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Diastereoselective Synthesis of Cyclopentapyridazinones via Radical Cyclization: Synthetic Studies Toward Halichlorine

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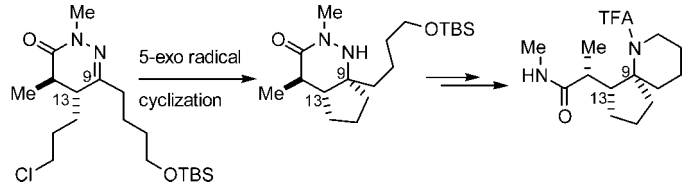
ABSTRACT

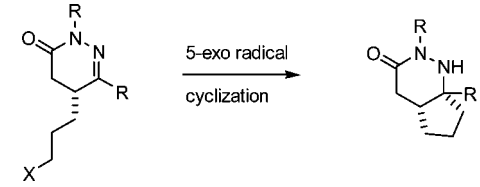


The pyridazinone ring system serves as an excellent scaffold for the diastereoselective preparation of novel *cis*-fused cyclopentapyridazinones utilizing the directed 5-*exo* radical cyclization approach. This overall approach was successfully employed in the preparation of a functionalized aza-spirocycle.

Intramolecular radical additions offer a powerful means for constructing both carbo- and heterocyclic ring systems.[1] There are numerous examples employing alkenes and alkynes as radical acceptors for ring formation,[2] and over the past decade, interest in imine-like[1d,3] acceptors for radical cyclization reactions has steadily grown. Specifically, among these examples, the formation of cyclic structures using exocyclic imine-like acceptors has ample precedent.[1d,3e,4] However the formation of fused ring systems using cyclic hydrazone acceptors as part of both stereodefining and directing templates has been virtually unexplored.

In our pursuit to develop general methods for the synthesis of structural motifs found in biologically relevant molecules, pyridazinones appeared to be promising candidates for the synthesis of synthetically useful fused bicycles (Scheme 1). The embedded hydrazone could function as a radical acceptor, and the ring's inherent rigidity could provide for the diastereose-

Scheme 1. Formation of Cyclopentapyridazinone



(1) (a) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (b) Marco-Contelles, J.; Ruiz, P.; Sanchez, B.; Jimeno, M. L. *Tetrahedron Lett.* **1992**, *33*, 5261. (c) Curran, D. P.; Sisko, J.; Yeske, P. E.; Liu, H. *Pure Appl. Chem.* **1993**, *65*, 1153. (d) Keck, G. E.; Wager, T. T.; McHardy, S. F. *J. Org. Chem.* **1998**, *63*, 9164.

(2) (a) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564. (b) Stork, G.; Mook, R.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741. (c) Choi, J.-K.; Hart, D. J. *Tetrahedron* **1985**, *41*, 3959. (d) Fukuzawa, S.-i; Tsuchimoto, T. *Synlett* **1993**, 803. (e) Miyata, O.; Nishiguchi, A.; Ninomiya, I.; Aoe, K.; Okamura, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 6922.

(3) For examples of hydrazone acceptors, see: (a) Sturino, C. F.; Fallis, A. G. *J. Am. Chem. Soc.* **1994**, *116*, 7447. (b) Marco-Contelles, J.; Balme, G.; Bouyssi, D.; Destabel, C.; Henriet-Bernard, C. D.; Grimaldi, J.; Hatem, J. M. *J. Org. Chem.* **1997**, *62*, 1202. (c) Tauh, P.; Fallis, A. G. *J. Org. Chem.* **1999**, *64*, 6960. (d) Friestad, G. K.; Fioroni, G. M. *Org. Lett.* **2005**, *7*, 2393For examples of imine acceptors, see: (e) Tomaszewski, M. J.; Warkentin, J. *Chem. Commun.* **1993**, 966. (f) Bowman, W. R.; Stephenson, P. T.; Terrett, N. K.; Young, A. R. *Tetrahedron Lett.* **1994**, *35*, 6369. (g) Kim, S.; Yoon, K. S.; Kim, Y. S. *Tetrahedron* **1997**, *53*, 73. For examples of *N*-aziridinylimine acceptors, see: (h) Kim, S.; Kee, I. S.; Lee, S. *J. Am. Chem. Soc.* **1991**, *113*, 9882. (i) Lee, H.-Y.; Kim, D-I.; Kim, S. *Chem. Commun.* **1996**, 1539For examples of oxime acceptors, see: (j) Keck, G. E.; Wager, T. T. *J. Org. Chem.* **1996**, *61*, 8366. (k) Miyata, O.; Muroya, K.; Koide, J.; Naito, T. *Synlett* **1998**, 271. (l) Keck, G. E.; Wager, T. T.; Rodriquez, J. F. D. *J. Am. Chem. Soc.* **1999**, *121*, 5176. (m) Clive, D. L. J.; Pham, M. P.; Subedi, R. *J. Am. Chem. Soc.* **2007**, *129*, 2713.

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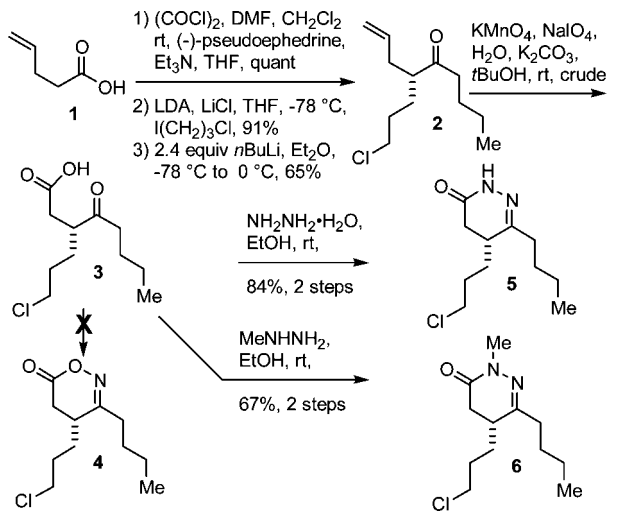
lective installation of the fused cyclopentane via a facile 5-*exo* radical cyclization. In addition, it was our intent to explore this radical reaction's potential to provide a key intermediate for use in efforts directed at the synthesis of the natural product halichlorine.

The chiral pyridazinone was easily accessed in five steps starting with 4-pentenoic acid **1** (Scheme 2). Initial amide

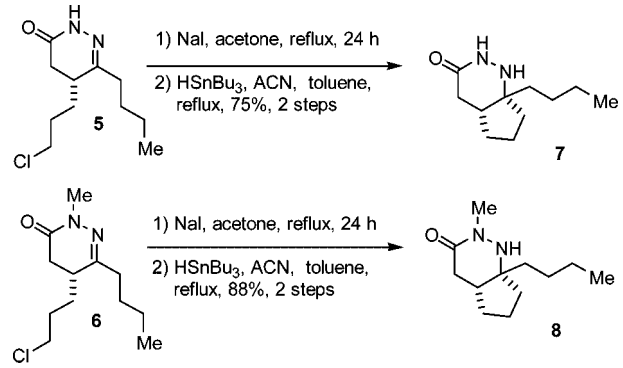
Scheme 2. Synthesis of Functionalized Pyridazinones



coupling with (1*R*,2*R*)-(−)-pseudoephedrine was followed by the Myers' diastereoselective alkylation protocol[5] using 1-chloro-3-iodo-propane. The auxiliary was subsequently removed with *n*-BuLi providing chiral ketone **2**.[6] The terminal olefin in ketone **2** was then cleaved to give γ-keto acid **3**. Initial attempts to transform this substrate into the corresponding oxazinone **4** under a variety of conditions were fruitless.[7] However, we were delighted to find that treatment of carboxylic acid **3** with hydrazine hydrate produced pyridazinone **5** in high yield and that the use of methyl hydrazine led to *N*-methyl pyridazinone **6**.[7,8] It is important to recognize that oxazinone **4**, pyridazinone **5**, and *N*-methyl pyridazinone **6** represent essentially equivalent substrates for our purposes; both oxime ethers and hydrazones have been shown to perform well as radical acceptors.[3]

In preparation for the radical cyclization, the chlorides in compounds **5** and **6** were exchanged for iodides using Finkelstein conditions (Scheme 3). To our delight, both

Scheme 3. 5-*Exo* Radical Cyclization



pyridazinones **5** and **6** provided cyclopentapyridazinones **7** and **8** in good yield upon exposure to $HSnBu_3$ and azobiscyclohexylnitrile (ACN) in toluene at reflux. As expected, the *cis*-fused bicycles were the only detectable diastereomers formed in the reaction. Thus, the initial pyridazinone scaffold provides the necessary rigidity for efficient transfer of stereochemical information during the 5-*exo* radical cyclization. This addition thus leads to the generation of a new stereogenic center bearing a masked amino group.

In light of these successful radical cyclizations, we decided to explore this new method in a strategy directed at the synthesis of the biologically relevant natural product halichlorine. Specifically, we hoped to exploit this powerful method as the initial stereochemistry-defining reaction in the generation of the aza-spirocyclic core of halichlorine.

Halichlorine **9**[9] is an alkaloid that was isolated from the marine sponge *Halichondria okadai* Kadota in 1996 by Uemura and co-workers (Scheme 4).[10] The 15-membered macrolide has been shown to significantly inhibit the expression of VCAM-1 (vascular cell adhesion molecule). VCAM-1 is involved in promoting and regulating leukocyte uptake into inflamed tissue. Inhibition of this process is relevant to a variety of disease states, including asthma, atherosclerosis, coronary artery diseases, and noncardiovascular inflammatory diseases.[10,11]

Retrosynthetically, halichlorine **9** can be dissected through a hydrolysis of the C_1-C_{21} lactone followed by a disconnection of the $C_{15}-C_{16}$ olefin giving rise to the halichlorine spiroquinolizidine core **10** as well as *Z*-vinyl chloride **11** (Scheme 4). The core **10** can then be simplified by extrusion

(4) (a) Parker, K. A.; Spero, D. M.; Van Epp, J. *J. Org. Chem.* **1988**, *53*, 4628. (b) Takano, S.; Suzuki, M.; Kijima, A.; Ogasawara, K. *Chem. Lett.* **1990**, 315. (c) Booth, S. E.; Jenkins, P. R.; Swain, C. J.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3499. (d) Clive, D. L. J.; Zhang, J.; Subedi, R.; Bouetard, V.; Hiebert, S.; Ewanuk, R. *J. Org. Chem.* **2001**, *66*, 1233.

(5) (a) Myers, A. G.; Yang, B. G.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361. (b) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

(6) During our initial studies, the enantiomer of the compounds shown in Schemes 2, 3, 5, and 6 was used. For simplicity, only one enantiomer is consistently shown throughout all schemes.

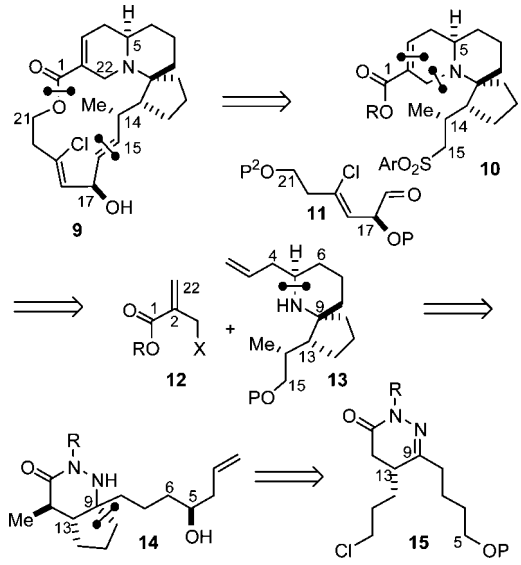
(7) (a) El Hashash, M. A.; El Kady, M. Y.; Mohamed, M. M. *Ind. J. Chem. Sect. B: Org. Chem. Incl. Med. Chem.* **1979**, *18*, 136. (b) Best, W. M.; Brown, R. F. C.; Tiso, P. D.; Watson, K. G. *Aust. J. Chem.* **1990**, *43*, 427. (c) Essawy, S. A. *Ind. J. Chem. Sect. B: Org. Chem. Incl. Med. Chem.* **1991**, *30*, 371.

(8) (a) Cignarella, G.; Barlocco, D.; Pinna, G. A.; Loriga, M.; Curzu, M. M.; Tofanetti, O.; Germini, M.; Cazzulani, P.; Cavalletti, E. *J. Med. Chem.* **1989**, *32*, 2277. (b) Combs, D. W.; Rampulla, M. S.; Demers, J. P.; Falotico, R.; Moore, J. B. *J. Med. Chem.* **1992**, *35*, 172. (c) Stajer, G.; Szabo, A.; Bernath, G.; Sohar, P. *Heterocycles* **1994**, *38*, 1061.

(9) For total syntheses of halichlorine, see: (a) Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3542. (b) Christie, H. S.; Heathcock, C. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12079. For a comprehensive review of synthetic approaches, see: (c) Clive, D. L. J.; Yu, M.; Wang, J.; Yeh, V. S. C.; Kang, S. *Chem. Rev.* **2005**, *105*, 4483. For recent synthetic approaches not covered in ref 9c, see: (d) Andrade, R. B.; Martin, S. F. *Org. Lett.* **2005**, *7*, 5733. (e) Kim, H.; Seo, J. H.; Shin, K. J.; Kim, D. J.; Kim, D. *Heterocycles* **2006**, *70*, 143. (f) Sinclair, A.; Arini, L. G.; Rejzek, M.; Szeto, P.; Stockman, R. A. *Synlett* **2006**, *14*, 2321. (g) Hurley, P. B.; Dake, G. R. *J. Org. Chem.* **2008**, *73*, 4231.

(10) Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867.

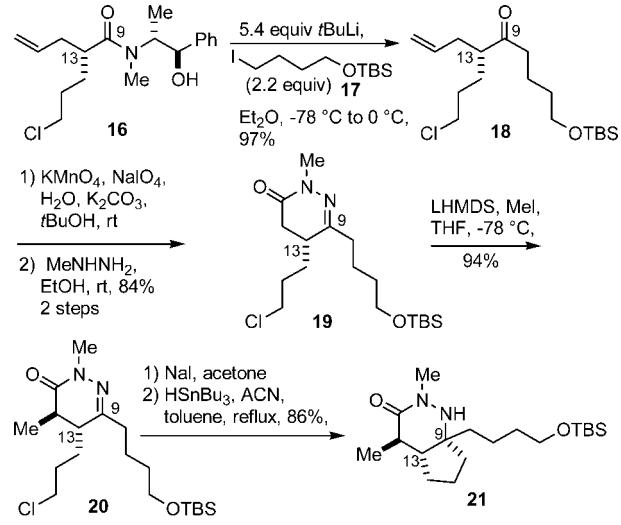
Scheme 4. Retrosynthetic Analysis of Halichlorine **9**



of the C_1,C_2,C_{22} segment **12** to unveil the aza-spirocycle **13**. The spirocycle **13** was envisioned to arise through an S_N2 displacement using a N−N bond-cleaved derivative of cyclopentapyridazinone **14**. This intermediate could be constructed stereoselectively using the 5-*exo* radical cyclization approach from pyridazinone **15**.

To access the pyridazinone with the desired substitution in place, the alkylated pseudoephedrine analogue **16** was treated with the alkyl lithium reagent derived from alkyl iodide **17** (Scheme 5). The olefin in the resulting ketone **18**

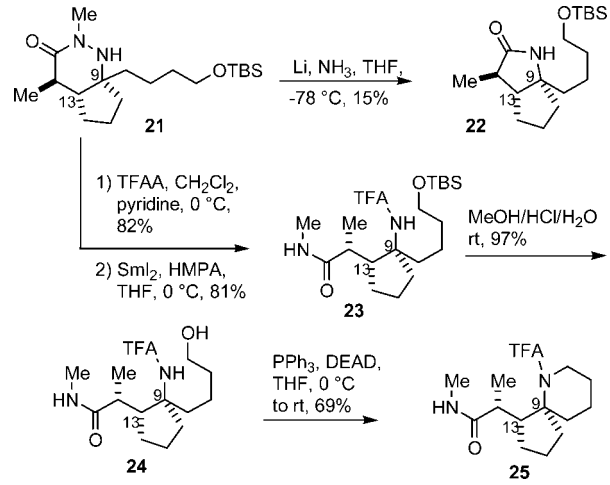
Scheme 5. Installation of C_{14} Methyl and C_9−C_{13} Cyclopentane



was oxidatively cleaved with $NaIO_4$ and catalytic $KMnO_4$ to give the carboxylic acid that was then condensed with methyl hydrazine to provide the "*N*-methyl protected" pyridazinone **19**. This was then followed by a rather daring alkylation of compound **19** with methyl iodide which afforded compound **20** in 94% yield and as a single diastereomer.[12] The chloride in compound **20** was exchanged for an iodide, and as expected, cyclopentapyridazinone **21** was formed upon exposure to $HSnBu_3$ and ACN in toluene at reflux, in 86% yield over the two-step sequence.

Elaboration to a simplified aza-spirocycle was next explored (Scheme 6). Initially the N−N bond cleavage was

Scheme 6. Formation of Aza-Spirocycle via Mitsunobu



attempted using dissolving metal conditions. Interestingly, while cyclopentapyridazinone **21** was fully consumed, only 15% of *cis*-fused cyclopentalactam **22** was isolated; none of the desired uncyclized compound was observed. This unexpected result prompted us to use alternative conditions. After acylation of the amine nitrogen, the N−N bond was reductively cleaved using SmI_2 to give the ring-opened trifluoroacetamide **23**.[13] The TBS group was then removed, and the primary alcohol **24** was treated under Mitsunobu conditions, which afforded the target aza-spirocycle **25** in 69% yield.

The initial stereocenter obtained through Myers' alkylation, coupled with the rigidity of the pyridazinone radical accepter, ultimately provided access to three of the four stereocenters found in halichlorine. We envisioned that the remote C_5 stereocenter of the aza-spirocycle found in the natural product might be accessed using the catalytic asymmetric allylation (CAA) reaction.[14] Toward this end, the C_5 silyl ether **20** was converted into aldehyde **26** by removal of the TBS group followed by Swern oxidation (Scheme 7). Aldehyde **26** was

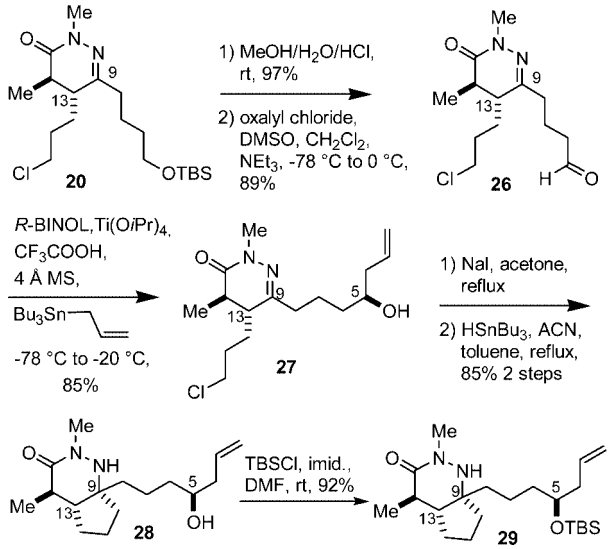
(11) (a) Bevilacqua, M. P.; Nelson, R. M.; Mannori, G.; Cecconi, O. *Annu. Rev. Med.* **1994**, *45*, 361. (b) Carlos, T. M.; Harlan, J. M. *Blood* **1994**, *84*, 2068. (c) Foster, C. A. *J. Allergy Clin. Immunol.* **1996**, *98*, S270. (d) Yusuf-Makagiansar, H.; Anderson, M. E.; Yakovleva, T. V.; Murray, J. S.; Siahaan, T. J. *Med. Res. Rev.* **2002**, *22*, 146.

(12) The more obvious sequence of alkylation after radical cyclization was found to give much lower levels of diastereoselectivity for introduction of the methyl group (ca. 2:1).

(13) (a) Ding, H.; Friestad, G. K. *Org. Lett.* **2004**, *6*, 637. (b) Friestad, G. K.; Marie, J.-C.; Deveau, A. M. *Org. Lett.* **2004**, *6*, 3249.

(14) (a) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (b) Keck, G. E.; Krishnamurthy, D. *Org. Synth.* **1998**, *75*, 12.

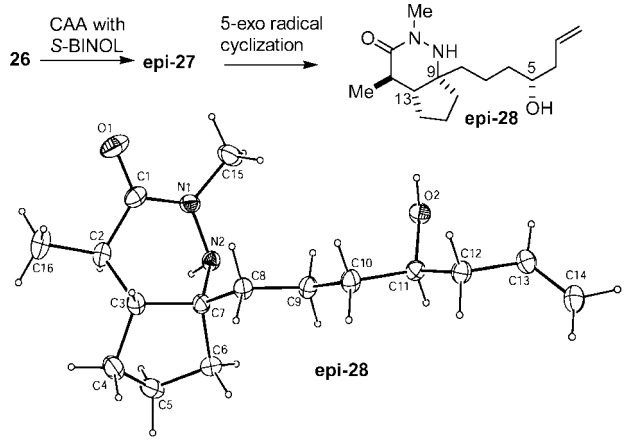
Scheme 7. CAA and 5-*Exo* Radical Cyclization



then treated under the CAA conditions using *R*-BINOL. This reaction gave alcohol **27** in an excellent 85% yield as only one detectable diastereomer. In addition, aldehyde **26** was converted to the C_5 epimeric alcohol **epi-27** using *S*-BINOL under otherwise identical conditions; this ultimately proved important for establishing the relative and absolute configurations in this series.

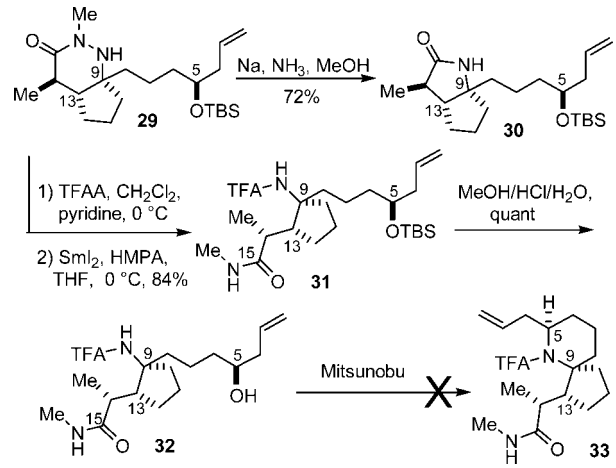
The pyridazinone **27**was then treated under the radical cyclization conditions to give *cis*-fused cyclopentapyridazinone **28** in 85% yield (Scheme 7). Similarly the pyridazinone **epi-27** was treated under these radical cyclization conditions and yielded cyclopentapyridazinone **epi-28**. Assignment of the relative and absolute configuration of our compounds was verified by X-ray analysis of compound **epi-28** (Scheme 8).

Scheme 8. Synthesis and ORTEP Representation of **epi-28**



Finally, we have examined application of this methodology to the aza-spirocycle found in halichlorine. Initially, we explored the potential of cleaving the N−N bond in **29** using dissolving metal conditions with sodium in place of lithium. Use of sodium in ammonia provided the bicyclic lactam **30** in 72% yield (Scheme 9). It should be recognized that the

Scheme 9. Approach to Halichlorine's Aza-Spirocycle



cyclopentalactams **22** and **30** could also serve as potential intermediates for accessing halichlorine.[15]

Acylation of **29** with TFAA followed by treatment with SmI_2 afforded the ring opened product **31** (Scheme 9). The TBS group was removed, and alcohol **32** was treated under Mitsunobu conditions. Unfortunately, all attempts to cause the S_N2 displacement of the C_5 alcohol and its derivatives to give the aza-spirocycle **33** were futile; elimination products were formed predominately.

In summary, the pyridazinone ring system has served as an excellent scaffold for preparing novel *cis*-fused cyclopentapyridazinones utilizing the directed 5-*exo* radical cyclization approach discussed above. This strategy to access compounds like **7**, **8**, **21**, and **28** presents a direct, diastereoselective method to access these substructures that contain a new quaternary stereocenter in essentially enantiomerically pure form.

In the context of an approach to halichlorine, the rigid pyridazinone ring system led to the facile and highly diastereoselective installation of the *cis*-C_9−C_{13} cyclopentane ring as well as the C_{14} methyl found in halichlorine. The CAA reaction provided a highly stereoselective method to generate the remote hydroxy stereocenter that was slated to provide the C_5−N bond of the aza-spirocycle. However, the ring closure from this intermediate will require further study.

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Supporting Information Available: Full experimental details as well as spectral and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) See intermediate **6** in ref 9a.