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Asymmetric Total Syntheses of (−)-Renieramycin M and G and (−)-Jorumycin Using Aziridine as a Lynchpin

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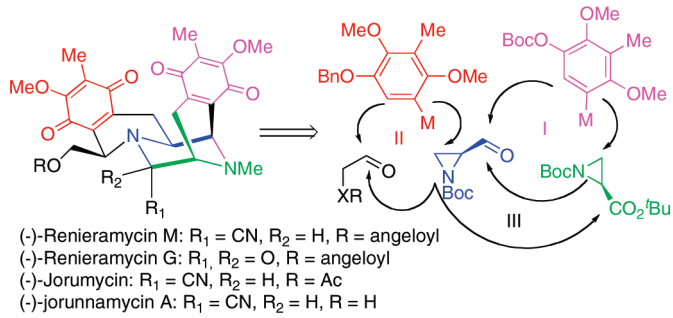
ABSTRACT



By exploring the triple reactivity of two aziridines and double nucleophilicity of two aromatics, convergent and versatile syntheses of the above four natural products were developed.

Antitumor antibiotic renieramycin M (**1**, Figure 1) has been isolated from the marine sponge *Xestospongia* sp. in 2003,[1] which belongs to a growing family of bioactive tetrahydroisoquinoline alkaloids including renieramycin G (**2**), jorumycin (**3**), saframycins (**4**), and ecteinascidin 743 (Et 743, **5**) etc.[2] These natural products show potent antitumor antibiotic activities, and one of them, the Et 743 (**5**), has received in 2007 marketing authorization from the European commission for the treatment of advanced soft-tissue sarcomas.[3] The fascinating molecular architecture and potent bioactivities of these natural products have attracted a great deal of attention from the organic-synthesis community.[4] The synthetic efforts have not only led to the development of new synthesis strategies but also led to the discovery of several medicinally significant analogues such as zalypsis that are currently in advanced human clinical trials as an anticancer agent.[5,6] Williams et al.[7] have developed convergent asymmetric syntheses of renieramycin G (**1**) and

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(2) (a) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730. (b) Siengalewicz, P.; Rinner, U.; Mulzer, J. *Chem. Soc. Rev.* **2008**, *37*, 2676–2690.

(3) Cuevas, C.; Francesch, A. *Nat. Prod. Rep.* **2009**, *26*, 322–337.

(4) For recent total syntheses of this family of alkaloids, see: (a) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552–6554. (b) Ashley, E. R.; Cruz, E. G.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 15000–15001. (c) Kwon, S.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 16796–16797. (d) Chan, C.; Heid, R.; Zheng, S.; Guo, J.; Zhou, B.; Furuuchi, T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 4596–4598. (e) Chen, J.; Chen, X.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2006**, *128*, 87–89. (f) Chen, J.; Chen, X.; Willot, M.; Zhu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 8028–8032. (g) Chen, X.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 3962–3965. (h) Vincent, G.; Williams, R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1517–1520. (i) Kaniskan, H. U.; Garner, P. *J. Am. Chem. Soc.* **2007**, *129*, 15460–15461. (j) Wu, Y.-C.; Liron, M.; Zhu, J. *J. Am. Chem. Soc.* **2008**, *130*, 7148–7152. (k) Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 17270–17271.

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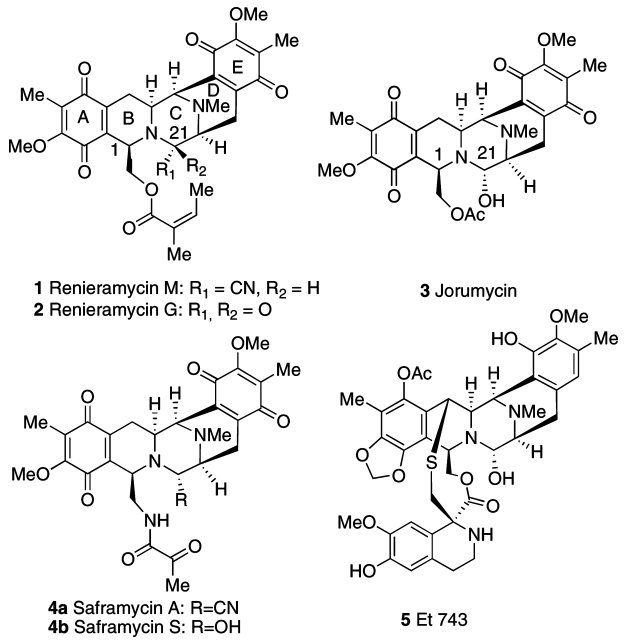
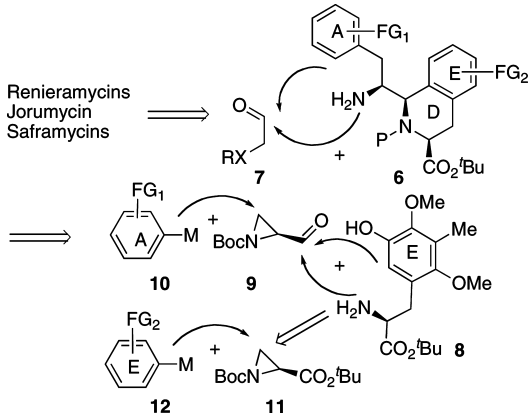


Figure 1. Examples of bistetrahydroisoquinoline alkaloids.

jorumycin (**3**) taking advantage of the latent symmetry of these molecules.[8,9] Liu et al. have very recently reported a synthesis of (−)-renieramycin G (**1**) based on a similar strategy.[10] In addition, Magnus and co-workers have described a synthesis of racemic renieramycin G (**1**).[11] Construction of the bicyclic A−B ring system followed by N-acylation and elaboration of the central bridged C−D ring is a common feature of these reported syntheses.[7,10−12]

From a structural point of view, the main differences among these alkaloids reside on the aromatic A and E rings, the C_1 substituent (CH_2OR or CH_2NHR), and the C_{21} functionalities (carbinolamine, amionitrile vs amide). We thought to develop a modular approach that allows the introduction of these structural elements at the late stage of the synthesis (Scheme 1). Tetrahydroisoquinoline **6** deemed

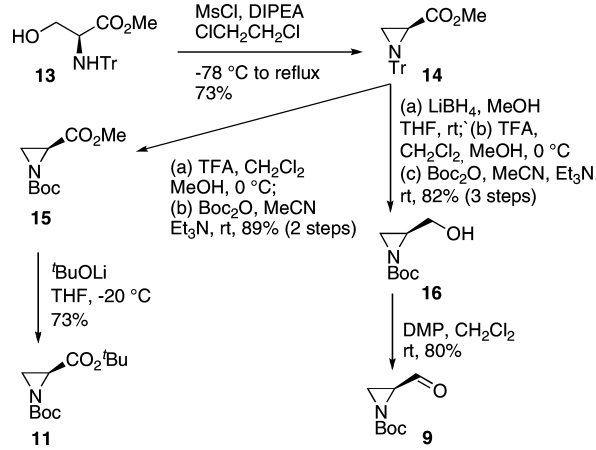
Scheme 1. Retrosynthetic Analysis of Renieramycin Alkaloids



to satisfy this criterion since it is potentially amenable to all members of renieramycin/saframycin alkaloids. Compound **6** was thought to be prepared by the Pictet−Spengler reaction of aminoester **8** and (*S*)-2-formyl-aziridine (**9**), followed by ring-opening of aziridine with organometallic regent **10**. Aminoester **8** could in turn be synthesized by coupling of aziridine **11** with nucleophile **12**. We report herein the realization of this strategy by developing the first total synthesis of renieramycin M (**1**), as well as the syntheses of renieramycin G (**2**) and jorumycin (**3**).

Syntheses of aziridines **9** and **11** are shown in Scheme 2. Treatment of a 1,2-dichloroethane solution of commercially

Scheme 2. Synthesis of Aziridines **9** and **11**



available *N*-trityl-L-serine methyl ester (**13**) with MsCl and DIPEA at −78 °C followed by heating to reflux afforded directly the aziridine **14** in 73% yield. Removal of the *N*-trityl group under mild acidic conditions followed by *N*-*tert*-butoxycabonylation afforded *N*-Boc aziridine **15** in 89% overall yield, which was in turn converted to the desired (*S*)-di-*tert*-butyl aziridine-1,2-dicarboxylate (**11**) (85%) by a

(5) (a) Martinez, E. J.; Owa, T.; Schreiber, S. L.; Corey, E. J. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 3496–3501. (b) Myers, A. G.; Plowright, A. T. *J. Am. Chem. Soc.* **2001**, *123*, 5114–5115.

(6) Gallerani, E.; Yap, T. A.; Lopez, A.; Coronado, C.; Shaw, H.; Florez, A.; de las Heras, B.; Cortés-Funes, H.; de Bono, J.; Paz-Ares, L. *J. Clin. Oncol., ASCO Meeting Abstr.* **2007**, *25*, 2517.

(7) Lane, J. W.; Chen, Y.; Williams, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 12684–12690.

(8) (a) Myers, A. G.; Kung, D. W.; Zhong, B.; Movassaghi, M.; Kwon, S. *J. Am. Chem. Soc.* **1999**, *121*, 8401–8402. (b) Myers, A. G.; Kung, D. W. *J. Am. Chem. Soc.* **1999**, *121*, 10828–10829. (c) Myers, A. G.; Kung, D. W. *Org. Lett.* **2000**, *2*, 3019–3022. (d) Myers, A. G.; Lanman, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 12969–12971.

(9) See also: (a) Fukuyama, T.; Yang, L.; Ajeck, K. L.; Sachleben, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 3712–3713. (b) Saito, N.; Yamauchi, R.; Nishioda, H.; Ida, S.; Kubo, A. *J. Org. Chem.* **1989**, *54*, 5391–5395. (c) Shawe, T. T.; Liebeskind, L. S. *Tetrahedron* **1991**, *47*, 5643–5646.

(10) Wang, X. W.; Liu, W.; Dong, W. F.; Guan, B. H.; Chen, S. Z.; Liu, Z. Z. *Tetrahedron* **2009**, *65*, 5709–5715.

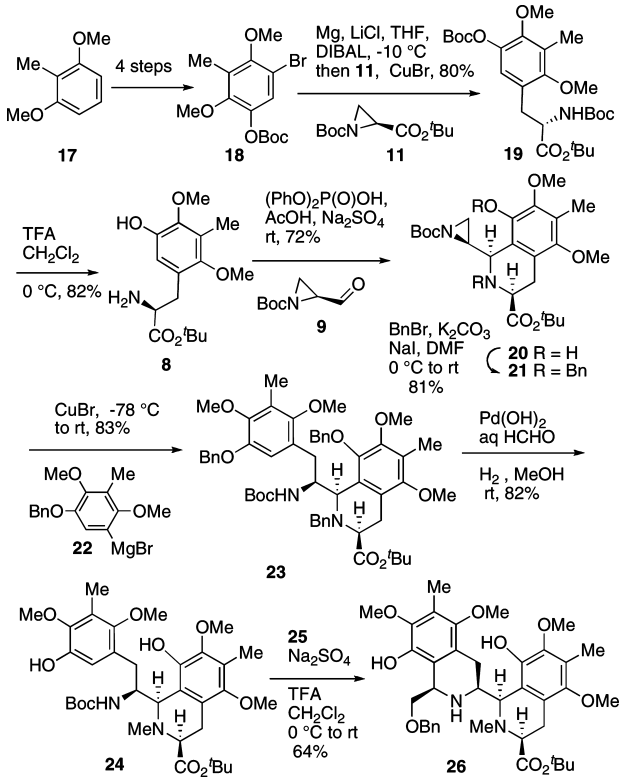
(11) Magnus, P.; Matthews, K. S. *J. Am. Chem. Soc.* **2005**, *127*, 12476–12477.

(12) Synthesis of renieramycin A: (a) Fukuyama, T.; Linton, S. D.; Tun, M. M. *Tetrahedron Lett.* **1990**, *31*, 5989–5992. (b) Saito, N.; Yamauchi, R.; Kubo, A. *Heterocycles* **1991**, *32*, 1203–1206.

transesterification with lithium *tert*-butoxide.[13] Following a conventional three-step sequence, aziridine **14** was converted to (*S*)-*N*-Boc-2-(hydroxymethyl) aziridine (**16**) in 82% overall yield, which was then oxidized (DMP, CH_2Cl_2, rt) to furnish the (*S*)-2-formyl-aziridine (**9**) in 80% yield.

Synthesis of bistetrahydroisoquinoline **26** is depicted in Scheme 3. The commercially available 2,6-dimethoxytoluene

Scheme 3. Synthesis of Bistetrahydroisoquinoline **26**



(**17**) was converted to aryl bromide **18** in four conventional steps with 84% overall yield. Arylmagnesium formation from **18** under Knochel's conditions[14] followed by a copper bromide-promoted coupling with aziridine **11**[15] afforded aminoester **19** in 80% yield. Simultaneous O- and N-deprotection of **19** under acidic conditions provided aminoester **8**.[16] The Pictet−Spengler reaction of **8** and **9** turned out to be challenging. No reaction occurred under mild acidic conditions (LiCl-HFIP, 2,6-di-*tert*-butyl-4-methyl phenol),[17] while degradation was observed in the presence of stronger Brønsted acids (HCl, HOTf, HBF_4, etc.) or Lewis acids (lanthanide triflates). Fortuitously, when the reaction was performed in acetonitrile in the presence of a catalytic amount of diphenylphosphoric acid [$(PhO)_2P(O)OH$, 0.1 equiv], the desired tetrahydroisoquinoline **20** was isolated in 27% yield.[18] Further optimization based on this observation by varying the solvents (MeCN, PhMe, CH_2Cl_2), the temperature (0 °C to rt), and the additives (molecular sieves, Na_2SO_4, other acidic components) allowed us to identify the optimum reaction conditions (cf. Supporting Information). Thus, slow addition of a CH_2Cl_2 solution of **9** (1.2 equiv) to the mixture of **8** (1.0 equiv), acetic acid (AcOH, 1.0 equiv), $(PhO)_2P(O)$-OH (0.1 equiv), and Na_2SO_4 in CH_2Cl_2 at room temperature afforded **20** in 72% yield. It is interesting to note that using acetic acid as a promoter in the absence of $(PhO)_2P(O)OH$ under otherwise identical conditions **20** was produced in less than 5% yield. Concurrent N- and O-benzylation of **20** furnished compound **21** in 81% yield.[19] Copper bromide-mediated coupling between Grignard reagent **22**, generated in situ from the corresponding aryl bromide, and aziridine **21** proceeded smoothly to afford compound **23** in 83% yield. The N- and O-debenzylation and in situ N-methylation of **23** were realized under hydrogenolysis conditions [$Pd(OH)_2$, H_2, HCHO, MeOH] to provide compound **24** in 82% yield. The tandem *N*-Boc deprotection and Pictet−Spengler reaction of **20** with benzyloxyacetaldehyde (**25**, CH_2Cl_2, TFA) afforded bistetrahydroisoquinoline **26** in 64% yield.

Syntheses of title natural products are detailed in Schemes 4 and 5. Conversion of *tert*-butyl ester in **26** to aldehyde (LAH, then Swern oxidation) followed by the Strecker reaction afforded pentacycle **27** (Scheme 3). The O-debenzylation of **27** was best realized in the presence of BCl_3 to afford alcohol **28** in 93% yield. Oxidation of phenol **28** with DDQ afforded jorunnamycin A (**29**).[20]

Acylation of alcohol **29** with angelic acid under modified Yamaguchi conditions[21] provided (−)-renieramycin M (**1**).[20] Similarly, acylation of alcohol **29** with acetic anhydride afforded cyanojorumycin (**30**) that, upon treatment with silver nitrate, was converted to (−)-jorumycin (**3**).[20] On the other hand, hydrolysis of the *tert*-butyl ester of **26** followed by amide bond formation under carefully controlled conditions (HATU, HOAt, DIPEA) afforded pentacycle **31** in 90% yield (Scheme 4). Hydrogenolysis of **31** in the presence of Pearlman's catalyst afforded alcohol **32**, which was converted

(13) Shtrumfs, B.; Chernyak, D.; Kalvins, I.; Trapencieris, P. *Chem. Heterocycl. Compd.* **2004**, *40*, 725–733.

(14) Piller, F. M.; Metzger, A.; Schade, M. A.; Haag, B. A.; Gavryushin, A.; Knochel, P. *Chem.—Eur. J.* **2009**, *15*, 7192–7202.

(15) (a) Baldwin, J. E.; Farthing, C. N.; Russell, A. T.; Schofield, C. J.; Spivey, A. C. *Tetrahedron Lett.* **1996**, *37*, 3761–3764. (b) Endo, A.; Kann, T.; Fukuyama, T. *Synlett* **1999**, 1103–1105. (c) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006.

(16) For an alternative synthesis, see :Wu, Y.-C.; Bernadat, G.; Masson, G.; Couturier, C.; Schlama, T.; Zhu, J. *J. Org. Chem.* **2009**, *74*, 2046–2052.

(17) (a) Chen, X. C.; Chen, J.-C.; De Paolis, M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 4397–4408. (b) Willot, M.; Chen, J.-C.; Zhu, J. *Synlett* **2009**, 577–580.

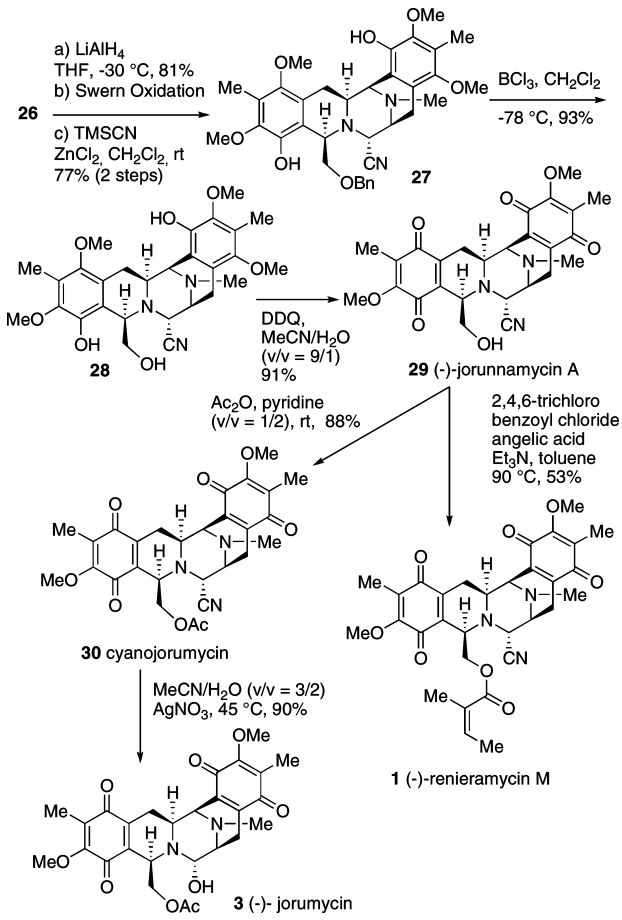
(18) Chiral phosphoric-acid-catalyzed enantioselective Pictet−Spengler reactions of tryptamine derivatives and aldehydes, see: (a) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086–1087. (b) Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7485–7487.

(19) The 1,3-*cis* stereochemistry of **17** was determined based on the observed NOE correlation between H1 and H3. See Supoting information.

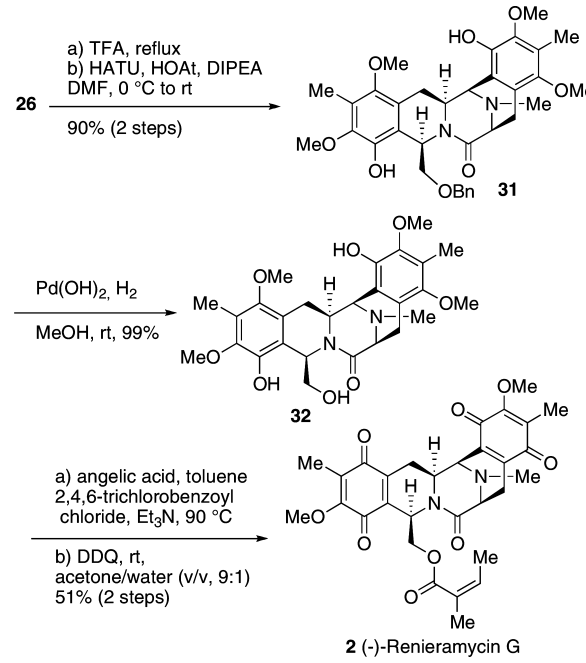
(20) The physical, spectroscopic, and spectrometric data of synthetic materials are identical to those described for natural (−)-jorunnamycin A, (−)-renieramycin M, (−)-jorumycin, and (−)-renieramycin G. See: (a) Charupant, K.; Suwanborirux, K.; Amnuoypol, S.; Saito, E.; Kubo, A.; Saito, N. *Chem. Pharm. Bull.* **2007**, *55*, 81–86. (b) Fontana, A.; Cavaliere, P.; Wahidulla, S.; Naik, C. G.; Cimino, G. *Tetrahedron* **2000**, *56*, 7305–7308. (c) Davidson, B. S. *Tetrahedron Lett.* **1992**, *33*, 3721–3724, and refs 1 and4a−c.

(21) Hartmann, B.; Kanazawa, A. M.; Depres, J.-P.; Greene, A. E. *Tetrahedron Lett.* **1991**, *32*, 5077–5080.

Scheme 4. Syntheses of (−)-Renieramycin M and (−)-Jorumycin



Scheme 5. Synthesis of (−)-Renieramycin G



to (−)-renieramycin G (**2**)[20] by selective acylation of the primary alcohol with angelic acid followed by DDQ oxidation.

In conclusion, we described efficient syntheses of four natural products: renieramycin M (17 steps in the longest linear sequence from 2,6-dimethoxytoluene with 3.9% overall yield), renieramycin G (16 steps with 6.4% overall yield), jorumycin (18 steps with 5.8% overall yield), and jorunnamycin A (16 steps with 10.9% overall yield) using highly functionalized bistetrahydroisoqinoline **26** as a common intermediate. The key feature of the present syntheses is the use of (*S*)-serine-derived aziridines **9** and **11** as lynchpins to connect the left and right part of the molecules. It is interesting to note that three out of four C and N atoms of aziridines **9** and **11**, except for the chiral carbon, participated in the bond forming processes for the effective construction of **27** and **31** (Figure 2). All transformations were highly diastereoselective, and no epimerization and stereochemical correction were required in these syntheses. We are currently exploiting this strategy for the syntheses of other members of bistetrahydroisoquinoline alkaloids as well as analogues for detailed structural−activity relationship studies.

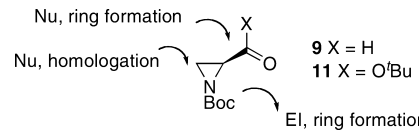


Figure 2. Full exploitation of the serine-derived aziridines.

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Supporting Information Available: Experimental details and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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