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A Concise Total Synthesis of (+)-Scholarisine A Empowered by a Unique C−H Arylation

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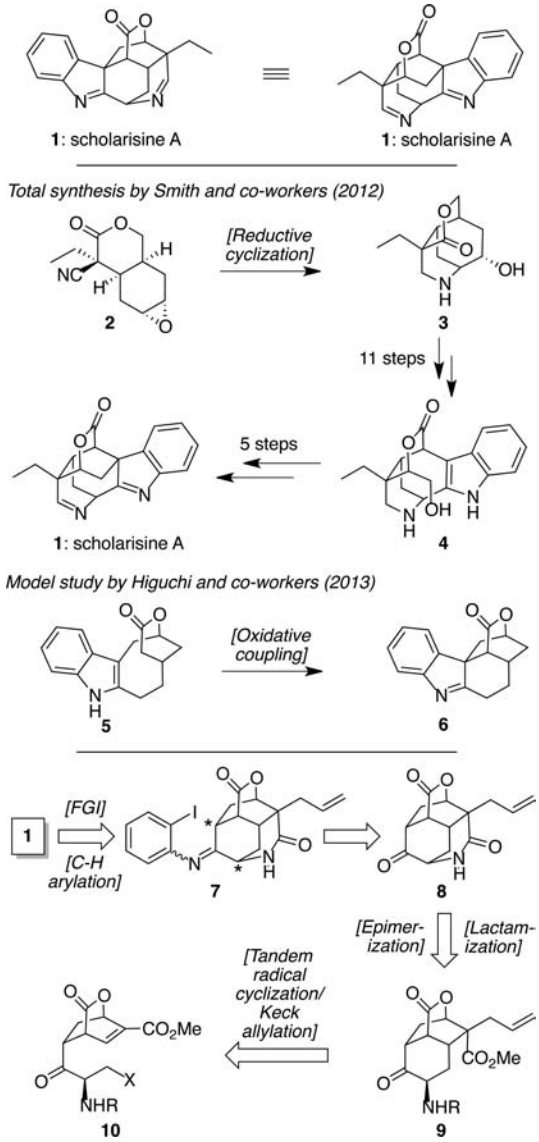
Supporting Information

ABSTRACT: The structurally unique akuammiline alkaloid (+)-scholarisine A was synthesized in 14 steps from a known enone (15 steps from commercial materials) through a route empowered by a unique C−H arylation reaction to forge its polycyclic core. Additional key steps include a pyrone Diels−Alder reaction and a radical cyclization/Keck allylation to fashion the core cage polycycle and one of the molecule's quaternary centers, as well as the use of a carefully positioned pendant hydroxyl group to facilitate the chemoselective reduction of an extremely unreactive lactam in the presence of a readily reduced lactone.

Monoterpenoid indole alkaloids have a long and storied history in treating disease, elucidating core biochemical pathways, and advancing the power of synthetic chemistry through efforts to fashion and derivatize their structural intricacies. One recent addition to the family is the akuammiline alkaloid scholarisine A (**1**, Scheme 1), a dense, polycyclic compound isolated from *Alstonia scholaris*, a plant used in traditional Chinese medicine to treat various respiratory diseases.[1] Its structure is quite unique within the class[2] given that it possesses an indolenine fused to a strained carbocyclic cage, itself adorned with several tertiary and quaternary stereocenters as well as potentially labile imine and bridging lactone functional groups; its specific biological properties, however, remain unexplored. Given this profile, it is unsurprising that chemists have been drawn to its challenges and its potential. In 2012, the Smith group developed an elegant, enantioselective total synthesis of (+)-**1** which proceeded in 20 steps from a known compound (25 steps from commercial materials).[3] Key elements of their approach, which constitutes the only complete solution to this target, are shown in Scheme 1. In addition, Higuchi and co-workers recently reported model studies toward the spiroindolenine portion of **1** using an oxidative coupling to forge that domain.[4] Herein, as part of a program interested in rapidly accessing unique polycyclic frameworks,[5] we report a distinct analysis of the synthetic challenges posed by scholarisine A. That approach sought to develop a unique C−H arylation to attach the indolenine domain directly to a near fully functionalized core, itself prepared rapidly and efficiently through the use of Diels−Alder chemistry and a radical cyclization/capture cascade.

Our retrosynthetic analysis of **1** is delineated in the lower part of Scheme 1. Describing its logic in the forward sense, we were guided by the general notion that the target's core

Scheme 1. Unique Structure of Scholarisine A (1), Past Synthetic Approaches, and a Distinct Retrosynthetic Analysis of the Target Molecule



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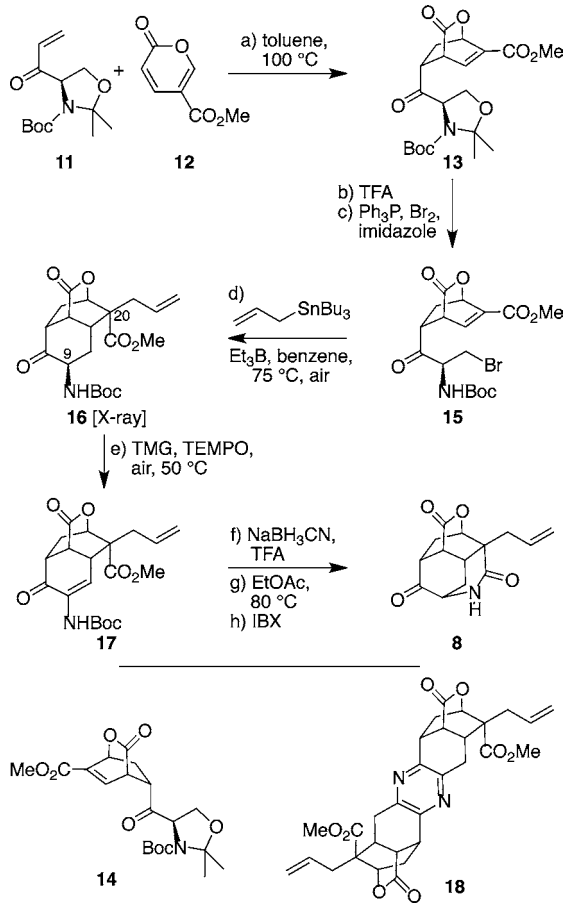
carbocyclic substructure could potentially be fashioned rapidly if we could access a material such as **10** with an oxabicyclo[2.2.2]octane. The key event for its preparation was envisioned to be an *endo*- and diastereoselective pyrone Diels–Alder reaction,[6] setting the stage for a tandem 6-*exo*-trig radical cyclization/Keck allylation[7] to then access **9**. This cascade operation was expected to form the quaternary center with high diastereoselection via *exo*-face delivery of the allyl group to an intermediate α-carbonyl radical. From here, completion of the last ring of the caged core through epimerization of the amine-bearing stereocenter and lactamization would enable attempts to directly incorporate the indolenine domain via imine formation (to form **7**) followed by a novel, late-stage tertiary C–H arylation reaction. Although such processes are known in specific contexts to occur with activated, enolizable carbons, to the best of our knowledge no examples involving nonenolizable,[8] and potentially labile, imines are known.[9] Moreover, as an additional challenge, positional selectivity between two different tertiary centers (the starred carbons within **7**) would be required, assuming that the initial imine stereochemistry would not be product-determining.[10] However, if these variables could be addressed successfully, then (+)-scholarisine A (**1**) could result from a final chemoselective reduction of a hindered lactam in the presence of a fairly accessible lactone. To aid in that task, the functionality of the strategically positioned allyl side chain could potentially prove useful.

As shown in Scheme 2, our synthetic efforts began with a Diels–Alder reaction between dienophile **11**[11] (available in decagram quantities in three steps from *N*-Boc-D-Serine, see Supporting Information) and a slight excess (1.2 to 1.8 equiv) of methyl coumalate (**12**) at 100 °C in toluene for 33 h. These conditions afforded the desired product (**13**) alongside a minor amount of its separable diastereomer **14** and another very minor component of unknown structure (3:1:0.1), in 83% combined yield. A priori, this cycloaddition would seem to be unfavorable, given the electron-deficient nature of both components; as such, it is notable that it proceeds with such efficiency.[12] Moreover, the protecting groups on the serine-derived dienophile had a significant effect on both the yield and diastereoselectivity of the reaction; for instance, the corresponding *O*-TBS-protected congener of **11** afforded Diels–Alder adducts in 47% yield and a dr of 1.7:1:0.1.

With **13** in hand, we next set about transforming its protected alcohol into an appropriate radical cyclization precursor. That task was accomplished using TFA in $CHCl_3$[13] at 0 °C to remove the acetonide chemoselectively followed by bromination under Appel-type conditions to afford bromide **15** in 86% yield. With the stage now set for our key cascade, we were pleased to find, after a screen of several carbon-based radical traps, that following exposure of **15** to allyltributylstannane and Et_3B as a radical initiator[14] under an air atmosphere **16** could be obtained in 59% yield as a single diastereomer possessing the desired stereochemistry at the C-20 quaternary center (as confirmed by X-ray analysis).

Having reached this critical staging area, we next envisaged deprotecting the nitrogen atom and effecting epimerization/lactamization to access **8** directly through treatment with the appropriate base. However, exploration of various conditions along these lines revealed that the deprotected α-amino ketone underwent facile dimerization and oxidation instead to give pyrazine **18**. Fortunately, a solution presented itself during epimerization attempts on **16** using DBU as base when we

Scheme 2. Preparation of the Core of Scholarisine A[a]



[a]Reagents and conditions: (a) **12** (1.8 equiv), toluene, 100 °C, 33 h, 83% (**13**:**14**:unk = 3.0:1.0:0.1); (b) TFA (6% v/v), $CHCl_3$, 0 °C, 12 h, 83%; (c) Ph_3P (1.5 equiv), imidazole (1.5 equiv), Br_2 (1.5 equiv); CH_2Cl_2, 0 °C, 40 min, 86%; (d) allyltributylstannane (3.0 equiv), Et_3B (5 × 0.2 equiv), benzene, air, 75 °C, 5 h, 59%; (e) TMG (1.1 equiv), TEMPO (1.1 equiv), air, THF, 50 °C, 12 h, 68%; (f) $NaBH_3CN$ (5.0 equiv), TFA (17.6 equiv), CH_2Cl_2, 0 °C, 40 min; (g) EtOAc, 80 °C, 2 h, 91% over two steps; (h) IBX (3.5 equiv), EtOAc, 80 °C, 12 h, >85%. TFA = trifluoroacetic acid, TMG = tetramethylguanidine, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical, IBX = *o*-iodoxybenzoic acid.

noticed that adventitious oxygen could readily oxidize this compound to its corresponding unsaturated congener **17**, presumably due to the ease of forming a captodative radical intermediate; an optimized process using TMG and TEMPO in THF under air gave enone **17** in 68% yield.[15] This outcome presented the possibility of a deprotection/*exo*-face reduction/lactamization sequence. Gratifyingly, treatment of a CH_2Cl_2 solution of **17** with $NaBH_3CN$ and TFA at 0 °C followed by heating in EtOAc afforded the desired caged compound in excellent yield (91%) with concomitant reduction of the ketone to the *endo* alcohol (structure not shown). Although the latter event was undesired, control experiments showed that ketone reduction was necessary to prevent pyrazine dimer formation. The constitution of the full cage structure was secured by extensive 2-D NMR studies as well as X-ray analysis of a crystalline derivative. Reoxidation with IBX then completed the synthesis of ketone **8** in >85% yield.

We were now poised to attempt the challenging late-stage arylation reaction to append the indolenine domain onto our

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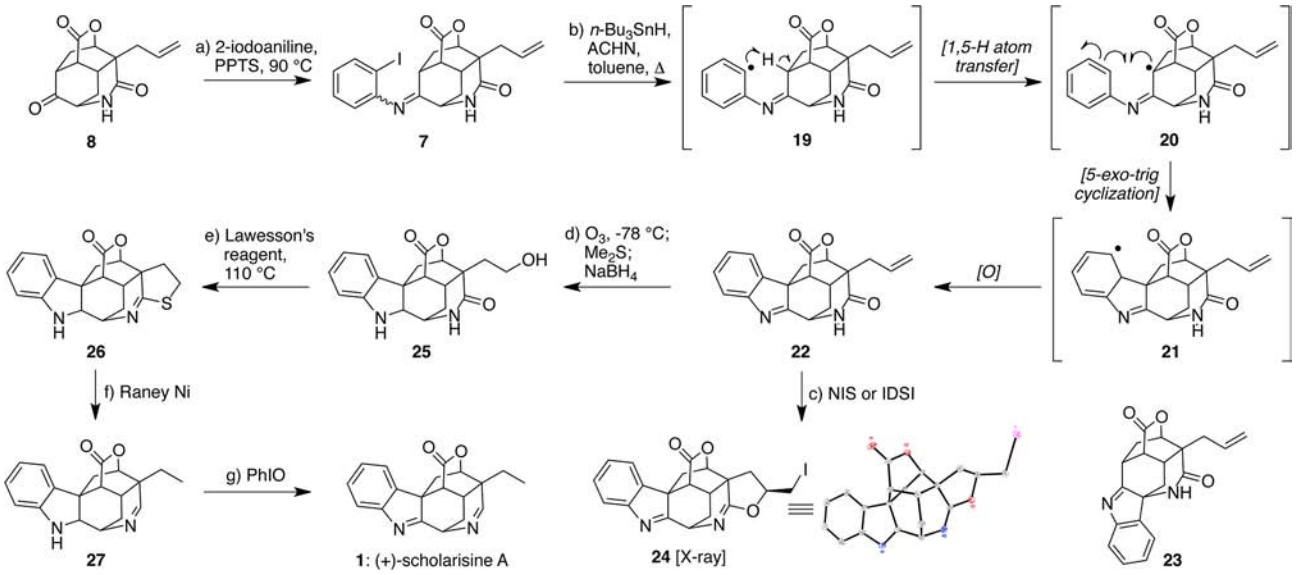
Scheme 3. Completion of the Total Synthesis of (+)-Scholarisine A (1)[a]



[a]Reagents and conditions: (a) 2-iodoaniline (1.1 equiv), PPTS (0.09 equiv), PhMe, THF, 4 Å m.s., 90 °C, 18 h; (b) *n*-Bu_3SnH (1.2 equiv), ACHN (1.2 equiv), toluene, 110 °C, 4.5 h, 25% (3 steps), **22**:**23** = 3.0:1.0; (c) NIS (2.0 equiv), CH_2Cl_2, 23 °C, 20 h, 72% or IDSI (1.7 equiv), CH_2Cl_2, −20 °C, 45 min, 27%; (d) O_3, CH_2Cl_2, MeOH, −78 °C, 2 min; Me_2S (22 equiv), −78→23 °C; $NaBH_4$ (2.6 equiv), EtOH, CH_2Cl_2, −40 → −10 °C, 1.5 h, 68%; (e) Lawesson's Reagent (2.1 equiv), THF, toluene, 110 °C, 16 h, 47%; (f) Raney Ni, THF, 23 °C, 1 h, 86%; (g) PhIO (5.4 equiv), CH_2Cl_2, 23 °C, 98%. PPTS = pyridinium 4-toluenesulfonate, ACHN = 1,1′-azobis(cyclohexanecarbonitrile), NIS = *N*-iodosuccinimide, IDSI = $(Et_2SI)_2Cl\cdot SbCl_6$.

caged framework. In the event, crude ketone **8** (Scheme 3) was directly subjected to a condensation reaction with 2-iodoaniline to provide the corresponding imine **7** as a 2.4−2.8:1 mixture of geometric isomers (batch dependent).[16] This material was then treated without purification with *n*-Bu_3SnH and 1,1′-azobis(cyclohexanecarbonitrile) to give the desired spiroindolenine **22** in 18% overall yield for the three steps starting from the precursor to carbocycle **8**. It also provided a small amount of product (6%, three steps) resulting from functionalization of the tertiary C−H bond at C-9 (i.e., **23**), revealing that relatively good positional selectivity could be achieved in this complex context.[17] Overall, the combined yield for the spiroindolenine products over the three-step sequence is 62% per step.[18] Several points about this critical sequence require mention. First, we believe the annulation likely proceeds in the mechanistic fashion shown via initial aryl radical formation, 1,5-H atom transfer and cyclization onto the aryl group, and terminating oxidation of the resulting cyclohexadienyl radical.[9b] Second, a transformation of this sort has not, to the best of our knowledge, been applied to the synthesis of such units, much less in a setting so complex.[9a,b,19] Third, multiple attempts at earlier aryl group installation, e.g. via Fischer indole synthesis or enolate arylation on compounds similar to **13** (cf. Scheme 2) or through aryl group incorporation into the original dienophile (i.e., **11**), proved fruitless.

From intermediate **22**, only functional group interconversions remained to reach the target, namely transformation of the allyl group and the lactam to the ethyl group and imine, respectively, of **1**. While the first of these tasks could be readily achieved in initial studies (not shown),[20] the reduction of the lactam in **22** (or its ethyl or propyl congener) proved extremely difficult, with >20 methods (both chemoselective or non-chemoselective) being unsuccessful.[21] The key clue toward an effective strategy came in the formation of iodoimidate **24** under iodocyclization conditions employing either IDSI[22] or NIS.[23] Although this intermediate (structure and absolute configuration verified by X-ray) ultimately proved to be unproductive in its own right, its synthesis prompted us to explore the allyl group, or some group derived from it, as a means to achieve chemoselective reduction of the lactam through intramolecular assistance. Thus, ozonolytic cleavage of the alkene and reduction of the resulting aldehyde to amino alcohol **25** provided a potential handle in the form of a primary alcohol. Pleasingly, treatment of **25** with Lawesson's reagent at 110 °C effected thiation/cyclodehydration to deliver thioimidate **26**. Without that handle, the lactam groups of **22**, or its di- and tetrahydro derivatives, did not undergo thionation under identical (and even more vigorous) conditions.[24] Subsequent excision of the S atom within **26** using Raney Ni in THF at 23 °C for 1 h simultaneously formed the ethyl group and imine function of **1** in the form of **27**. A final oxidation using PhIO at ambient temperature then gave (+)-scholarisine A (**1**) in near-quantitative yield, the spectroscopic data of which matching those of the naturally-derived material in all respects.

In conclusion, we have completed an enantioselective synthesis of (+)-scholarisine A (**1**) in 14 steps from known enone **11** (15 steps from commercial materials). This route compares favorably in terms of step count to the inaugural Smith synthesis[3] of **1**. Key discoveries include an efficient and diastereoselective pyrone Diels−Alder reaction to rapidly form the appropriately functionalized [2.2.2]-bicycle, a radical cyclization/Keck allylation to concurrently forge the [3.3.1]-bicycle and C-20 quaternary center, an indolenine annulation at a nonenolizable tertiary center via a novel late-stage radical C−H arylation, and the use of a pendant hydroxyl group to facilitate the chemoselective reduction of an extremely unreactive lactam. Current and future work is directed toward applying the developed strategy to related targets, exploring the scope of the C−H arylation step, and probing the biochemical potential of scholarisine A itself.

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■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, copies of all spectral data, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(4) Watanabe, T.; Kato, N.; Umezawa, N.; Higuchi, T. *Chem.—Eur. J.* **2013**, *19*, 4255.

(5) Selected examples from our group include the total synthesis of the terpenoid rippertenol and the polycycles of the securinega alkaloids: (a) Snyder, S. A.; Wespe, D. A.; von Hof, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 8850. (b) ElSohly, A. M.; Wespe, D. A.; Poore, T. J.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 5789.

(6) For a review, see: Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111.

(7) For an example of a tandem radical cyclization/Keck allylation, see: Evans, P. A.; Manangan, T. *Tetrahedron Lett.* **1997**, *38*, 8165.

(8) The aza-enolate derived from **7** would be extremely strained, formally containing an anti-Bredt olefin within a six-membered ring. This outcome would preclude the use of methods that proceed through enamine/aza-enolate intermediates.

(9) For radical-based H-atom transfer/cyclization approaches towards oxindoles, see: (a) Beckwith, A. L. J.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.* **1995**, 977. (b) Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 95. For selected Pd-catalyzed approaches to indolines involving activation of nonenolizable C–H bonds, see: (c) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759 (primary C–H). (d) Nakanishi, M.; Katayev, D.; Besnard, C.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7438 (secondary C–H). (e) Saget, T.; Perez, D.; Cramer, N. *Org. Lett.* **2013**, *15*, 1354 (tertiary cyclopropyl C–H).

(10) At the planning stage, we recognized that if isomerization of the imine geometric isomers was competitive (e.g., thermally) with the C–H functionalization process, then the initial *E*/*Z* ratio may not be important. Staab and co-workers have shown that the imine derived from acetone and aniline isomerizes rapidly on the NMR time scale at higher temperatures (*E*/*Z*-Me signal coalescence temperature = 126 °C) while its 2,6-dimethylaniline congener does so even more readily (110 °C). We expected our 2-iodoaniline derived imine to isomerize at an intermediate rate: (a) Wurmb-Gerlich, D.; Vögtle, F.; Mannschrek, A.; Staab, H. A. *Liebigs Ann. Chem.* **1967**, *708*, 36. In addition, any residual acid present would be expected to facilitate the isomerization process: (b) Jennings, W. B.; Al-Showiman, S.; Tolley, M. S.; Boyd, D. R. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1535.

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(12) Reported Diels–Alder reactions with methyl coumalate (**12**) typically involve electron-rich or highly electron-deficient dienophiles. See, for example: (a) Shimo, T.; Yoshimura, H.; Suishu, T.; Somekawa, K. *Nippon Kagaku Kaishi* **1988**, 1984 (maleimides). (b) Shimo, T.; Nagahama, H.; Yozoru, K.; Somekawa, K. *J. Heterocyclic Chem.* **1992**, *29*, 801 (*p*-benzoquinones). (c) Bates, R. W.; Pratt, A. J.; Rendle, P. M.; Thomson, W. T. *Aust. J. Chem.* **1998**, *51*, 383 (1,1-bis(methylthio) ethene). (d) Chen, C.-H.; Liao, C.-C. *Org. Lett.* **2000**, *2*, 2049 (2-methoxyfurans).

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(14) Use of AIBN as a radical initiator proved to be ineffective. For an example of another case where Et_3B was uniquely effective as a radical initiator, see: Reddy, L. R.; Fournier, J.-F.; Reddy, B. V. S.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 8974.

(15) In the absence of TEMPO, the reaction proceeded in ca. 40% yield. We suspect TEMPO is a more effective radical trap than O_2, leading to less decomposition/side reactions.

(16) Although this step might be envisioned to be difficult, condensations of anilines and 2-adamantanone, a material that is similar in structure to **8**, are known. For a representative example, see: Sasaki, T.; Eguchi, S.; Hirako, Y. *Tetrahedron* **1976**, *32*, 437.

(17) Given the starting ratio of imines, it is possible that the original stereochemistry of that functional group was product-determining. Since the initial isomers could not be readily isolated as pure components or their stereochemistry assigned, it is difficult to draw a conclusion in terms of whether isomerization is occurring prior to cyclization.

(18) Aside from the formation of several unidentifiable products generated in trace quantities, the only other characterizable species isolated (≤5% over three steps) was that derived from trapping of the intermediate cyclohexadienyl radical **21** by $C_6H_{10}CN\cdot$ (from ACHN).

(19) In model studies using the corresponding 2-adamantanone-derived imine with two identical tertiary C–H bonds, yields of ca. 60% could be obtained. Studies are continuing to explore the scope of this transformation: Rageot, D.; Snyder, S. A., unpublished results.

(20) This transformation was achieved through ozonolysis, dithiolane formation, and desulfurization with Raney Nickel.

(21) Selected reductions attempted: $Tf_2O/HSiEt_3$, Cp_2ZrHCl, $LiAlH_4$, Red-Al, AlH_3, $AlH_3\cdot EtNMe_2$, $BH_3\cdot THF$, $BH_3\cdot SMe_2$; reduction of corresponding methyl imidate (Me_3OBF_4): $LiAlH_4$, $BH_3\cdot THF$, AlH_3, $NaBH_4$, $NaBH_4$/HCl, Zn/AcOH, LiDBB, Ra-Ni. In all cases, no reduction of the lactam (or its derivative) was observed.

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(24) Nishio, T.; Sekiguchi, H. *Tetrahedron* **1999**, *55*, 5017. In the present case, their proposed mechanism involving initial thiation of the alcohol, thionation of the lactam, and cyclization with loss of H_2S seems unlikely given that **22** and its congeners lacking the alcohol group did not undergo thionation.