4.38 (m, 1 H), 4.05 (m, 1 H), 3.67 (ddd, J = 6.0, 6.0, 11.3 Hz, 1 H), 2.51−2.67 (m, 2 H), 2.30 (dd, J = 1.3, 17.4 Hz, 1 H), 2.23 (br d, J = 5.7 Hz, 1 H), 1.88−1.98 (m, 1 H), 1.50−1.71 (m, 3 H), 1.25−1.46 (m, 2 H); ^{13}C NMR (75 MHz) δ 171.9, 66.3, 61.5, 40.9, 40.1, 24.5, 23.9, 23.1. HRMS calcd for $C_8H_{13}NO_2$ 155.0946, found 155.0949.

(+)-(1*S*,8a*S*)-Octahydroindolizidin-1-ol (22): A solution of lactam alcohol **27b** (10.0 mg 0.065 mmol) in THF (1.5 mL) was added dropwise to $BH_3 \cdot SMe_2$ in ether (0.35 mL, 5 M). The mixture was refluxed at 80 °C for 1 h, and then stirred at rt temperature overnight. The reaction mixture was cooled to 0 °C and then quenched with ethanol (2 mL). The solvent was removed under reduced pressure, and to the residue was added 95% ethanol (5 mL), and the mixture was refluxed for 5 h, after which time the less polar **27**-borane complex was completely converted to a polar compound. The reaction mixture was cooled to rt and then treated with concentrated HCl (6 drops). Ethanol was evaporated off, and the white solid was dissolved in distilled water (5 mL) and then washed with CH_2Cl_2. The aqueous solution was concentrated under reduced pressure, and the residue was subjected to ion exchange chromatography (Dowex 50x2-400 ion-exchange resin, 200−400 mesh) eluting with water and then 5% NH_4OH solution as eluent. The fractions were combined and concentrated under reduced pressure. The residue was redissolved in CH_2Cl_2 (5 mL), dried, filtered, and evaporated to afford the indolizidine **22** (7 mg, 78%) as a clear light yellow oil: $[\alpha]^{26}_D$ +19.2 (c 0.13, $CHCl_3$), lit.[28a] $[\alpha]^{22}_D$ +17.4 (c 0.4, $CHCl_3$); IR ν_{max} 3525−3100, 1737 cm^{-1}; ^1H NMR (300 MHz) δ 3.97−4.06 (m, 1 H), 3.01−3.14 (m, 2 H), 2.06−2.20 (m, 2 H), 1.76−2.01 (m, 3 H), 1.37−1.73 (m, 6 H), 1.10−1.31 (m, 1 H); ^{13}C NMR (75 MHz) δ 72.8, 68.7, 53.4, 52.6, 30.0, 25.1, 24.9, 23.7; HRMS calcd for $C_8H_{15}NO$ 141.1154, found 141.1157.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council, Canada, and the University of Regina for financial support.

Supporting Information Available: Preparation and characterization of **2a**,**b**, (*S*)-**3**, (*R*)-**3**, (*S*)-**4**, (*R*)-**4**, (*S*)-**6**, (*S*)-**7**, (*S*)-**8**; data for (*S*,*S*)-**11**, **12a**,**b**, (*S*,*S*)-**14**, **15**; spectral data for compounds **2a**, (*S*)-**4**, (*R*)-**4**, (*S*)-**2b**, (*S*)-**3**, (*R*)-**3**, (*S*)-**6**, (*S*)-**7**, (*S*)-**8**, 9a, **10a**, (*S*,*S*)-**11**, **12a**(5*S*), **9b**, **10b**, **12b**(5*R*), **13**, **15**, **14***E*, **14***Z*, **19**, 20(*Z*/*E*), **18**, **21a**, **21b**, **17** · BH_3, **17** · HCl, **25**, **26a**, **26c**, **24**, **23**, **27a**, 27b, **22**. This material is available free of charge via the Internet at http://pubs.acs.org.