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Total Synthesis of the Marine Alkaloid Halichlorine: Development and Use of a General Route to Chiral Piperidines

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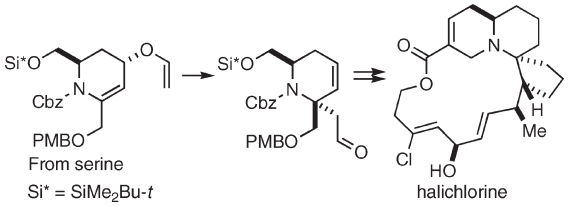

The total synthesis of the marine alkaloid halichlorine is described, based on an approach that involves constructing the fully substituted asymmetric center at an early stage. The five-membered ring is formed by 5-*exo-trig* radical cyclization and the unsaturated six-membered ring by a process that formally represents a sequential combination of conjugate addition and S_N2' displacement—a method that is general for making bicyclic compounds with nitrogen at a ring fusion position. A formal synthesis of (+)-halichlorine is also reported, based on the development of a general method for preparing optically pure piperidines. The key step of this method, which was used to make one of our intermediates, is the Claisen rearrangement of a 4-vinyloxy-3,4-dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester. Such *O*-vinyl compounds are easily generated in situ from the corresponding alcohols, which are themselves readily assembled from serine and terminal acetylenes.

Introduction

Halichlorine (**1**)[1] and the pinnaic acids, **2**[2,3] and **3**,[2,3] are structurally related natural products isolated from different marine organisms. The compounds possess significant biological properties and may have potential for use as biochemical tools or as leads for drug design. Halichlorine inhibits the induction of vascular cell adhesion molecule 1 (VCAM-1),[1] which is a property relevant to the study of inflammatory diseases and, importantly, the metastatic process of cancer cells.[4] The pinnaic acids inhibit cytosolic phospholipase A_2 ($cPLA_2$),[2] an enzyme involved at an early stage in the cascade of reactions that leads to the formation of certain inflammatory mediators.[5] The potential for biochemical and therapeutic applications, together with the synthetic challenges posed by the complicated structures, has attracted appreciable attention from organic chemists, and a large body of work has been reported.[6,7] Pioneering studies in Danishefsky's laboratory resulted in the total synthesis of both **1**[8] and **2**[3] in optically pure form, as well

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(2) Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett*. **1996**, *37*, 3871–3874.

(3) (a) Carson, M. W.; Kim, G.; Hentemann, M. F.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed*. **2001**, *40*, 4450–4452. (b) Carson, M. W.; Kim, G.; Danishefsky, S. J. *Angew. Chem., Int. Ed*. **2001**, *40*, 4453–4456.

(4) Biological properties of VCAM-1: (a) Foster, C. A. *J. Allergy Clin. Immunol*. **1996**, *98*, S270–S277. (b) Postigo, A. A.; Teixidó, J.; Sánchez-Madrid, F. *Res. Immunol*. **1993**, *144*, 723–735. (c) Vidal-Vanaclocha, F.; Fantuzzi, G.; Mendoza, L.; Fuentes, A. M.; Anasagasti, M. J.; Martin, J.; Carrascal, T.; Walsh, P.; Reznikov, L. L.; Kim, S.-H.; Novick, D.; Rubinstein, M.; Dinarello, C. A. *Proc. Natl. Acad. Sci. U.S.A*. **2000**, *97*, 734–739.

(5) Formation of certain inflammatory mediators: (a) Leslie, C. C. *J. Biol. Chem*. **1997**, *272*, 16709–16712. (b) Dennis, E. A. *J. Biol. Chem*. **1994**, *269*, 13057–13060. (c) Smith, W.; DeWitt, D. *Adv. Immunol*. **1996**, *62*, 167–215. (d) Holmeide, A. K.; Skatteboøl, L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2271–2276.

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(7) For references to model studies subsequent to, or not included in, ref 6, see: (a) Roulland, E.; Chiaroni, A.; Husson, H.-P. *Tetrahedron Lett*. **2005**, *46*, 4065–4068. (b) Keck, G. E.; Heumann, S. A. *Org. Lett*. **2008**, *10*, 4783–4786. (c) Hurley, P. B.; Dake, G. R. *J. Org. Chem*. **2008**, *73*, 4131–4138. (d) Sinclair, A.; Arini, L. G.; Rejzek, M.; Szeto, P.; Stockman, R. A. *Synlett* **2006**, 2321–2324. (e) Yang, S.-H.; Caprio, V. *Synlett* **2007**, 1219–1222.

(8) Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed*. **1999**, *38*, 3542–3545.

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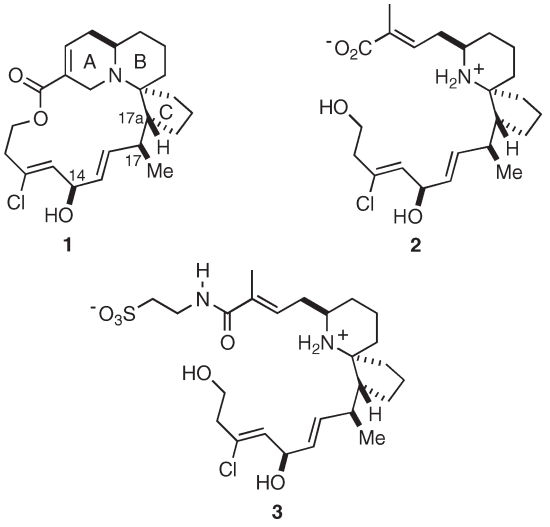
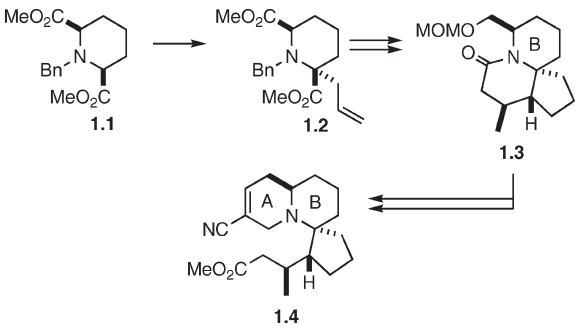
as clarification of certain configurational assignments and insights into the stereochemistry at nitrogen for the natural products and some of their synthetic precursors.[9] A synthesis, in racemic form, of halichlorine and the two pinnaic acids—each elegantly derived from a β-lactam—has been reported by Heathcock and Christie,[10] and a third total syntheses of pinnaic acid **2** was subsequently accomplished by Xu, Arimoto, and Uemura.[11] The remainder of the many publications in this area have dealt very largely with construction of the spirocyclic core system[6,7] and with formal syntheses[12] reliant on the Danishefsky routes. We report here an independent total synthesis of halichlorine and, based on this route, a formal synthesis of the optically pure compound. Our approach involved the development of new general methods to make six-membered nitrogen heterocycles in optically pure form, including substances with fully substituted asymmetric carbons.



Synthetic Plan

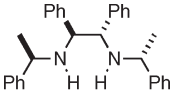
After extensive exploratory studies,[13] we decided to adopt a route (Scheme 1)[14] in which the asymmetric spiro center is introduced very early in the synthesis, and to this end, we based our approach on the allylation of the symmetrical diester **1.1** to the unsymmetrical product **1.2**, in which the eventual spiro center is already set. Procedures were then developed for elaborating **1.2**, via intermediates **1.3** and **1.4**, into halichlorine. Formation of ring A (see **1.3** → **1.4**) was achieved by a new general method for cyclization (intramolecular conjugate displacement),[15,16] which has now been explored with a wide range of examples to generate cyclic amines[15] and also carbocycles.[16] The conversion of **1.1** into **1.2** is one of a series of asymmetric alkylations suggested[17] to proceed with high enantiomeric excess (ee). However, in our hands, this particular reaction[17] gives only a modest ee (ca. 67%) when run on a useful scale (> 5 g of **1.1**)—a fact which we discovered when we were much further advanced in our studies.[19] At that time, we decided to accept this level of enantioselectivity, but we later developed a new and general approach to optically pure piperidines having a fully substituted center adjacent to nitrogen (see Schemes 8 and 9). Such piperidines are expected to have a variety of uses besides the original application described here because of the widespread occurrence of the piperidine substructure in the medicinal chemical literature[20] and as a feature of many natural products.[21]

SCHEME 1. General Synthetic Plan



Results and Discussion

Construction of the Fully Substituted Asymmetric Center—First Route. The *cis*-diester **1.1** was prepared by hydrogenation (Pd/C) of the hydrochloride salt of dimethyl 2,6-pyridinedicarboxylate,[22] followed by N-benzylation[23] (BnBr, K_2CO_3), according to published procedures (Scheme 2). The critical allylation **1.1** → **1.2** was then carried out using the chiral base **4**[17,24] to give the desymmetrized product **1.2**.



This is a key intermediate because it contains the eventual spiro center of halichlorine. We had assumed that the optical

(9) Trauner, D.; Churchill, D. G.; Danishefsky, S. J. *Helv. Chim. Acta* **2000**, *83*, 2344–2351.
(10) Heathcock, C. H.; Christie, H. S. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12079–12084.
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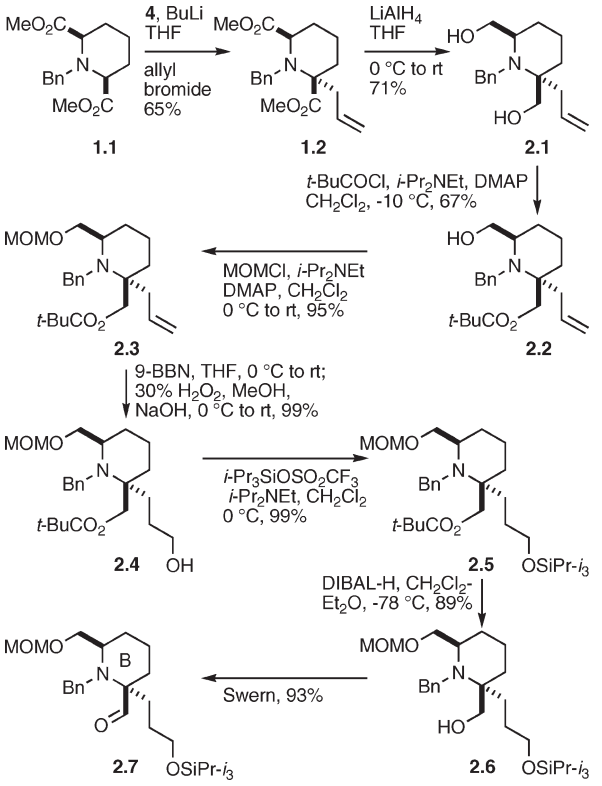
(13) (a) Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1999**, *40*, 8503–8507. (b) For other studies from this laboratory, but not described here, see: Clive, D. L. J.; Wang, J.; Yu, M. *Tetrahedron Lett.* **2005**, *46*, 2853−2855.
(14) Preliminary communications: (a) Yu, M.; Clive, D. L. J.; Yeh, V. S. C.; Kang, S.; Wang, J. *Tetrahedron Lett.* **2004**, *45*, 2879–2881. (b) Clive, D. L. J.; Yu, M.; Li, Z. *J. Chem. Soc., Chem. Commun.* **2005**, 906–908.
(15) Clive, D. L. J.; Li, Z.; Yu, M. *J. Org. Chem.* **2007**, *72*, 5608–5617.
(16) Wang, L.; Prabhudas, B.; Clive, D. L. J. *J. Am. Chem. Soc.* **2009**, *131*, 6003–6012.
(17) (a) Goldspink, N. J.; Simpkins, N. S.; Beckmann, M. *Synlett* **1999**, 1292−1294, especially footnote 9. (b) Huxford, T.; Simpkins, N. S. *Synlett* **2004**, 2295−2298, especially footnote 9. (c) In our hands, when we made **1.2** using 100 mg of **1.1**, the product had $[\alpha]^{25}_D$ +40.1 (c 2.7, $CHCl_3$), but on a larger scale (5 g of **1.1**), the product had $[\alpha]^{25}_D$ +26.5 (c 2.7, $CHCl_3$). Various modes of addition were tried, including the use of special apparatus (see ref 18) for addition of cold solutions.
(18) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 4718–4726.
(19) We were alerted to the poor enantioselectivity of the allylation when X-ray analysis of a more advanced intermediate showed the material to be a racemate. See Supporting Information for structure and CCDC registry number.
(20) For comments on the pharmaceutical significance of piperidines, see: Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679−3681.
(21) The piperidine substructure occurs in many natural products. See, for example: Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556−1575.
(22) Chênevert, R.; Dickman, M. *J. Org. Chem.* **1996**, *61*, 3332–3341.
(23) Chong, H.-S.; Garmestani, K.; Bryant, L. H., Jr.; Brechbiel, M. W. *J. Org. Chem.* **2001**, *66*, 7745–7750.
(24) Bambridge, K.; Begley, M. J.; Simpkins, N. S. *Tetrahedron Lett.* **1994**, *35*, 3391–3394.

SCHEME 2. Synthesis of the Key Aldehyde 2.7

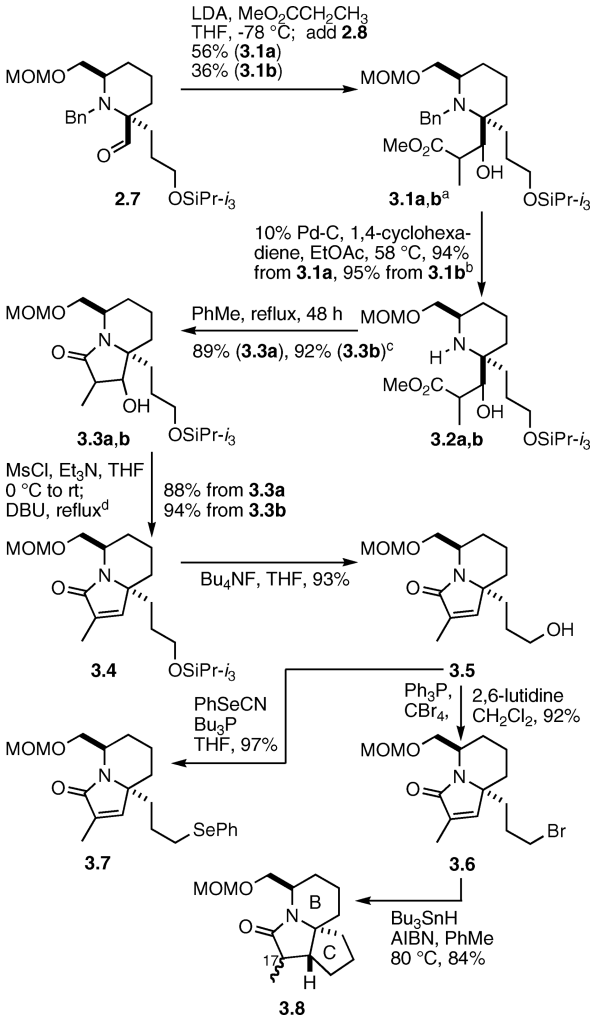


purity would be high,[17] but as indicated above, we later found that not to be the case and we were unable to identify the factors that gave us inferior results to those reported.[17] Nonetheless, we continued our investigation using this material, with the intention of later developing our own method for setting the asymmetric spiro center.

Both ester groups of **1.2** were reduced, and the resulting diol was monoprotected as its pivaloate (**1.2** → **2.1** → **2.2**). Our plan had been to protect the less hindered hydroxyl, but the reaction took a surprisingly different course, and we obtained the product of acylation at the more hindered site. In contrast, silylation with *t*-BuMe$_2$SiCl (imidazole, DMAP, CH_2Cl_2, 87%) occurred at the less hindered hydroxyl. The peculiar outcome with pivaloyl chloride made no change to our approach because the essential requirement was that the two hydroxyls of **2.1** be differently protected. The remaining hydroxyl of **2.2** was masked as its MOM ether, and the pendant allyl group was subjected to hydroboration (**2.2** → **2.3** → **2.4**). The resulting terminal alcohol was then protected by silylation (**2.4** → **2.5**). Next, the pivaloyl group was removed by reaction with DIBALH (**2.5** → **2.6**), and Swern oxidation then gave aldehyde **2.7**. This monocyclic compound, which represents ring B of halichlorine, contains all of the stereochemical and structural features required for elaboration of rings A and C and is also properly constituted to allow stereocontrolled introduction of the C(17) methyl group by the sequence described later.

Formation of Ring C. Having reached aldehyde **2.7**, the next task was to generate ring C, and to prepare for that, the compound was converted sequentially into **3.7** (Scheme 3) and **4.3a**,**b** (Scheme 4), which each contains an additional ring that is subsequently dismantled after it has served its purpose. Aldehyde **2.7** was subjected to aldol condensation

SCHEME 3. Initial Approach to the Construction of Ring C

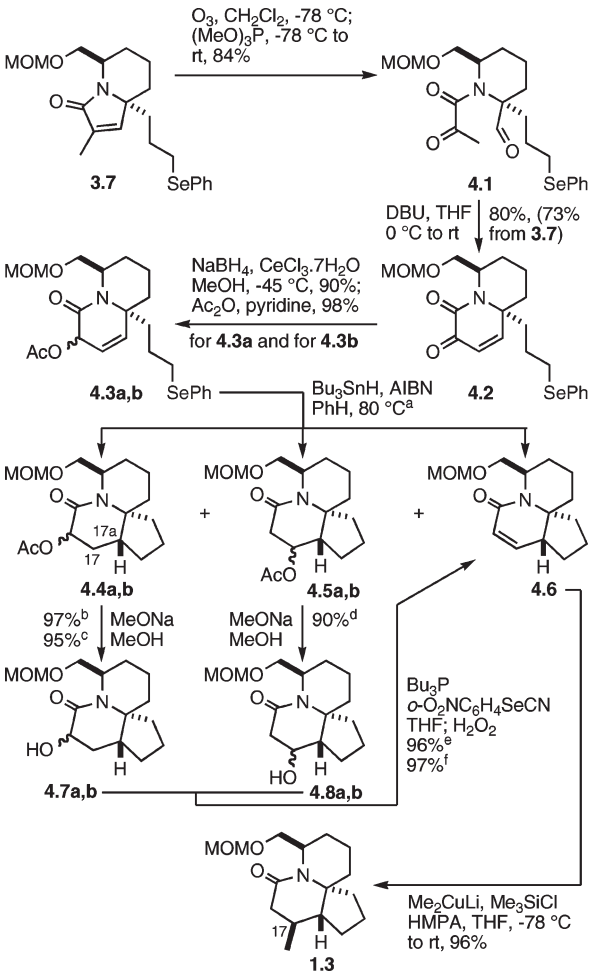


[a] **3.1a** = less polar isomer; **3.1b** = more polar isomer. [b] The benzyl group can also be removed by using Pd−C/H_2; under these conditions, when **3.1a**,**b** are hydrogenolyzed as a mixture and the product is heated in PhMe, all of the material is converted into a mixture of **3.3a** and **3.3b** (83% overall). [c] When **3.2a** and **3.2b** are processed as a mixture, the yield of the **3.3a**,**b** mixture was 89%. [d] When **3.3a**,**b** are processed as a mixture, the yield of **3.4** was 93%.

with methyl propanoate (Scheme 3) so as to provide a mixture of the diastereoisomeric alcohols **3.1a** and **3.1b**. These were separable, but the stereochemistry at the two newly created asymmetric centers was not established and is actually of no consequence. At this point, in order to provide some conformational rigidity to the system, and as a prelude to generating further asymmetric centers, the benzyl group was removed by hydrogenolysis and the rigid bicyclic lactams **3.3a**,**b** were then formed by heating the hydrogenolysis product in PhMe; again, two isomers were obtained from the corresponding isomeric amines **3.2a**,**b**. The alcohols **3.3a**,**b** were individually dehydrated via their mesylates to enone **3.4**, and finally, the pendant triisopropylsiloxy group was replaced by bromide (**3.4** → **3.5** → **3.6**) and, later, also by a phenylseleno group (**3.4** → **3.5** → **3.7**).

When the bromide was subjected to radical cyclization, the required five-membered ring was produced (**3.6** → **3.8**) but the stereochemical outcome at C(17) (halichlorine numbering)

SCHEME 4. Formation of Ring C and Introduction of the Eventual C(17) Methyl Group



[a]Less polar isomer (**4.3a**) gave **4.4a** in 66% yield, **4.5a** (18%) and **4.6** (13%); more polar isomer (**4.3b**) gave **4.4b** (67%), **4.5b** (< 14%), and **4.6** (15%). [b]Starting with **4.4a** containing some **4.5a**, the yield of the mixture of **4.7a** and **4.8a** is 97%. [c]Starting with **4.4b** that contains some **4.5b**, the yield of the mixture of **4.7b** and **4.8b** is 95%. [d]From **4.5a**. Compound **4.5b** was hydrolyzed only as a minor component of a mixture with **4.4b**. [e]Over two steps for mixture of **4.7a** and **4.8a**. [f]Over two steps for mixture of **4.7b** and **4.8b**.

was unfavorable, with the major isomer (4:1) having the C(17) methyl group *anti* to the adjacent ring fusion hydrogen. Although the isomer ratio could be nearly reversed (1:3) by base-catalyzed equilibration (*t*-BuOK, *t*-BuOH, reflux), we were unable to separate the isomers on a useful scale, and so we had to modify the radical cyclization and associated steps. These changes required a base-stable homolyzable substituent, and we turned to the phenylseleno group, which proved to be an ideal choice.

A noteworthy feature of the sequence in Scheme 3 is that the nitrogen of **3.2a**,**b** is subsequently protected by an intramolecular process; that nitrogen is hindered and, at least with related compounds, often resisted protection by intermolecular reactions.[25] The inaccessibility of the nitrogen in related intermediates posed serious restrictions, and a number of seemingly attractive synthetic routes that we examined, and which involved attachment of functionalized units to the nitrogen, were thwarted by steric factors.

The phenyl selenide **3.7** was subjected to ozonolysis and in situ reduction at a low temperature (Scheme 4). By this procedure, the initially formed selenoxide was reduced back to the selenide under conditions in which the selenoxide did not fragment to an olefin.[26] Accordingly, the product of this sequence was the tricarbonyl selenide **4.1**, and on treatment with DBU, it underwent consecutive intramolecular aldol condensation and dehydration to afford **4.2**. When the same sequence was tried with the bromide **3.6**, the aldol condensation did not work because of the base sensitivity of the primary bromide.

Our plan had been to carry out a radical cyclization using **4.2**, but the enone system of this compound was too easily reduced by Bu_3SnH and so its reactivity was lowered by reduction under Luche conditions[27] to the corresponding α-hydroxy lactams (90%); these were then protected by acetylation (98%), bringing the route to **4.3a**,**b**. The radical cyclization of **4.3a** and **4.3b** (which were processed individually) took an interesting course. The major products were the expected acetates **4.4a** [AcO and C(17a)H *syn*] and **4.4b** [AcO and C(17a)H *anti*] from **4.3a** and **4.3b**, respectively, but the corresponding rearranged acetates **4.5a** and **4.5b** and the enone **4.6** were also isolated. Formation of all these products is readily understandable: the acetates **4.4a**,**b** are the result of simple radical closure, while **4.5a**,**b** presumably arise by intervention of an acyloxy migration[28] of the radical produced after cyclization. The enamide **4.6** is simply the result of spontaneous elimination, probably from the rearranged acetates **4.5a**,**b**. The structure of acetate **4.4a** was confirmed by X-ray analysis.

The formation of a mixture in the radical cyclization is of little consequence because all of the material in the mixture can be converted into **4.6**. Thus **4.4a** and **4.4b** were hydrolyzed (usually as a mixture) to the corresponding alcohols (MeONa, MeOH) in at least 95% yield, and these could be converted, either by mesylation and base treatment, into **4.6** or, more efficiently, by treatment with *o*-$(O_2N)C_6H_4SeCN$ and Bu_3P,[29] followed by oxidation with 30% H_2O_2. Similarly, **4.5a**,**b** were hydrolyzed and converted into **4.6**. The structure of alcohol **4.8a** [i.e., hydroxyl and C(17a)H *syn*) was also confirmed by X-ray analysis.

At this point, we needed to introduce a methyl group at the eventual C(17) position. Conjugate addition of cuprates to unsaturated lactams is not well-known,[30] but in the present case, reaction with Me_2CuLi worked in good yield (96%), and the convex shape of the starting lactam **4.6** ensured that the methyl group was delivered in the correct stereochemical sense to provide saturated lactam **1.3**.

Although the conversion of **3.6** into **3.8** (Scheme 3) and the corresponding processes with **4.3a**,**b** (Scheme 4) were

(25) See Supporting Information for structures of the compounds involved.

(26) (a) Reich, H. J.; Shah, S. K.; Chow, F. *J. Am. Chem. Soc.* **1979**, *101*, 6648–6656. (b) Clive, D. L. J.; Postema, M. H. D. *J. Chem. Soc., Chem. Commun.* **1994**, 235–236.

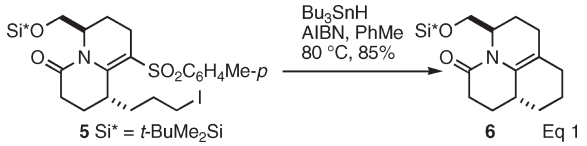
(27) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.

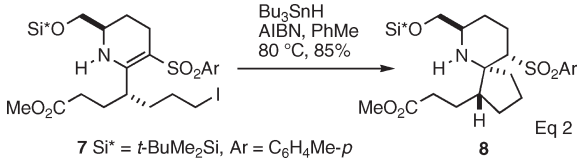
(28) Beckwith, A. L. J.; Crich, D.; Duggan, P. J.; Yao, Q. *Chem. Rev.* **1997**, *97*, 3273–3312.

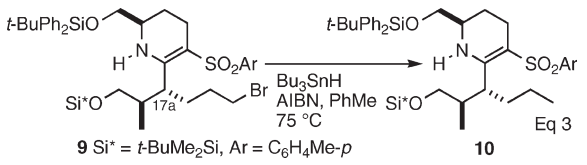
(29) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485–1486.

(30) (a) Amat, M.; Prez, M.; Llor, N.; Bosch, J.; Lago, E.; Molins, E. *Org. Lett.* **2001**, *3*, 611–614. (b) Herdeis, C.; Kaschinski, C.; Karla, R.; Lotter, H. *Tetrahedron: Asymmetry* **1996**, *7*, 867–884.

efficient, the use of radical cyclization in our studies on the synthesis of halichlorine uncovered some unexpected reactions. In early explorations, we found that the unsaturated sulfone **5** underwent 6-*endo* closure instead of following the desired 5-*exo* pathway (eq 1).[13a] The related substrate **7** behaved as expected (eq 2),[13a] but the bromide **9** led only to the simple reduction product **10** (eq 3). The contrasting behavior of **5** and **7** might be attributable to the rigidity of the bicyclic system **5**, as this rigidity could prevent the derived radical from easily following the required Bürgi−Dunitz trajectory, while the more flexible system **7** is not restricted in this respect. The factors responsible for the different outcomes with **7** and **9** are not obvious; possibly, the additional bulk of the C(17a) substituent in **9** introduces unfavorable nonbonded interactions in the conformation needed for ring closure.



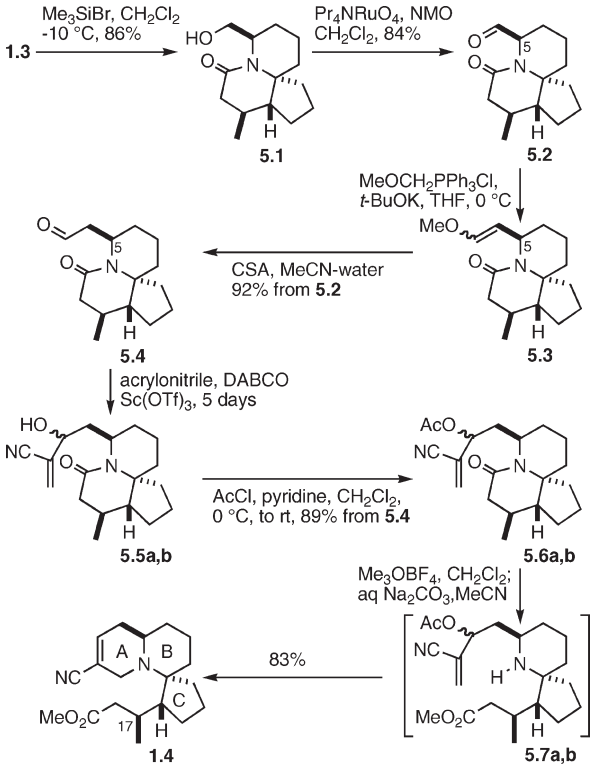




Formation of Ring A. We initially felt that the appropriate next step from **1.3** would be hydrolysis of the lactam. This transformation required a very extensive effort, but we eventually found that the lactam ring could be opened by treatment with the Meerwein salt $Me_3O^+BF_4^-$, followed by aqueous Na_2CO_3.[31] However, by the time we had achieved this lactam opening, our plans for constructing ring A had been changed, and the new approach, which also requires opening of the lactam (but at a later stage), was now implemented as follows (Scheme 5).

The MOM group of **1.3** was removed by the action of Me_3SiBr, and the resulting alcohol was homologated by oxidation, Wittig olefination with $Ph_3P{=}CH(OMe)$, and then acid hydrolysis (**1.3** → **5.1** → **5.2** → **5.3** → **5.4**). The oxidation step was unreliable when done by the Swern method, as this gave variable and usually low yields. However, the use of *n*-Pr_4NRuO_4[32] was consistently successful

SCHEME 5. Construction of Ring A



and gave aldehyde **5.2** in 84% yield, evidently with no epimerization since the aldehyde could be reduced back to the starting alcohol **5.1**. Likewise, due to the vulnerability of the C(5) configuration in **5.2** to the basic conditions of the Wittig reaction, we also checked that formation of the enol ethers **5.3** did not incur any epimerization at C(5): ozonolysis and reduction gave back alcohol **5.1**.

In order to build up ring A, aldehyde **5.4** was subjected to a Baylis−Hillman reaction with acrylonitrile. That process was slow but provided the desired alcohols **5.5a**,**b**[33] in high yield, and these were immediately converted into the corresponding acetates **5.6a**,**b**, the overall yield from the homologated aldehyde **5.4** being 89%. We used AcCl and not Ac_2O for the acetylation because, in model studies, acetate was found to add to the terminal double bond of structures related to **5.5a**,**b**, but this side reaction was not observed with AcCl. Finally, the method we had found earlier for opening the lactam ring[31] of **1.3** was now applied to the acetates **5.6a**,**b** so as to release the lactam carbonyl as a methyl ester and the nitrogen as a free amine. The resulting amines (**5.7a**,**b**) underwent spontaneous intramolecular conjugate displacement[15,34] to afford the unsaturated nitrile **1.4**, with the A, B, and C rings of halichlorine in place. In our preliminary studies,[14b] we had used methyl acrylate as the Michael acceptor in the Baylis−Hillman condensation to eventually give a diester corresponding to **1.4** (CO_2Me in place of CN), but we later found that an essential chemoselective reduction of the two ester groups—one to an aldehyde and the other to an alcohol—could not be effected reproducibly, and so we

(31) (a) Overman, L. E.; Robichaud, A. J. *J. Am. Chem. Soc.* **1989**, *111*, 300–308. (b) Deslongchamps, P.; Lebreux, C.; Taillefer, R. *Can. J. Chem.* **1973**, *51*, 1665–1669. (c) A very similar method has been used to open a five-membered lactam in the halichlorine series: See ref 12b.

(32) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.

(33) A small amount of the starting aldehyde was recovered, indicating that the aldehyde did not epimerize (by retro-Michael addition and Michael addition).

(34) For a mechanistically related method, see ref 10.

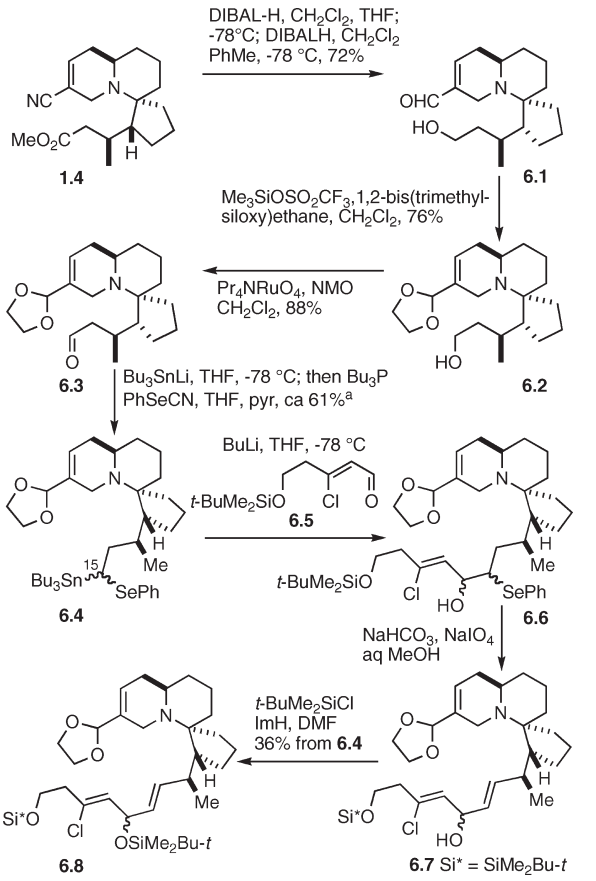
had to retrace our steps and try acrylonitrile, which proved to be a satisfactory choice. As mentioned earlier, this method (cf. **5.4** → **1.4**) of constructing bicyclic compounds with nitrogen at a ring junction is general.[15,34] An important feature of the nitrile ester **1.4** is the fact that the stereogenic center in the side chain is β to a carbonyl, as opposed to α, and consequently, the danger of stereochemical scrambling at C(17) is avoided.

Side Chain Extension and Macrocyclization. The route we followed in order to reach halichlorine from **1.4** required extension of the side chain on the five-membered ring, followed by macrocyclization. To this end, the best of several approaches that we examined began with reduction of the nitrile ester **1.4** with DIBALH in two stages. These specifically involved treatment with DIBALH (2 mol per mol nitrile ester) in CH_2Cl_2−THF at −78 °C, followed by workup and re-exposure at −78 °C to DIBALH (4 mol per mol of original nitrile ester) in CH_2Cl_2−PhMe. Under these conditions, the nitrile was converted to an aldehyde (after aqueous workup) and the ester to an alcohol (**1.4** → **6.1**). The aldehyde group was protected as a cyclic ketal, and oxidation (n-Pr_4NRuO_4) then generated aldehyde **6.3**.

At this stage, we wished to form a carbanion at the aldehyde carbon [C(15) of halichlorine] and decided to use a selenium-stabilized carbanion, the aim being to later employ the selenium unit to make the C(15)−C(16) double bond. The usual method of generating selenium-stabilized carbanions[35] is from seleno ketals, themselves obtained by acid-catalyzed reaction of aldehydes and PhSeH.[36] However, our experience in handling compounds of type **6.3** gave us the impression that they were sensitive to Lewis and protic acids, and so we felt obliged to produce the selenium-stabilized carbanion by a method that avoids the use of acids. Accordingly, aldehyde **6.3** was treated with Bu_3SnLi, and the resulting mixture of stannyl alcohols was immediately converted into the corresponding selenides **6.4**, which were isolated in modest yield (61%). When this material was treated with BuLi (to generate the required selenium-stabilized carbanion[37] by preferential C−Sn heterolysis), and then with the known chloro aldehyde **6.5**,[8,38] a mixture of β-hydroxyselenides **6.6** was obtained. On oxidation, the selenium was removed to liberate the double bond (**6.6** → **6.7**). ^{1}H NMR measurements showed that the double bond had the required E geometry (J = 15.6 Hz). Finally, the hydroxyl group of **6.7** was protected by silylation (Scheme 6, **6.7** → **6.8**).

To prepare for the macrocyclization, the ketal unit was hydrolyzed (Scheme 7) by using $Me_3SiOSO_2CF_3$ in the presence of 2,6-lutidine.[39] This experiment released aldehydes **7.1**, which were converted by Pinnick oxidation[40] to the corresponding acids **7.2**. Next, the primary siloxy group

SCHEME 6. Side Chain Extension and Preparation for Macrocyclization



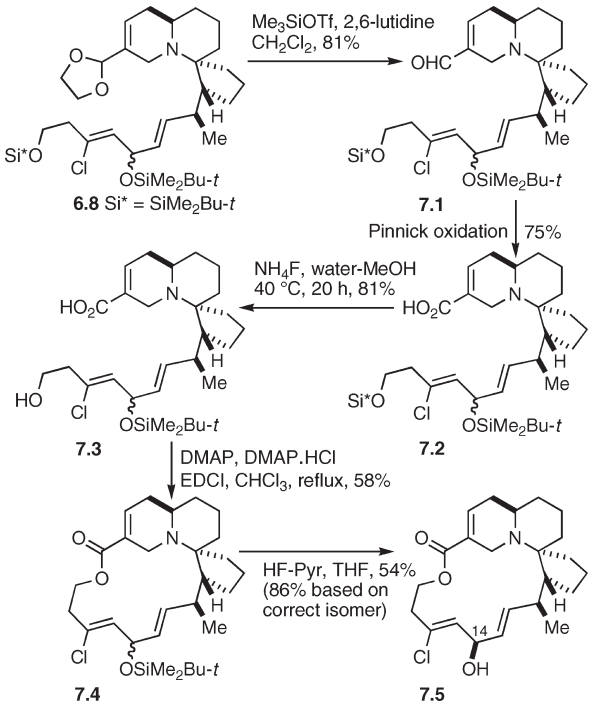
[a]Contains slight impurities.

was selectively deprotected with NH_4F,[41] which had also been used by Danishefsky et al.,[8] and the resulting hydroxy acids were cyclized (58%) by the Keck macrocyclization protocol.[42] Finally, removal of the remaining hydroxyl protecting group [54 or 86% corrected for the proportion of the correct C(17) isomer present in the macrolactone] gave halichlorine **7.5** (≡**1**), whose NMR spectra corresponded to those reported for the natural substance[1] and for racemic synthetic[10] material. The undesired C(14) isomer of **7.5** was obtained in very small amount, and we did not to attempt to recycle it.

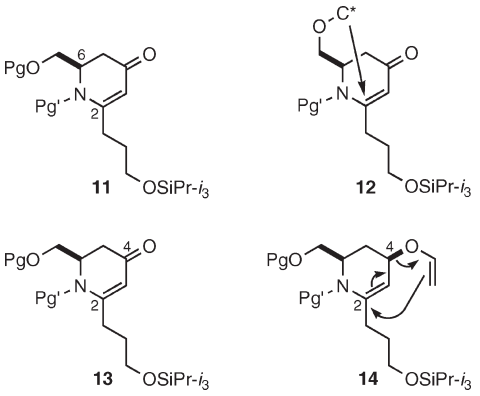
Formation of an Optically Pure Intermediate—A New Route to Piperidines. Having established a synthetic route to halichlorine, we returned to the key problem of making one of our intermediates as a single enantiomer so as to develop a formal synthesis of the optically pure alkaloid based on the approach summarized in the above schemes. To this end, we needed to devise a method for preparing a suitable 2,2,6-trisubstituted piperidine. The structure of the early intermediate **2.1** suggested the use of serine as a starting material, and the requirement that this amino acid be converted into a piperidine with a fully substituted asymmetric carbon led us to consider compounds of type **11**

(35) Review on selenium-stabilized carbanions: Clive, D. L. J. *Organic Compounds of Sulphur, Selenium, and Tellurium*, Specialist Periodical Reports; Royal Society of Chemistry: London, 1981; Vol. 6, pp 112−126.
(36) Review on the chemistry of selenoacetals: Krief, A.; Hevesi, L. *Janssen Chimica Acta* **1984**, *2*, 3−14.
(37) This method of generating selenium-stabilized carbanions is general: Fernandopulle, S.; Clive, D. L. J.; Yu, M. *J. Org. Chem.* **2008**, *73*, 6018−6021.
(38) Keen, S. P.; Weinreb, S. M. *J. Org. Chem.* **1998**, *63*, 6739–6741.
(39) Fujioka, H.; Okitsu, T.; Sawama, Y.; Murata, N.; Li, R.; Kita, Y. *J. Am. Chem. Soc.* **2006**, *128*, 5930–5938.
(40) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096.
(41) Selective deprotection of primary t-$BuMe_2SiOR$ in the presence of secondary t-$BuMe_2SiOR$: (a) Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031–1069. (b) White, J. D.; Porter, W. J.; Tiller, T. *Synlett* **1993**, 535–538.
(42) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394–2395.

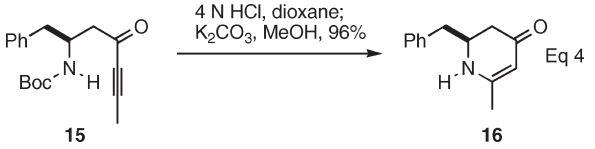
SCHEME 7. Modification of Functional Groups, Macrolactonization, and Formation of Halichlorine



(Pg = protecting group), our intention being to use the asymmetric center at C(6) to control the stereochemical outcome when we converted C(2) to an sp^3 center. Preliminary experiments were aimed at delivering a functionalized carbon intramolecularly along the lines summarized in **12**, where C* is a stabilized carbanion. Our attempts to carry out such a reaction, however, were unsuccessful, as were attempts at conjugate addition to **13** (Pg = *t*-BuMe$_2$Si, Pg′ = Bn), using vinylmagnesium bromide and CuBr•SMe$_2$ in the presence of Me$_3$SiCl, with or without HMPA. A consequence of this unrewarding effort was that we decided to try the Claisen rearrangement of enol ethers of type **14**, which we expected to be available[43,44] from dihydropyridinones **13**. In view of the very large amount of research published on the construction of piperidines,[45] and the importance of this compound class,[20,21] it is surprising that the procedure summarized in **14** has not been reported before. Related rearrangements in the oxygen series (glycals) are, of course, part of the classical repertoire of Ireland-ester enolate rearrangements,[46] but the Claisen rearrangement defined by the arrows in **14** has not been explored before and, in the form described below, represents a general synthetic method. We initially set out to examine the rearrangement using compounds with the stereochemistry shown in **14** but encountered several difficulties: carbonyl reduction of the parent dihydropyridinone **13** is most efficiently done in a manner (NaBH$_4$/CeCl$_3$•7H$_2$O)[44] that gives the undesired stereochemistry (hydroxyl *anti* to PgOCH$_2$), so that a Mitsunobu inversion is required. Second, the ease of the rearrangement depends on the stereochemistry at C(4): the reaction is very slow for the stereochemistry shown in **14** (Pg = Cbz or *t*-BuMe$_2$Si, Pg′ = Cbz) but occurs at a satisfactory rate for the opposite C(4) stereochemistry. Once these facts had emerged, we were able to plan the synthesis of an intermediate that overlaps with our route to halichlorine because we were then in position to make a proper choice of the C(2) substituent for the starting dihydropyridinone of type **13**.



A convenient method for preparing dihydropyridinones was already available,[47] and the transformation shown in eq 4 served as a model for our needs, although it was not certain that the route we intended to follow would preserve the stereochemical integrity of the starting material, as several related cyclizations[47] incurred some epimerization.



L-Serine methyl ester hydrochloride was converted in four simple steps into the iodide **8.1**, using a reported procedure,[48] and treatment with lithium divinyl cuprate then generated the known oxazolidinone[49] **8.2** (Scheme 8). Ozonolysis of the double bond and reaction with the lithium acetylide derived

(43) NaBH$_4$/CeCl$_3$ reduction of piperidinones: Comins, D. L.; Foley, M. A. *Tetrahedron Lett*. **1988**, *29*, 6711−6714.

(44) Comins, D. L.; Kuethe, J. T.; Miller, T. M.; Février, F. C.; Brooks, C. A. *J. Org. Chem*. **2005**, *70*, 5221–5234.

(45) Reviews: (a) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729. (b) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem*. **2003**, 3693–3712. (c) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953–2989. (d) Bates, R. W.; Sa-Ei, K. *Tetrahedron* **2002**, *58*, 5957–5978. (e) Enders, D.; Thiebes, C. *Pure Appl. Chem*. **2001**, *73*, 573–578. (f) Husson, H.-P.; Royer, J. *Chem. Soc. Rev*. **1999**, *28*, 383–394. (g) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781–1813. (h) Deiters, A.; Martin, S. F. *Chem. Rev*. **2004**, *104*, 2199–2238. (i) Rubiralta, M.; Giralt, E.; Diez, A. *Piperidines, Structure, Preparation, Reactivity, and Synthetic Applications of Piperidine and Its Derivatives*; Elsevier: Amsterdam, 1991. Routes to non-racemic piperidines: (j) Coombs, T. C.; Zhang, Y.; Garnier-Amblard, E. C.; Liebeskind, L. S. *J. Am. Chem. Soc*. **2009**, *131*, 876–877. (k) Abrunhosa-Thomas, I.; Roy, O.; Barra, M.; Besset, T.; Chalard, P.; Troin, Y. *Synlett* **2007**, 1613–1615. (l) Adriaenssens, L. V.; Hartley, R. C. *J. Org. Chem*. **2007**, *72*, 10287–10290. (m) Gotchev, D. B.; Comins, D. L. *J. Org. Chem*. **2006**, *71*, 9393–9402. (n) Back, T. G.; Nakajima, K. *J. Org. Chem*. **1998**, *63*, 6566–6571. (o) Waldmann, H.; Braun, M.; Dräger, M. *Angew. Chem., Int. Ed. Engl*. **1990**, *29*, 1468–1471. (p) Kunz, H.; Pfrengle, W. *Angew. Chem., Int. Ed. Engl*. **1989**, *28*, 1067–1068.

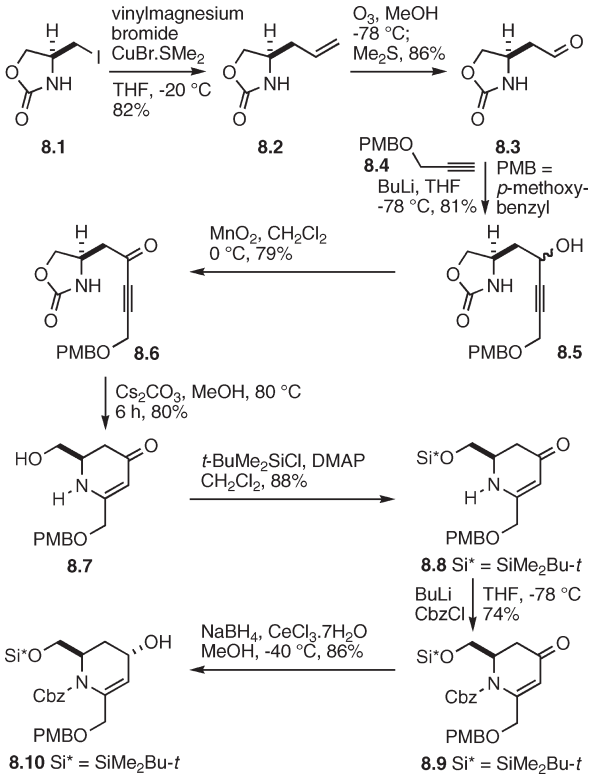
(46) (a) Castro, A. M. M. *Chem. Rev*. **2004**, *104*, 2939–3002. (b) Pereira, S.; Srebnik, M. *Aldrichimica Acta* **1993**, *26*, 17–29. (c) Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847–1882. (d) Overman, L. E. *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 579–586. (e) Lutz, R. P. *Chem. Rev*. **1984**, *84*, 205–247. (f) Rhoads, S. J.; Raulins, N. R. *Org. React*. **1975**, *22*, 1–252.

(47) Turunen, B. J.; Georg, G. I. *J. Am. Chem. Soc*. **2006**, *128*, 8702–8703.

(48) Sibi, M. P.; Rutherford, D.; Renhowe, P. A.; Li, B. *J. Am. Chem. Soc*. **1999**, *121*, 7509–7516.

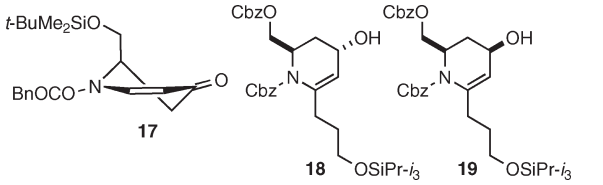
(49) We found this method more convenient than that reported in the literature (Kim, S.-G.; Ahn, K. H. *Synth. Commun*. **1998**, *28*, 1387−1397).

SCHEME 8. Synthesis of the Precursor to the Rearrangement Substrate 8.10



from **8.4**[50] gave the expected alcohols **8.5**, which were oxidized to ketone **8.6**. On treatment with Cs_2CO_3 in hot MeOH, the ketone was transformed into the dihydropyridinone **8.7** in 80% yield. The use of a *p*-methoxybenzyl-protected oxygen for the propargylic component was necessary as *t*-BuMe_2Si and *t*-BuPh_2Si groups were labile under the cyclization conditions. The presence of additional functionality in our case (**8.6**), compared with compound **15** (eq 2), necessitated the use of different conditions for the ring closure from those reported,[47] and we avoided the use of HCl[47] or Me_3SiI.[47] Silylation[51] of the free hydroxyl of **8.7** and protection of nitrogen as a carbamate took the route as far as **8.9**. Finally, reduction under Luche conditions[27] gave alcohol **8.10**, setting the stage for the intended rearrangement. The choice of a Cbz group for nitrogen protection was based on the finding that reduction of the ketone carbonyl in analogous compounds was unsuccessful when the nitrogen is protected with a benzyl group and the fact that related reductions have been reported[43] where the nitrogen carries a PhOCO group. Reduction was stereoselective (95:5) in favor of the indicated isomer **8.10**. Presumably, the reduction involves conformation **17**,[43,44] which is adopted in order to alleviate $A^{1,3}$ strain, and complexation occurs *anti* to the siloxymethyl substituent so that the hydride is delivered axially (*syn* to the substituent).

The optical purity of the starting serine was preserved during the above sequence, as indicated by the following experiments: N-acylation of **8.8** with (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride gave a product with a vinyl signal in the ^{1}H NMR spectrum at 5.93 ppm (400 MHz, $CDCl_3$). With the enantiomeric reagent, the corresponding signal is at 5.88 ppm; this signal is absent in the spectrum of the derivative formed with the *S*-reagent and so **8.8** must be a single enantiomer.



The crucial rearrangement was done in situ by heating alcohol **8.10** in butyl vinyl ether in the presence of $Hg(OAc)_2$ and Et_3N (Scheme 9). Under these conditions (110 °C, 36 h), the expected vinyl ether (cf. **14**) was formed and it rearranged in the required way to give **9.1**, but attempts to isolate the intermediate vinyl ether (before the reaction was complete) were not successful because the material is unstable to chromatography, during which it appears to undergo elimination (^{1}H NMR). The required conditions are mild compared with those that are usual[46f] for the Claisen rearrangement; possibly, mercuric ion catalysis is involved.[46d,e] We can find no examples of Claisen rearrangement in which the distal terminus of the allylic double bond system carries nitrogen—as is the case in the present work—and only one report of a correspondingly substituted acyclic Ireland-ester enolate rearrangement.[52]

Although alcohol **8.10** was made specifically for the reactions described, it should also have provided an opportunity for generating the fully substituted center by way of an S_N2' displacement.[53,54] However, the earlier studies that led us to develop the route shown in Schemes 8 and 9 did include experiments along such lines, and we had found that *O*-acyl derivatives of alcohol **18**[55] decomposed on chromatography (silica gel).[56] When the crude *O*-acyl derivatives were treated with vinyl metals, under conditions that normally result[53,54,57] in an S_N2' pathway, they failed to react, decomposed, or (in one case[53]) appeared to undergo both S_N2' and S_N2 displacement.

Because of the unfavorable properties of the *O*-acyl derivatives, access to the inverted alcohol **19** was gained by DIBALH-BHT reduction[44] of the parent ketone (63% yield), and with both **18** and **19** in hand, the effect of stereochemistry on the Claisen rearrangement could be examined, as mentioned above. Alcohol **18** behaves as required, but the isomer

(50) Clive, D. L. J.; Yang, W.; MacDonald, A. C.; Wang, Z.; Cantin, M. *J. Org. Chem.* **2001**, *66*, 1966–1983.

(51) The route would have been a little shorter if the hydroxyl had been protected as a MOM ether; this was not tried, however, because attempts to so protect a related compound (i-$Pr_3SiOCH_2CH_2CH_2$ instead of $PMBOCH_2$) were unsuccessful and gave complex mixtures.

(52) Ylioja, P. M.; Mosley, A. D.; Charlot, C. E.; Carbery, D. R. *Tetrahedron Lett.* **2008**, *49*, 1111–1114.

(53) (a) Kiyotsuka, Y.; Acharya, H. P.; Katayama, Y.; Hyodo, T.; Kobayashi, Y. *Org. Lett.* **2008**, *10*, 1719–1722. (b) Kiyotsuka, Y.; Katayama, Y.; Acharya, H. P.; Hyodo, T.; Kobayashi, Y. *J. Org. Chem.* **2009**, *74*, 1939–1951.

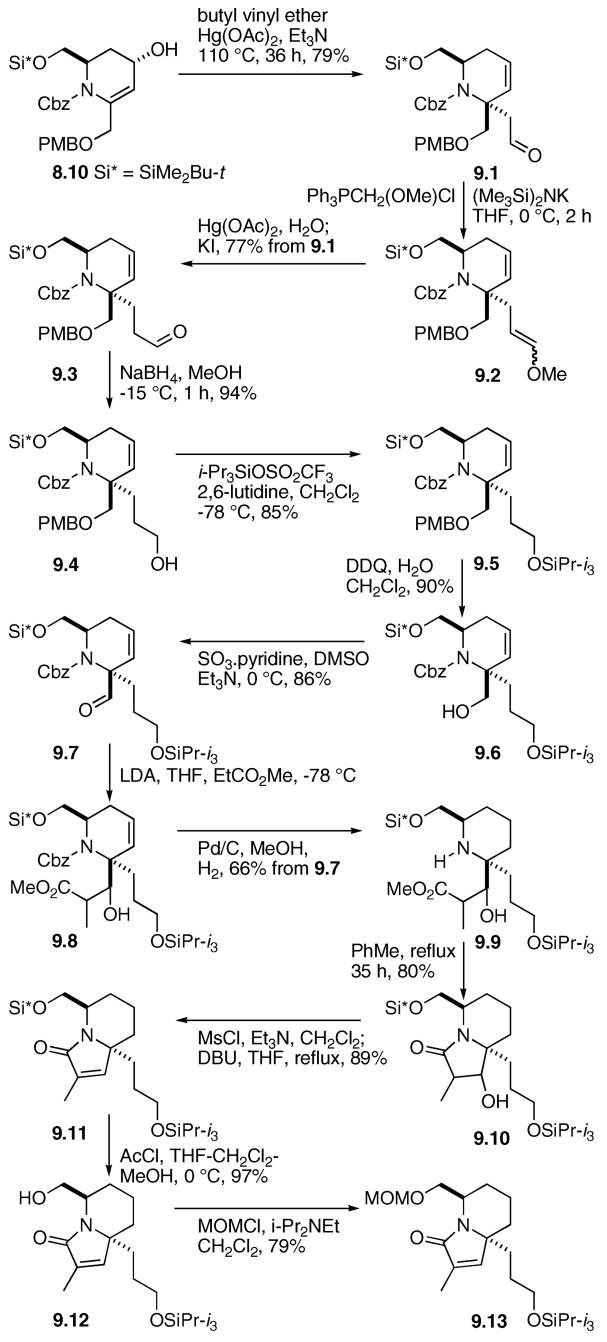
(54) (a) Calaza, M. I.; Hupe, E.; Knochel, P. *Org. Lett.* **2003**, *5*, 1059–1061. (b) Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Kneisel, F. F.; Knochel, P. *Org. Lett.* **2003**, *5*, 2111–2114.

(55) The alcohol was coupled (EDCI, DMAP) with picolinic acid or $MeOCH_2CO_2H$, and we attempted unsuccessfully to phosphorylate it with $(EtO)_2P(O)Cl$.

(56) For a related pivaloate that is stable to chromatography, see ref 44. For related isolable acetates, see: (a) Dransfield, P. J.; Gore, P. M.; Prokes, I.; Shipman, M.; Slawin, A. M. Z. *Org. Biomol. Chem.* **2003**, *1*, 2723–2733. (b) Hanson, G. J.; Russell, M. A. *Tetrahedron Lett.* **1989**, *30*, 5751–5754.

(57) Nakata, K.; Kiyotsuka, Y.; Kitazume, T.; Kobayashi, Y. *Org. Lett.* **2008**, *10*, 1345–1348.

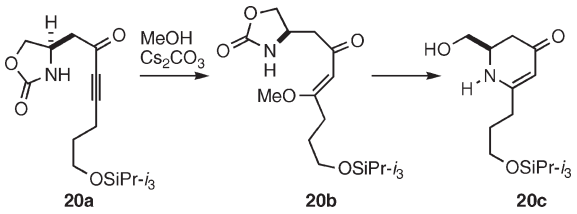
SCHEME 9. Claisen Rearrangement and Synthesis of Optically Pure Intermediate 9.13 [Formal Synthesis of (+)-Halichlorine]



19 did not provide a rearrangement product; the main compound obtained appeared to be the intermediate vinyl ether (^{1}H NMR), which again could not be isolated. The reluctance of the vinyl ether derived from **19** to rearrange must be due to unfavorable steric interactions, as both the $CbzOCH_2$ group and the vinyloxy substituent would have to occupy a pseudoaxial conformation; in the vinyl ether derived from **18**, only the $CbzOCH_2$ group is pseudoaxial in the reacting conformation.

At this point, aldehyde **9.1**, in which two key stereogenic centers have been set, was elaborated into (+)-**9.13**, largely by the methods used earlier, as summarized in Scheme 9. This compound is the optically pure version of **3.4**, which is an intermediate in our route to halichlorine; formation of (+)-**9.13** constitutes a formal synthesis of (+)-halichlorine because none of the remaining steps in our sequence can cause racemization.

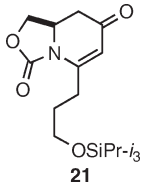
SCHEME 10. Mechanistic Pathway



Mechanistic Considerations. The cyclization of **8.6** to **8.7** (and related cyclizations) clearly represents the outcome of a number of consecutive steps, and we wanted to identify the point in the overall sequence at which the oxazolidinone is hydrolyzed. When ketone **20a**, which was made[58] along lines developed for **8.6**, was treated with Cs_2CO_3 in MeOH for 3 h at room temperature (i.e., under milder conditions than used for **8.6**), we isolated the vinylogous ester **20b** as the major product, together with the expected dihydropyridinone **20c** (**20b**/**20c** = ca. 2:1) (Scheme 10). The ee of **20c** was 99%, based on the ^{1}H NMR method described above for **8.8**; the olefin geometry shown for **20b** is arbitrary.[59] If the reaction is stopped after 20 min, the only products isolated were again **20b** (major) and **20c** (ca. 4:1). When **20b** was subjected to the normal conditions for cyclization (Cs_2CO_3, MeOH, room temperature and then 65 °C), it was converted into **20c**. When this reaction was stopped during the heating period, but before completion, ^{1}H NMR examination of the crude mixture showed the signals for **20b** and **20c**, together with signals of what were obviously minor components, but which we were unable to isolate.

It would appear that the final dihydropyridinone is always produced by an addition−elimination mechanism (cf. **20a** → **20b** → **20c**), similar to that proposed by Turunen and Georg.[47]

We also converted **20c** into the cyclic carbamate **21** and found that it rapidly yields **20c** on treatment with Cs_2CO_3 in MeOH at room temperature; in contrast, the oxazolidinone **8.2**, which we used as a reference model, is largely unchanged under the same conditions (Cs_2CO_3, MeOH, 4 h at room temperature, 4 h at 65 °C), suggesting that cyclization occurs with the oxazolidinone subunit intact, and the resulting vinylogous imide (e.g., **21**) undergoes rapid methanolysis.[60]



21

Conclusion

The halichlorine structure represents a complicated target for total synthesis, a view that is supported by the fact that an

(58) See Supporting Information.
(59) Dabrowski, J.; Tencer, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 981−986.
(60) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424–2426.

unusually large number of model studies have been undertaken. The synthesis reported here had two unanticipated consequences: the development of the general process of intramolecular conjugate displacement (cf. **5.6** → **1.4**, Scheme 5)[15] and the route to piperidines. The former was devised specifically for constructing ring A but is broadly general for the preparation of nitrogen-containing heterocycles[15] and also, in a suitably modified form, for the preparation[16] of carbocycles. The approach to optically active piperidines, which is based on a Claisen rearrangement of readily accessible vinyl ethers of defined stereochemistry, is also general[61] and can lead, as applied here, to the formation of compounds having a fully substituted carbon. The stereochemistry of that center is controlled by the stereochemistry of the starting alcohol and the choice of substituent on the double bond of the parent dihydropyridinone. This method for making piperidines is expected to be useful in its own right because piperidines represent a pharmaceutically privileged compound class[20] and are a common subunit in natural products.[21] In addition, intermediates of type **9.1** should be amenable to many modifications, so as to give access to a wide range of optically pure compounds.

Experimental Section

(2*R*,6*R*)-rel-1-(1,2-Dioxopropyl)-6-[(methoxymethoxy)methyl]-2-[3-(phenylseleno)propyl]-2-piperidinecarboxaldehyde (4.1). First Method. A solution of **3.7** (500 mg, 1.18 mmol) in CH_2Cl_2 (40 mL) was cooled to −78 °C. A steady stream of O_3 in O_2 (dried by passing through a trap at −78 °C) was bubbled through the solution for 35 min. The solution was then flushed with O_2 for 20 min to remove the excess of O_3, and Ph_3P (1.2 g, 4.7 mmol) was added in one portion. The cold bath was left in place but not recharged, and stirring was continued overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 20 cm), using 1:2 EtOAc.hexane, gave **4.1** (451 mg, 84%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1768, 1731, 1714, 1624 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.49−2.07 (m, 9 H), 2.20−2.26 (m, 1 H), 2.32 (s, 3 H), 2.87−2.90 (m, 2 H), 3.32 (s, 3 H), 3.45 (dd, J = 4.1, 9.6 Hz, 1 H), 3.60 (t, J = 10.3 Hz, 1 H), 4.43−4.46 (m, 1 H), 4.58−4.61 (m, 2 H), 7.20−7.25 (m, 3 H), 7.45−7.47 (m, 2 H), 9.39 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.0 (t), 21.7 (t), 24.6 (t), 25.7 (t), 27.1 (q), 28.2 (t), 33.4 (t), 51.0 (q), 55.6 (d), 65.2 (s), 70.5 (t), 96.2 (t), 126.9 (d), 129.0 (d), 130.0 (s), 132.7 (d), 168.4 (s), 196.8 (s), 197.0 (d); exact mass m/z calcd for $C_{21}H_{29}NO_5{}^{80}Se$ 455.1211, found 455.1200.

Second Method (Batch Process). A solution of **3.7** (0.539 g, 1.27 mmol) in CH_2Cl_2 (40 mL) was cooled to −78 °C, and a steady stream of O_3 in O_2 (dried by passing through a trap at −78 °C) was bubbled through the solution for 30 min. Then the mixture was flushed with O_2 for 20 min to remove the excess of O_3, and Ph_3P (1.2 g, 4.7 mmol) was added in one portion. The mixture was stirred for 1 min and was then transferred to a cooled (−78 °C) round-bottomed flask (500 mL containing a magnetic stirring bar) using CH_2Cl_2 (ca. 3 mL) as a rinse. The mixture was stirred at −78 °C.

Another solution of **3.7** (0.539 g, 1.27 mmol) in CH_2Cl_2 (40 mL) was subjected to ozonolysis following the above conditions. After the addition of Ph_3P (1.2 g, 4.7 mmol), the mixture was transferred to the same 500 mL round-bottomed flask using CH_2Cl_2 (ca. 3 mL) as a rinse. After five more experiments carried out using the same amounts of starting material and reagents, all of the solutions had been combined in the 500 mL round-bottomed flask. The cooling bath was left in place but not recharged, and stirring was continued overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 30 cm), using 1:3 to 1:1 EtOAc/hexane, gave **4.1** as a colorless oil. The combined material from the above seven batches together with the total product from a further five batches was converted, as described below, into the unsaturated keto amide **4.2** in an overall yield of 73% (4.89 g) for the two steps.

(4*R*,9a*R*)-rel-1,3,4,9a-Tetrahydro-4-[(methoxymethoxy)methyl]-9a-[3-(phenylseleno)propyl]-2*H*-quinolizine-6,7-dione (4.2). First Procedure. DBU (15.51 mL, 103.7 mmol) was added dropwise over 20 min to a stirred and cooled (−10 °C) solution of **4.1** (4.72 g, 10.4 mmol) in THF (200 mL). Stirring at this temperature was continued for 1 h, the cold bath was removed, and after 1 h, the solution was stirred and refluxed overnight. The solution was cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (3 × 25 cm), using 2:1 EtOAc/hexane, gave **4.2** (3.63 g, 80%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1747, 1666 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.42−1.73 (m, 5 H), 1.83−2.07 (m, 4 H), 2.44−2.59 (m, 1 H), 2.80−3.00 (m, 2 H), 3.34 (s, 3 H), 3.44−3.58 (m, 1 H), 4.06−4.20 (m, 2 H), 4.62 (AB q, J = 6.4 Hz, $\triangle\nu_{AB}$ = 11.4 Hz, 2 H), 6.36 (d, J = 10.2 Hz, 1 H), 6.83 (d, J = 10.2 Hz, 1 H), 7.23−7.28 (m, 3 H), 7.43−7.48 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.7 (t), 23.5 (t), 26.7 (t), 27.4 (t), 34.1 (t), 37.3 (t), 55.4 (q), 56.3 (d), 64.4 (s), 69.4 (t), 96.8 (t), 126.4 (d), 127.2 (d), 129.2 (d), 129.5 (s), 132.8 (d), 156.1 (d), 158.5 (s), 179.1 (s); exact mass (electrospray) m/z calcd for $C_{21}H_{27}NNaO_4{}^{80}Se$ (M + Na) 460.0998, found 460.0994.

Second Procedure. Seven combined batches of freshly obtained ketoaldehyde **4.1** (see above) were immediately treated with base as follows: DBU (7.4 mL, 50 mmol) was added dropwise over 5 min to a stirred and cooled (0 °C) solution of the ketoaldehyde in THF (170 mL). The ice bath was left in place but not recharged, and stirring was continued overnight. Evaporation of the solution and flash chromatography of the residue over silica gel (3 × 25 cm), using 3:1 EtOAc/hexane, gave **4.2**. A further five batches of ketoaldehyde were processed in the same way to obtain **4.2** (4.89 g in all, 73% over two steps) as a colorless oil.

(4*R*,7*R*,8a*R*,11a*S*)-rel-7-(Acetyloxy)decahydro-4-[(methoxymethoxy)methyl]-6*H*-cyclopenta[*i*]quinolizin-6-one (4.4a), (4*R*,8*S*,8a*S*,11a*S*)-rel-8-(Acetyloxy)decahydro-4-[(methoxymethoxy)methyl]-6*H*-cyclopenta[*i*]quinolizin-6-one (4.5a), and (4*R*,8a*R*,11a*S*)-rel-1,2,3,4,8a,9,10,11-Octahydro-4-[(methoxymethoxy)methyl]-6*H*-cyclopenta[*i*]quinolizin-6-one (4.6). Bu_3SnH (0.53 mL, 2.0 mmol) and AIBN (65 mg, 0.40 mmol) in PhH (25 mL) were added over 10 h (syringe pump) to a refluxing solution of **4.3a** (0.64 g, 1.3 mmol) in PhH (260 mL). After the addition, the solution was refluxed for 4 h, cooled to room temperature, and evaporated. Flash chromatography of the residue over silica gel (2×10 cm), using 1:1 EtOAc/hexane, gave acetate **4.4a** (combined yield of two batches run on the same scale, 0.566 g, 66%), **4.5a** (combined yield of the two batches, 0.151 g, 18%), and **4.6** (combined yield of the two batches, 89 mg, 13%) as colorless oils.

Acetate **4.4a**: FTIR (CH_2Cl_2 cast) 1694, 1667 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.47−2.05 (m, 15 H), 2.13 (s, 3 H), 3.33 (s, 3 H), 3.71 (dd, J = 9.6, 3.8 Hz, 1 H), 3.77 (t, J = 9.3 Hz, 1 H), 3.85−3.89 (m, 1 H), 4.60 (AB q, J = 6.34 Hz, $\triangle\nu_{AB}$ = 19.25 Hz, 2 H), 5.24 (dd, J = 10.9, 5.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.2 (t), 21.0 (q), 23.0 (t), 23.5 (t), 30.1 (t), 30.5 (t), 35.6 (t), 38.3 (t), 42.6 (d), 53.7 (q), 55.2 (d), 67.2 (s), 67.3 (d), 69.0 (t), 96.6 (t), 168.5 (s), 170.3 (s); exact mass (electrospray) m/z calcd for $C_{17}H_{27}NNaO_5$ (M + Na) 348.1781, found 348.1782.

Acetate **4.5a**: FTIR (CH_2Cl_2 cast) 2948, 2879, 1737, 1653 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.46−2.02 (m, 15 H), 2.20 (ddd,

(61) See Supporting Information for the preparation and subsequent Claisen rearrangement, in the presence of butyl vinyl ether, of **18** and **20a**.

J = 12.2, 5.7, 2.7 Hz, 1 H), 2.42 (dd, J = 16.7, 7.3 Hz, 1 H), 2.67 (dd, J = 16.7, 3.7 Hz, 1 H), 3.36 (s, 3 H), 3.77 (dd, J = 9.7, 4.1 Hz, 1 H), 3.81 (dd, J = 8.6, 8.6 Hz, 1 H), 3.91 (ddd, J = 10.6, 8.2, 4.1 Hz, 1 H), 4.63 (AB q, J = 6.4 Hz, $\Delta\nu_{AB}$ = 17.0 Hz, 2 H), 4.92 (ddd, J = 6.8, 6.4, 3.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.99 (t), 21.11 (q), 22.91 (t), 23.69 (t), 28.52 (t), 36.40 (t), 36.47 (t), 38.14 (t), 50.29 (d), 53.80 (d), 55.26 (q), 66.35 (s), 68.95 (t), 70.39 (d), 96.62 (t), 168.30 (s), 170.26 (s); exact mass m/z calcd for $C_{17}H_{27}NO_5$ 325.1889, found 325.1888.

(4*R*,8*S*,8a*R*,11a*S*)-rel-Decahydro-β-hydroxy-8-methyl-α-methylene-6-oxo-6*H*-cyclopenta[*i*]quinolizine-4-butanenitrile (5.5a, b). A mixture of **5.4** (0.20 g, 0.80 mmol), DABCO (0.72 g, 6.4 mmol), and acrylonitrile (5 mL) was stirred at room temperature for 5 days. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 10 cm), using 1.5:1 EtOAc/hexane, gave the adduct **5.5a**,**b** as a mixture of epimers which was used directly in the next step.

Acetic Acid 2-Cyano-1-[(4*R*,8*S*,8a*R*,11a*S*)-rel-[decahydro-8-methyl-6-oxo-6*H*-cyclopenta[*i*]quinolizin-4-yl]methyl]-2-propenyl ester (5.6a,b). The above mixture of the alcohols **5.5a**,**b** was dissolved in CH_2Cl_2 (7 mL), and the solution was cooled to 0 °C. Pyridine (0.39 mL, 4.8 mmol) and AcCl (0.28 mL, 3.9 mmol) were added successively, and the mixture was stirred at 0 °C for 30 min. The ice bath was removed, and stirring was continued for 2 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm), using 1:1 EtOAc/hexane, gave the acetates **5.6a**,**b** (0.255 g, 89% over two steps) as a colorless oil, which was an inseparable mixture of two isomers: FTIR (CH_2Cl_2 cast) 2223, 1746, 1649 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) (mixture of two isomers) δ 0.88 (d, J = 6.2 Hz, 1.5 H), 0.90 (d, J = 6.2 Hz, 1.5 H), 1.24−2.03 (m, 15 H), 2.067 (s, 1.5 H), 2.071 (s, 1.5 H), 2.14−2.26 (m, 1.5 H), 2.33 (t, J = 4.5 Hz, 0.5 H), 2.39 (t, J = 4.2 Hz, 0.5 H), 2.74−2.84 (m, 0.5 H), 2.97−3.06 (m, 0.5 H), 3.19−3.37 (m, 1 H), 5.21−5.32 (m, 1 H), 5.97−6.05 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (mixture of two isomers) δ 19.1 (d), 19.2 (d), 20.9 (t), 21.0 (q), 21.1 (q), 21.7 (t), 23.5 (t), 27.4 (t), 28.4 (t), 30.6 (t), 30.9 (t), 31.6 (q), 31.9 (q), 35.8 (t), 36.0 (t), 37.1 (t), 37.4 (t), 38.4 (t), 39.0 (t), 41.3 (t), 41.8 (t), 52.8 (d), 53.51 (d), 53.52 (d), 53.8 (d), 68.9 (s), 69.3 (s), 71.4 (d), 71.8 (d), 116.25 (s), 116.28 (s), 122.90 (s), 123.0 (s), 133.0 (t), 133.4 (t), 169.78 (s), 169.85 (s), 174.8 (s), 175.2 (s); exact mass (electrospray) m/z calcd for $C_{20}H_{28}N_2NaO_3$ (M + Na) 367.1992, found 367.1992.

(β*R*,1*R*,2*S*,9′a*S*)-rel-7′-Cyano-1′,2′,3′,6′,9′,9′a-hexahydro-β-methylspiro[cyclopentane-1,4′-[4*H*]quinolizine]-2-propanoic acid methyl ester (1.4). $Me_3O^+BF_4^-$ (0.52 g, 3.5 mmol) was added in one portion to a stirred and cooled (0 °C) solution of 2,6-di-*tert*-butyl-4-methylpyridine (0.88 g, 4.3 mmol) and **5.6a**,**b** (mixture of two isomers, 0.245 g, 0.712 mmol) in CH_2Cl_2 (7 mL). The ice bath was removed, and stirring was continued for 2 h. The solvent was then evaporated. The residue was taken up in MeCN (14 mL) and cooled to 0 °C, and aqueous Na_2CO_3 (20% w/v, 7 mL) was added. The ice bath was removed, and the mixture was stirred vigorously for 3 h. The aqueous phase was extracted with EtOAc (3 × 15 mL), and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:5 EtOAc/hexane, gave **1.4** (0.176 g, 83%) as a colorless solid: mp 67−69 °C; FTIR (CH_2Cl_2 cast) 2217, 1735, 1654 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) δ 0.70 (m, 1 H), 0.90 (d, J = 6.5 Hz, 3 H), 0.96−1.26 (m, 8 H), 1.39−1.60 (m, 6 H), 1.81−1.84 (m, 1 H), 2.06−2.12 (m, 1 H), 2.16−2.21 (m, 1 H), 2.77 (d, J = 16.1 Hz, 1 H), 3.10 (d, J = 16.0 Hz, 1 H), 3.16 (d, J = 13.6 Hz, 1 H), 3.39 (s, 3 H), 5.87−5.89 (m, 1 H); ^{13}C NMR (C_6D_6, 125 MHz) δ 20.2 (d), 21.5 (t), 21.6 (t), 23.5 (t), 29.3 (t), 31.9 (q), 35.5 (t), 41.3 (t), 49.13 (t), 49.17 (t), 50.8 (d), 52.3 (d), 56.6 (q), 67.4 (s), 111.5 (s), 118.2 (s), 141.1 (d), 173.1 (s); exact mass (electrospray) m/z calcd for $C_{19}H_{29}N_2O_2$ (M + H) 317.2224, found 317.2219.

(1*R*,2*S*,9′a*S*)-rel-7′-[1,3-Dioxolan-2-yl]-1′,2′,3′,6′,9′,9′a-hexahydro-2-[(1*R*-rel)-1-methyl-3-(phenylseleno)-3-(tributylstannyl)propyl]spiro[cyclopentane-1,4′-[4*H*]quinolizine] (6.4). *n*-BuLi (2.5 M in hexane, 0.14 mL, 0.35 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (0.055 mL, 0.390 mmol) in THF (0.5 mL). Stirring was continued at this temperature for 10 min, and then Bu_3SnH (0.11 mL, 0.39 mmol) was added. Stirring was continued for 15 min, and then the ice bath was replaced by a dry ice−acetone bath. A solution of **6.3** (23.6 mg, 0.071 mmol) in THF (0.5 mL plus 0.5 mL as a rinse) was added, and stirring was continued at −78 °C for 1 h. The mixture was quenched by addition of saturated aqueous NH_4Cl (2 mL), the cold bath was removed, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to give an oily residue which was kept under oil pump vacuum for 1 h and used directly in the next step without purification.

Pyridine (0.1 mL), PhSeCN (52 μL, 0.42 mmol), and Bu_3P (0.11 mL, 0.42 mmol) were added successively dropwise to a stirred and cooled (0 °C) solution of the above crude hydroxystannanes in THF (1 mL). The ice bath was removed, and the mixture was stirred for 4 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 × 15 cm), using hexane to 10:1 hexane/EtOAc, gave selenides **6.4** contaminated by impurities (33.1 mg, ca. 61% over two steps) as a yellowish oil: FTIR (CH_2Cl_2 cast) 2954, 2927, 1463 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.91 (t, J = 7.4 Hz, 12 H), 1.01 (dd, J = 15.9, 7.4 Hz, 6 H), 1.33 (dd, J = 14.8, 7.4 Hz, 9 H), 1.49−1.55 (m, 11 H), 1.60−1.70 (m, 3 H), 1.78−2.10 (m, 6 H), 2.35 (td, J = 12.4, 2.6 Hz, 2 H), 2.79 (dd, J = 15.6, 1.8 Hz, 1 H), 3.02 (d, J = 16.1 Hz, 1 H), 3.12 (dd, J = 12.2, 4.7 Hz, 1 H), 3.86−3.96 (m, 4 H), 5.13 (s, 1 H), 5.81 (s, 1 H), 7.18−7.25 (m, 3 H), 7.48 (d, J = 7.1 Hz, 2 H); exact mass m/z calcd for $C_{38}H_{62}NO_2{}^{80}Se^{120}Sn$ (M − H) 764.2962, found 764.2966.

(1*R*,2*S*,9′a*S*)-rel-2-[(1*R*-rel,5*Z*)-6-Chloro-8-[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-4-hydroxy-1-methyl-2-(phenylseleno)-5-octenyl]-7′-[1,3-dioxolan-3-yl]-1′,2′,3′,6′,9′,9′a-hexahydrospiro[cyclopentane-1,4′-[4*H*]quinolizine (6.6). *n*-BuLi (2.5 M in hexane, 0.08 mL, 0.20 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of the tin selenides **6.4** (38.5 mg, 0.050 mmol) in THF (0.5 mL). Stirring at −78 °C was continued for 30 min. Then aldehyde **6.5**[8] (53 mg, 0.21 mmol) in THF (0.5 mL plus 0.5 mL as a rinse) was added dropwise. Stirring at −78 °C was continued for 30 min. Saturated aqueous NH_4C1 (2 mL) was then added, and the mixture was extracted with EtOAc (3 × 7 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 1:4 to 1:1 EtOAc/hexane, gave phenylseleno alcohols **6.6** which were dissolved in MeOH (2 mL) and used directly for the next step.

(1*R*,2*S*,9′a*S*)-rel-2-[(1*R*-rel,2*E*,5*Z*)-6-Chloro-8-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-4-hydroxy-1-methyl-2,5-octadienyl]-7′-[1,3-dioxolan-3-yl]-1′,2′,3′,6′,9′,9′a-hexahydrospiro[cyclopentane-1,4′-[4*H*]quinolizine] (6.7). Powdered $NaHCO_3$ (32 mg), $NaIO_4$ (32 mg, 0.15 mmol), and water (0.4 mL) were added successively to the above solution, and stirring was continued for 24 h. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 1:4 to 1:1 EtOAc/hexane, gave alcohols **6.7** as a colorless oil, which was used directly in the next step: ^{1}H NMR ($CDCl_3$, 500 MHz) (major isomer only) δ 0.059 (s, 6 H), 0.89 (s, 9 H), 1.00 (d, J = 6.8 Hz, 3 H), 1.10−1.26 (m, 3 H), 1.33−1.52 (m, 7 H), 1.71−1.95 (m, 4 H), 2.05−2.14 (m, 2 H), 2.35−2.39 (m, 1 H), 2.46−2.60 (m, 3 H), 2.84 (dd, J = 15.6, 2.7 Hz, 1 H), 3.10 (d, J = 15.6 Hz, 1 H), 3.78−3.82 (m, 2 H), 3.88−4.00 (m, 4 H), 5.03 (t, J = 7.2 Hz, 1 H), 5.16 (s, 1 H), 5.43 (dd, J = 15.6, 6.6 Hz, 1 H) 5.63 (d, J = 7.8 Hz, 1 H), 5.79−5.85

(m, 1 H), 6.04 (dd, J = 15.6, 7.6 Hz, 1 H); exact mass m/z calcd for $C_{31}H_{53}{}^{35}ClNO_4Si$ (M + H) 566.3427, found 566.3426.

(4*R*,12*Z*,14*R*,15*E*,17*S*,17a*R*,20a*S*)-rel-12-Chloro-1,2,3,4,10,11,14,17,17a,18,19,20-dodecahydro-14-hydroxy-17-methyl-8*H*-4,7-ethanylylidene-6*H*-cyclopenta[*f*]pyrido[1,2-*e*][1,5]oxaazacyclopentadecin-8-one [(±)-Halichlorine (7.5)]. *N*-Ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (68 mg, 0.35 mmol) was added to a stirred solution of DMAP (77 mg, 0.63 mmol) and DMAP·HCl (88 mg, 0.55 mmol) in $CHCl_3$ (10 mL), and the resulting solution was refluxed. A solution of **7.3** [a 1.7:1 mixture of C(17) epimers] (3.4 mg, 6.3 μmol) in $CHCl_3$ (1 mL) was added to the above solution over 5 h (syringe pump with gastight syringe). After two additional rinses of $CHCl_3$ (0.1 mL plus 0.1 mL) were added, the solution was refluxed for a further 1 h. Heating was stopped, and stirring was continued overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 6 cm), using 1:3 EtOAc/hexane, gave **7.4** (1.9 mg, 58%) as a mixture of two isomers which was used directly in the next step.

HF·pyridine (ca. 1.2 N, 0.2 mL) was added to a stirred solution of **7.4** (1.9 mg, 3.7 μmol) in THF (2.5 mL), and stirring was continued for 2 h. Saturated aqueous $NaHCO_3$ (5 mL) was added, and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1 × 6 cm), using 2:1 EtOAc/hexane, gave **7.5** as the more polar product [0.8 mg, 54%; this corresponds to 86% based on the proportion (ca. 63%) of the correct C(17) isomer in the starting material] as a colorless glass: FTIR (CH_2Cl_2 cast) 3407, 2929, 2872, 1715, 1659 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 1.01 (d, J = 6.8 Hz, 3 H), 1.13 (br d, J = 12.2 Hz, 1 H), 1.20−1.36 (m, 1 H), 1.43 (ddd, J = 12.0, 10.0, 3.0 Hz, 1 H), 1.50 (dddd, J = 13.0, 13.0, 13.0, 4.5 Hz, 1 H), 1.62−1.80 (m, 6 H), 1.95−2.03 (m, 1 H), 2.15−2.21 (m, 1 H), 2.55 (br d, J = 14.5 Hz, 1 H), 2.63 (dd, J = 19.5, 2.0 Hz, 1 H), 2.73 (dq, J = 7.1, 6.8 Hz, 1 H), 2.86 (ddd, J = 14.5, 12.5, 4.5 Hz, 1 H), 3.10−3.14 (m, 1 H), 3.21 (d, J = 17.5 Hz, 1 H), 3.44 (br d, J = 17.5 Hz, 1 H), 3.98 (ddd, J = 11.5, 4.5, 2.0 Hz, 1 H), 4.62 (ddd, J = 14.5, 11.5, 3.0 Hz, 1 H), 5.03 (dd, J = 6.5, 4.5 Hz, 1 H), 5.35 (dd, J = 15.5, 4.0 Hz, 1 H), 5.57 (d, J = 7.5 Hz, 1 H), 5.75 (dd, J = 15.0, 8.5 Hz, 1 H), 7.03 (br s, 1 H); ^{13}C NMR (CD_3OD, 125 MHz) δ 18.1, 22.1, 22.3, 24.6, 24.9, 27.1, 32.1, 33.5, 33.7, 38.7, 41.8, 51.8, 51.9, 62.3, 69.5, 70.9, 128.3, 128.8, 129.7, 133.1, 136.9, 139.2, 167.6; exact mass m/z calcd for $C_{23}H_{33}{}^{35}ClNO_3$ (M + H) 406.2144, found 406.2144.

The incorrect isomer of the starting material was separated, but no attempt was made to recycle it (by oxidation and reduction).

(2*R*)-2,3-Dihydro-2-(hydroxymethyl)-6-[[(4-methoxyphenyl)methoxy]methyl]-4(1*H*)-pyridinone (8.7). Cs_2CO_3 (0.65 g, 2.0 mmol) was added in three portions over ca. 15 min to a stirred solution of **8.6** (0.201 g, 0.663 mmol) in MeOH (12 mL). The mixture was stirred for 1 h at room temperature and then at 80 °C. When the reaction was complete (usually within 6 h, TLC control), the solution was cooled and evaporated. The residue was diluted with water (10 mL) and EtOAc (10 mL), and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the yellow residue over silica gel (2 × 10 cm), using 1:9 MeOH/EtOAc, gave **8.7** (0.147 g, 80% yield) as a greasy solid: $[\alpha]^{25}{}_D$ −158.3 (*c* 0.78, $CHCl_3$); FTIR ($CHCl_3$ cast) 3397, 3290, 1612, 1572, 1531, 1515 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.20−2.50 (m, 3 H), 3.60−3.85 (m, 3 H), 3.81 (s, 3 H), 4.13 (AB q, J = 14.4 Hz, $\Delta\nu_{AB}$ = 36.8 Hz, 2 H), 4.48 (s, 2 H), 4.93 (s, 1 H), 6.04 (br s, 1 H), 6.89 (d, J = 8.5 Hz, 2 H), 7.26 (d, J = 8.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.9 (t), 54.2 (d), 55.3 (q), 64.1 (t), 68.0 (t), 72.9 (t), 95.9 (d), 114.0 (d), 128.8 (s), 129.8 (d), 159.6 (s), 161.8 (s), 191.6 (s); exact mass (electrospray) m/z calcd for $C_{15}H_{20}NO_4$ (M + H) 278.1387, found 278.1387.

(2*R*,4*S*)-2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-3,4-dihydro-4-hydroxy-6-[[(4-methoxyphenyl)methoxy]methyl]-1(2*H*)-pyridinecarboxylic acid phenylmethyl ester (8.10). $NaBH_4$ (33 mg, 0.88 mmol) was added to a stirred and cooled (−40 °C) slurry of **8.9** (0.23 g, 0.44 mmol) and $CeCl_3{\bullet}7H_2O$ (326 mg, 0.875 mmol) in MeOH (9 mL). Stirring at −40 °C was continued for 45 min, and the reaction was quenched with acetone (0.2 mL) and saturated aqueous NH_4Cl. The dry ice bath was removed and replaced with an ice bath, and stirring was continued for 30 min. The aqueous phase was extracted with Et_2O (3 × 5 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the colorless residue over silica gel (1 × 10 cm), using 3:1 hexane/EtOAc, gave **8.10** (0.198 g, 86%) as an oil: $[\alpha]^{25}{}_D$ +44.2 (*c* 1.35, $CHCl_3$); FTIR ($CHCl_3$ cast) 3420, 1711, 1514, 1328, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ −0.001 (s, 3 H), −0.005 (s, 3 H), 0.86 (s, 9 H), 1.38 (d, J = 7.2 Hz, 1 H), 1.73 (ddd J = 13.2, 10.0, 5.0 Hz, 1 H), 2.40−2.50 (m, 1H), 3.56 (t, J = 9.6 Hz, 1 H), 3.69 (dd, J = 9.6, 6.0 Hz, 1 H), 3.81 (s, 3 H), 4.28−4.54 (m, 6 H), 5.10−5.18 (m, 2 H), 5.33 (s, 1 H), 6.86 (d, J = 8.5 Hz, 2 H), 7.22 (d, J = 8.5 Hz, 2 H), 7.30−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.53 (q), −5.47 (q), 18.2 (s), 25.8 (q), 31.9 (t), 55.3 (q), 55.8 (d), 60.7 (t), 62.2 (d), 67.8 (t), 70.3 (t), 71.9 (t), 112.9 (d), 113.7 (d), 128.1 (d), 128.2 (d), 128.5 (d), 129.2 (d), 130.3 (s), 135.9 (s), 136.2 (s), 153.7 (s), 159.1 (s); exact mass (electrospray) m/z calcd for $C_{29}H_{41}NNaO_6Si$ (M + Na) 550.2595, found 550.2593.

(2*R*,6*S*)-2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-3,6-dihydro-6-[[(4-methoxyphenyl)methoxy]methyl]-6-(2-oxoethyl)-1(2*H*)-pyridinecarboxylic acid phenylmethyl ester (9.1). A mixture of **8.10** (0.153 g, 0.290 mmol), $Hg(OAc)_2$ (9 mg, 0.03 mmol), and Et_3N (4 μL, 0.03 mmol) in *n*-butyl vinyl ether (3 mL) was heated at 110 °C (oil bath temperature) in a sealed glass tube (Teflon seal) for 36 h. Evaporation of volatile material and flash chromatography of the residue over silica gel (1 × 10 cm), using 1:5 EtOAc/hexane, gave **9.1** (0.127 g, 79%) as a colorless oil: $[\alpha]^{25}{}_D$ −42.0 (*c* 0.84, $CHCl_3$); FTIR ($CHCl_3$ cast) 1722, 1698, 1397, 1286 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ −0.08 (br s, 6 H), 0.83 (s, 9 H), 2.14−2.24 (m, 1 H), 2.39 (dd, J = 17.4, 6.8 Hz, 1 H), 2.54 (dd, J = 16.0, 2.5 Hz, 1 H), 3.34−3.43 (m, 1 H), 3.46−3.86 (m, 4 H), 3.80 (s, 3 H), 4.30−4.48 (m, 3 H), 5.13 (AB q, J = 12.4 Hz, $\Delta\nu_{AB}$ = 19.2 Hz, 2 H), 5.79 (dd, J = 10.4, 3.0 Hz, 1 H), 5.84−5.92 (m, 1 H), 6.85 (d, J = 8.5 Hz, 2 H), 7.18 (d, J = 8.5 Hz, 2 H), 7.28−7.40 (m, 5 H), 9.61 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.53 (q), −5.48 (q), 18.1 (s), 23.9 (t), 25.8 (q), 48.1 (t), 52.1 (d), 55.2 (q), 58.6 (t), 63.2 (t), 67.1 (t), 72.6 (s), 73.1 (t), 113.8 (d), 123.3 (d), 127.8 (d), 128.0 (d), 128.5 (d), 129.6 (d), 130.1 (s), 130.5 (d), 136.4 (s), 155.1 (s), 159.2 (s), 201.1 (d); exact mass (electrospray) m/z calcd for $C_{31}H_{44}NO_6Si$ (M + H) 554.2932, found 554.2929.

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Supporting Information Available: Experimental procedures, copies of NMR spectra for new compounds and crystallographic information in CIF format. The X-ray data has been deposited with the Cambridge Crystallographic Data Centre and assigned the registry numbers CCDC 733408 for **4.4a** and CCDC 733409 for **4.8a**. This material is available free of charge via the Internet at http://pubs.acs.org.