Synthetic Chemistry of Halichlorine and the Pinnaic Acids

Derrick L. J. Clive,* Maolin Yu, Jian Wang, Vince S. C. Yeh, and Shunzhen Kang

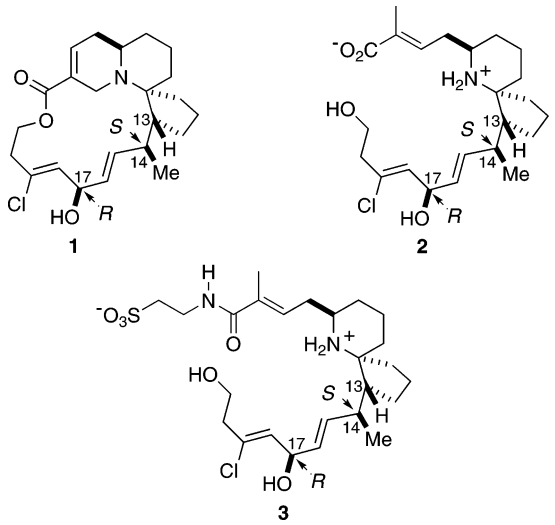
Chemistry Department, University of Alberta, Edmonton, Alberta T6G 2G2, Canada

Received April 25, 2005

Contents

1. Introduction

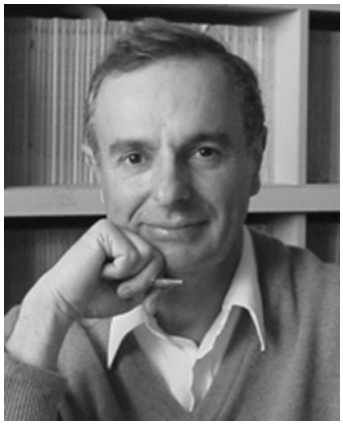
This review deals with synthetic work directed at the marine natural products halichlorine (**1**) and the pinnaic acids (**2** and **3**)—substances that have received a conspicuous degree of attention from synthetic chemists. The compounds present difficult constructional problems and also have potentially important biological properties.



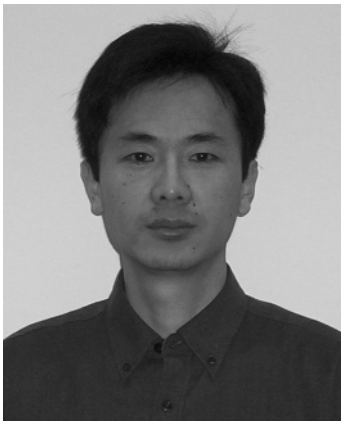
2. Isolation of Halichlorine and Establishment of Its Absolute Configuration[1]

As part of an extensive search for biologically active compounds in marine organisms a large batch of the black[2] marine sponge *Halichondria okadai* Kadota was collected in Japanese waters. Examination of the material showed that it contained[3] a substance—halichlorine (**1**)—which selectively inhibits the induction of vascular cell adhesion molecule-1 (VCAM-1) with an IC_{50} of 7 μg/mL.[1] The compound is crystalline (mp 183.5−185.5 °C) and was isolated in 3.5×10^{-7}% yield, corresponding to 70.8 mg from 200 kg of wet sponge. The structure was assigned[1] on the basis of

10.1021/cr0406209 CCC: $53.50
Published on Web 11/09/2005



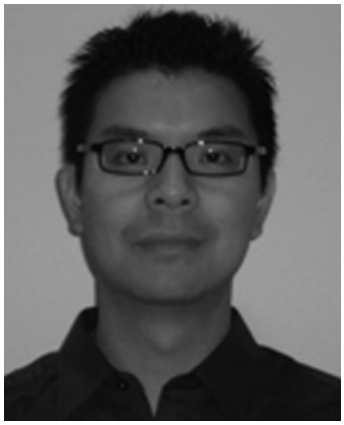
Derrick Clive was born in London and attended schools in South Africa and England. He received his B.Sc. and Ph.D. (D. H. R. Barton and J. E. Baldwin) degrees from Imperial College and held a postdoctoral position at Harvard University in Woodward's group. In 1975 he joined the Chemistry Department of the University of Alberta, where he is now Professor of Chemistry. He has published over 170 papers in two areas: synthetic methods—involving mainly selenium chemistry and radical cyclization—and the synthesis of complex natural products with significant biological properties.



Maolin Yu was born in Anhui province, China. He received his B.Sc. (1992) degree in Chemistry from Lanzhou University and M.Sc. (1995) degree from Zhejiang University. He then spent several years in the fine chemicals industry and joined the Chemistry Department at the University of Alberta in 2000. He is currently completing his Ph.D. thesis under the guidance of Professor Clive and will pursue postdoctoral work with Professor Danishefsky. His main research interests focus on natural product synthesis.

extensive spectroscopic measurements (mainly NMR), but establishment of the absolute configuration is based on the results of a partial degradation[4] (Scheme 1). Methanolysis of halichlorine (**1**) gave the dihydroxy ester **1.1**, which was then treated with O_3, followed by reductive workup ($NaBH_4$).[4] The water-soluble product was acetylated to yield a very small amount of triacetate **1.2**. This was characterized by comparison with a sample prepared from the known alcohol **2.1**, itself available from D-(+)-tartaric acid. The route from **2.1** to **1.2** is summarized in Scheme 2,[4] and two points are worthy of note: the glycidyl ether **2.3** was used in place of ethylene oxide (the former is regarded as a safer alternative), and the specification of chirality at C(17) is *S* in **1.2** but *R* in halichlorine, although there is no difference in the spatial arrangement of the key atoms. The enantiomer of **1.2** was made from L-tartaric acid, and HPLC

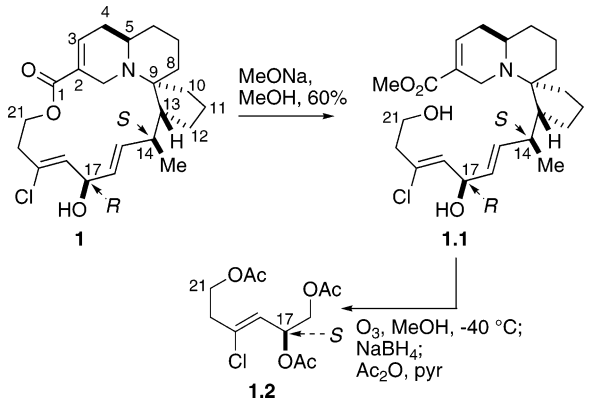
Jian Wang was born in Shanghai and received his B.S. (1993) degree in Chemistry from Fudan University. He then took an industrial position at ZhongXi Pharmaceutical Co. in Shanghai. In 1999 he entered graduate school at the University of Alberta and earned his Ph.D. (2004) degree in Chemistry under the supervision of Professor Clive. He then joined Professor Harran's group in UT Southwestern Medical Center, Dallas, and is currently a principle scientist at Wuxi PharmaTech Co., Ltd.



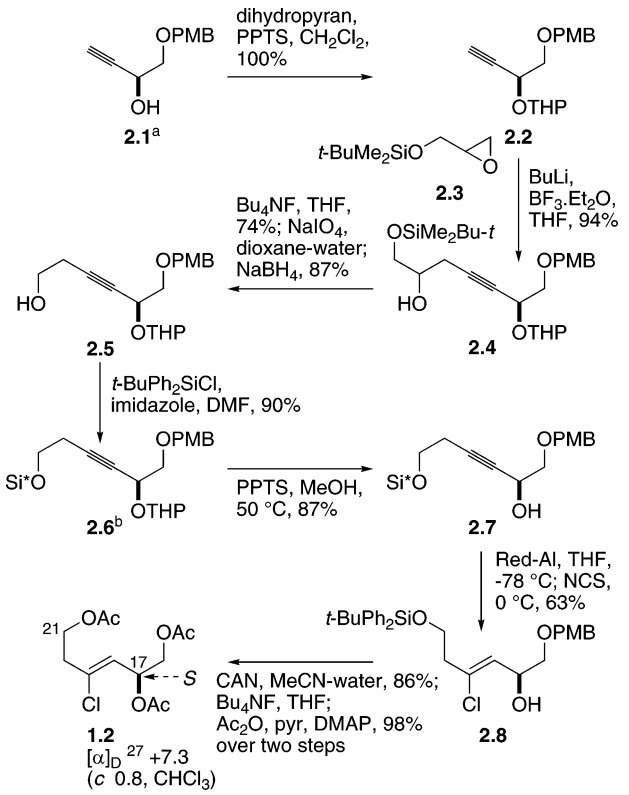
Vince Yeh received his B.S. (1994) degree from the University of British Columbia and Ph.D. (2001) degree from the University of Alberta, under the guidance of Professor Clive, where he studied the asymmetric syntheses of alkaloids. After postdoctoral research (2003) with Professor Trost at Stanford University, he joined Abbott Laboratories as a Senior Research Chemist working in the area of metabolic diseases. His research interests include asymmetric catalysis and natural product synthesis.

Shunzhen Kang obtained her B.Sc. (1994) and M.Sc. (1997) degrees in Chemistry from Zhongshan University in China. She started her Ph.D. program at the University of Alberta in 1997 under the supervision of Professor Clive. Her research was in the area of organic synthesis and involved radical transfer reactions and then synthetic studies on halichlorine. She was awarded her Ph.D. degree in 2002.

Scheme 1



Scheme 2



[a] PMB = *p*-methoxybenzyl. [b] Si* = *t*-BuPh$_2$Si.

analysis on a chiral column showed that **1.2** from D-tartaric acid corresponds to the degradation product from halichlorine, thereby establishing the absolute configuration of halichlorine as shown—a result subsequently confirmed by the Danishefsky[5] synthesis.

3. Isolation and Structure Determination of Pinnaic and Tauropinnaic Acids[2]

Uemura's program for identifying biologically active substances from marine organisms has resulted inter alia in the discovery of two azaspiro compounds **2** and **3** whose structures (arbitrarily drawn in the zwitterionic forms) clearly resemble that of halichlorine. The present compounds were named pinnaic acid (**2**) and tauropinnaic acid (**3**). They were isolated from the Okinawan bivalve *Pinna muricata* in very small amounts and found to inhibit a cytosolic phospholipase cPLA$_2$ with an IC$_{50}$ of 0.2 mM for **2** and 0.09 mM for **3**.[2] From 10 kg of the bivalves only 1 mg of **2** and 4 mg of **3** were obtained, and the gross structures were established in yet another tour de force of spectroscopic analysis. In this case, however, it was not possible to properly assign the C(17) stereochemistry, and that suggested for C(14) was not on a very secure basis; in the event, the Danishefsky synthesis[6,7] allowed assignment of both stereochemistries and showed that the suggested stereochemistry for C(14) required revision. The synthetic studies finalized the structural details as those shown in **2** and **3**, and later synthetic work by Christie and Heathcock[8] and by Hayakawa, Arimoto, and Uemura[9] is in accord with these assignments.

4. Biological Activity and Biogenesis

Because of the similarity in structure between halichlorine and the pinnaic acids it is tempting to consider—notwithstanding the fact that they were isolated from entirely different organisms—that the origin of these natural products is not actually their respective organisms but is a common symbiotic organism or a dietary source.[10]

VCAM-1, which is a member of the immunoglobulin superfamily,[11] is expressed on the surface of endothelium cells. It is involved in the interaction of endothelium with leukocytes and participates in the migration of leukocytes to inflammatory foci. While it has normal functions,[12] it has also been implicated in a number of inflammatory diseases and become a potential target for drug discovery.[12] VCAM-1 plays a role in rheumatoid arthritis, allergic reactions, and nephrotoxic nephritis.[13] The adhesive function of VCAM-1 is used by cancer cells in the metastatic process.[13,14]

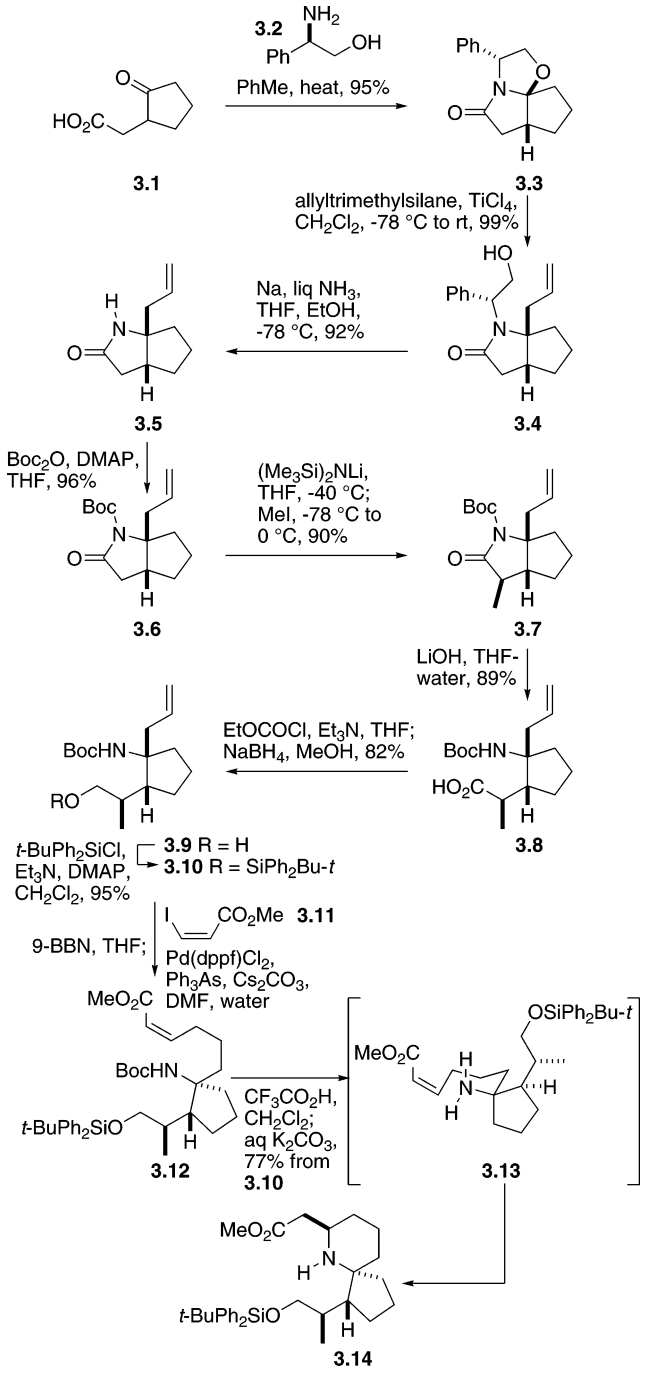
Inhibitors of cytosolic phospholipase A$_2$ (cPLA$_2$) are of potential value for treating inflammatory diseases since cPLA$_2$ is involved at an early stage in the cascade of reactions that leads to the formation of inflammatory mediators leukotrienes, lipoxins, prostaglandins, and thromboxanes.[15]

5. Studies in Danishefsky's Laboratory

5.1. First Total Synthesis of (+)-Halichlorine[5,16,17]

The first report in the halichlorine field from the Danishefsky laboratory[16] described an asymmetric synthesis of the spiroquinazoline core (see Scheme 4, **4.4** and **4.5**). The starting point for this work was the construction of the "Meyers lactam" **3.3**, which was made[16] (Scheme 3) by the simple step of heating γ-keto acid **3.1** with D-(−)-phenylglycinol. As expected,[18] **3.3** reacted with allyltrimethylsilane in the presence of a Lewis acid to produce the new lactam **3.4**. Removal of the nitrogen appendage by dissolving metal reduction and protection of the nitrogen (**3.4** → **3.5** → **3.6**) set the stage for introduction of the eventual C(14) methyl group. To this end, **3.6** was methylated stereoselectively from the convex face (**3.6** → **3.7**). The next task was to convert **3.7** into alcohol **3.9**. This could not be done directly but was easily accomplished by hydrolysis to an acid (LiOH,

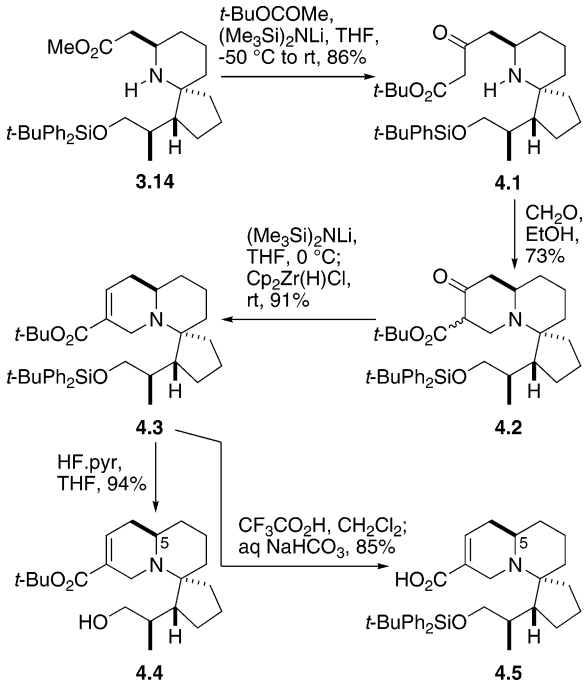
Scheme 3



3.7 → **3.8**) and then $NaBH_4$ reduction of the derived mixed anhydride formed with EtOCOCl. At this point the resulting primary hydroxyl was protected by silylation (**3.9** → **3.10**).

The allylic side chain was now elongated (**3.10** → **3.12**) by hydroboration and Suzuki coupling of the resulting borane with methyl *Z*-3-iodoacrylate (**3.11**). When the nitrogen was deprotected by the action of CF_3CO_2H, followed by neutralization with K_2CO_3, spontaneous intramolecular Michael addition occurred to afford the spirotricycle **3.14** in good overall yield (77% from **3.10**). The stereochemistry of the Michael addition presumably results from reaction via the conformation **3.13**, with the larger substituent (the more substituted carbon of the cyclopentane ring) pseudoequatorial. Use of the *Z*-3-iodoacrylate

Scheme 4

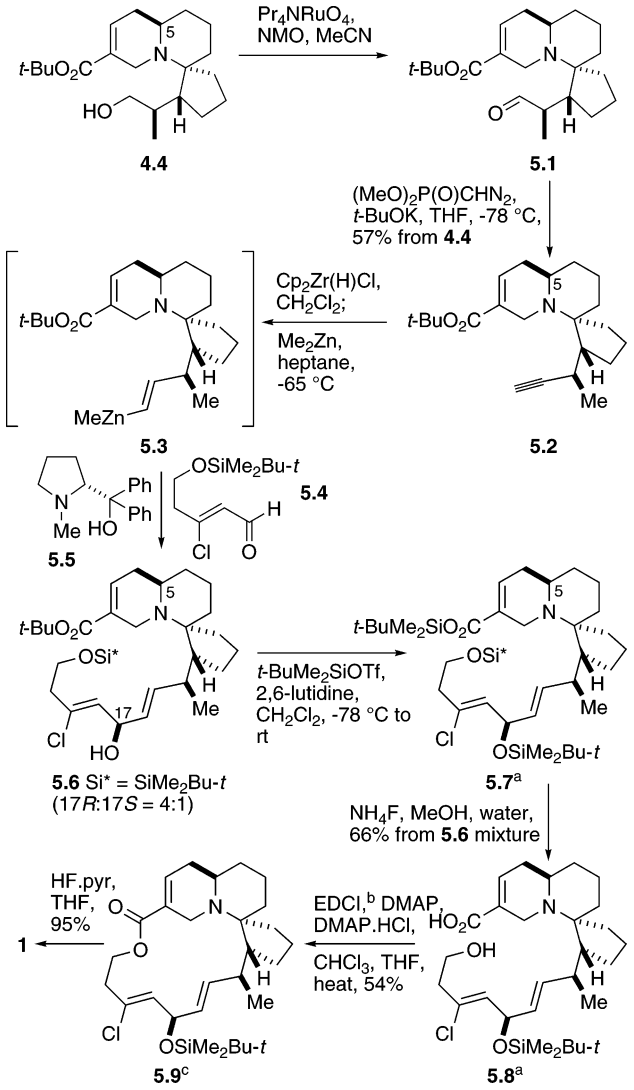


3.11 in this sequence was not essential since the *E*-isomer also gave **3.14** as the major (16:1:[16−20]1[17]) isomer and in good yield; however, the *Z*-alkene gave **3.14** exclusively.[17]

Claisen condensation of **3.14** with *t*-BuOCOMe (Scheme 4) produced the β-keto ester **4.1**, and the final ring closure (**4.1** → **4.2**) was effected by Mannich reaction with formaldehyde, the process giving the desired product as a mixture of diastereoisomers and tautomers. Desaturation, by formation of an enolate and reaction with $Cp_2Zr(H)Cl$,[19] led to **4.3**. This was selectively deprotected in two ways: desilylation gave alcohol **4.4**, and removal of the *tert*-butyl group released acid **4.5**. In the event, only the alcohol was taken on to halichlorine.

Oxidation of alcohol **4.4** (Scheme 5) produced the corresponding aldehyde **5.1**, but this seemingly simple operation required extensive effort; it was eventually achieved by use of Pr_4NRuO_4 in the presence of an excess amount of NMO. The aldehyde was very sensitive to epimerization (possibly because of the presence of the tertiary amino subunit) and did not behave properly during attempted Horner−Emmons−Wadsworth reactions. Homologation of the lower sidearm was finally achieved with the Gilbert reagent[20] (see **5.1** → **5.2**) in 57% yield from **4.4**. Even in this optimized process there was slight (<5%) epimerization. With the oxidation and homologation hurdles now overcome, the terminal alkyne was subjected to hydrozirconation and metal exchange with Me_2Zn (**5.2** → **5.3**). The resultant zinc species coupled smoothly with aldehyde **5.4** [readily available by DIBAL reduction of **66.7** (see Scheme 66)]. The reaction was done in the presence of the optically pure amino alcohol **5.5**[21] and led to a 4:1 mixture of the desired 17*R* epimer **5.6** and the corresponding 17*S* epimer, the stereochemistry of the major isomer being made on the basis of extensive precedent[21] for asymmetric addition to aldehydes in the presence of

Scheme 5

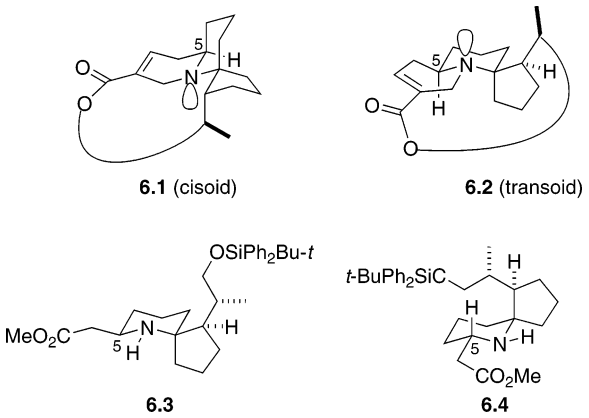


[a] 17*R*:17*S* mixture (17*R* major). [b] EDCI = 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide. [c] 17*R* isomer separated.

optically pure amines. (In the absence of the chiral amino alcohol the epimer ratio was ca. 1:1.) This mixture was used without separation. Modification of the *tert*-butyl ester was accomplished by the action of *t*-BuMeSiOSO$_2$CF$_3$, which also masked the newly installed secondary hydroxyl (**5.6** → **5.7**). Treatment with NH$_4$F in aqueous MeOH then brought about deprotection of the silyl ester as well as the primary hydroxyl (**5.7** → **5.8**) while leaving the protected secondary alcohol intact—all exactly as required. At this point macrolactonization (**5.8** → **5.9**) and separation of the C(17) epimers (now 8:1) gave **5.9** (54%). Finally, desilylation with HF·pyridine released synthetic (+)-halichlorine (**1**).

During the above synthesis it was noticed that the chemical shift of the C(5) hydrogen of a number of intermediates (e.g., **4.4**, **4.5**, **5.1**, **5.2**, **5.6**, **5.8**) was significantly different from the corresponding signal in halichlorine itself, and it was suggested[17] that the intermediate quinolizidines adopt a transoid ring fusion while the natural product, under the constraint of the macrocyclic ring, has a cisoid conformation (**6.1**, Scheme 6). Uemura et al. suggested[1] a transoid ring fusion for halichlorine on the basis of

Scheme 6



an apparent Bohlmann band; however, the chemical shift, coupling constant, NOE data, and molecular modeling results of the Danishefsky group provide a convincing argument for assigning a cisoid ring fusion to halichlorine,[22] and this stereochemistry was later established in the solid state by X-ray analysis.[8]

The stereochemistry at C(5) also had an influence on earlier intermediates in the synthesis. For example, the bicyclic amines **6.3** and **6.4**, which differ at that center, adopted preferred conformations in which in one case the bulkier substituent was axial and in the other equatorial. Attempts (conditions unspecified) to interconvert **6.3** and **6.4** (via retro-Michael reaction) were unsuccessful.[17] The pinnaic acids have been suggested to have a conformation resembling **6.3**.[2] Finally, it was appreciated[17] that these conformational effects might be important considerations in designing drugs based on the halichlorine and pinnaic acid leads.

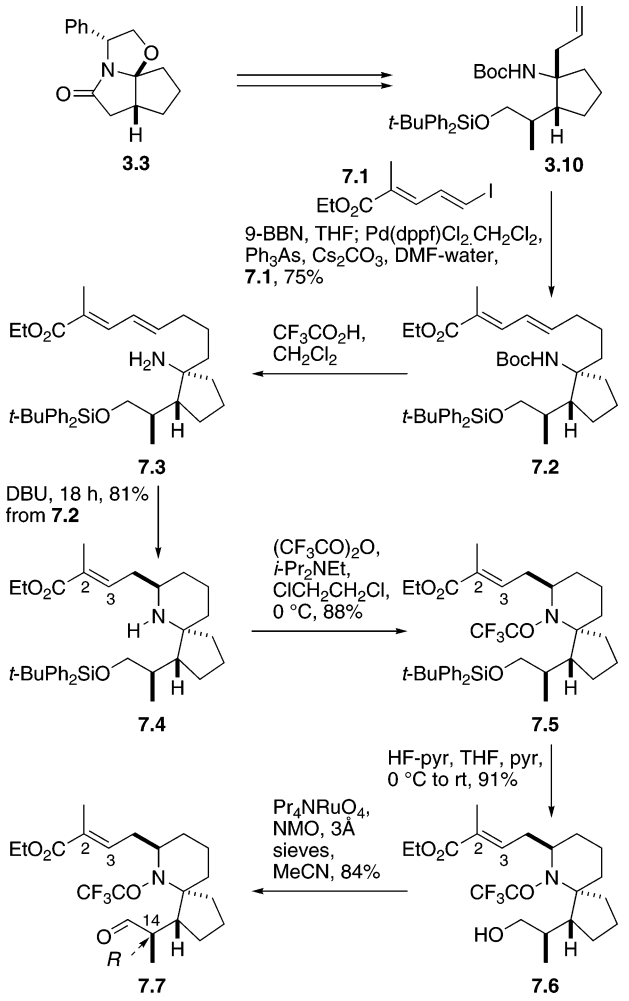
5.2. First Total Synthesis of Pinnaic Acid and Assignment of C(14) and C(17) Stereochemistry[6,7]

At the outset of this work the stereochemistry of pinnaic acid at C(14) and C(17) had not been settled, and so the synthetic route[6] had to give access to all four permutations. The original C(14) assignment was tentative, and no assignment had been made for C(17).

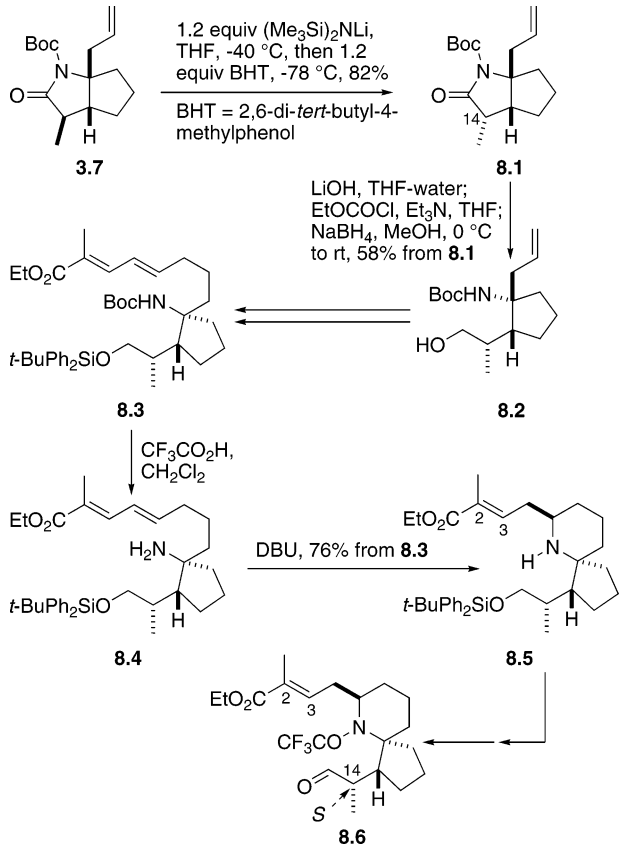
Compound **3.10**, obtained as before (see Scheme 3), was hydroborated with 9-BBN,[6] and the resulting borane was coupled with **7.1** in the presence of a palladium catalyst (Scheme 7, **3.10** → **7.2**). Deprotonation of nitrogen did not lead to the intended Michael addition. The bulk of the Boc group was evidently suppressing ring closure, since deprotection (CF$_3$CO$_2$H) and treatment with DBU led to smooth and stereoselective cyclization (**7.2** → **7.3** → **7.4**), and the double bond in the product (**7.4**) had the desired *E*-geometry. Desilylation gave an alcohol, but the hydroxyl could not be oxidized to the corresponding aldehyde—presumably because of the presence of the free NH. Accordingly, that functional group was masked as a trifluoroacetate, a choice of protecting group that was made only after considerable experimentation. Desilylation (**7.5** → **7.6**) and oxidation now took the route as far as aldehyde **7.7**.

At this point the C(14) epimer of **7.7** was synthesized (Scheme 8),[6] as both epimers would be neces-

Scheme 7



Scheme 8



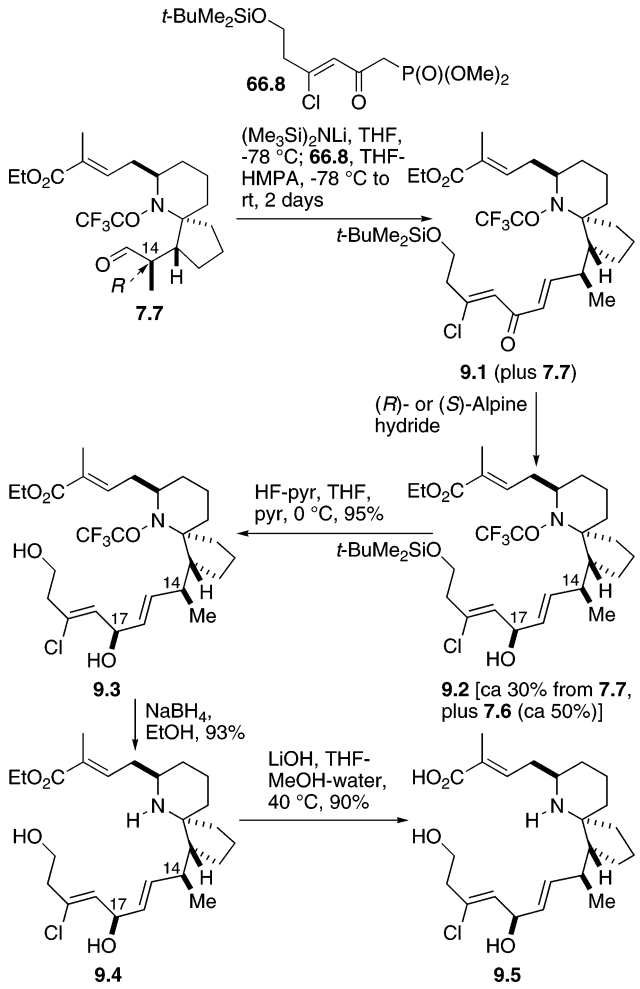
sary in order to establish the actual C(14) stereochemistry in natural pinnaic acid.

The lactam **3.7** was deprotonated[6] and reprotonated with 2,6-di-*tert*-butyl-4-methylphenol so as to generate, very largely, the inverted stereochemistry at the eventual C(14) (**3.7** → **8.1**). Lactam hydrolysis and reduction of the resulting acid, as before, via a mixed anhydride gave **8.2**. Following the earlier procedures this was converted first into **8.3** and then into the free amine **8.4**. Once again, the amine cyclized by Michael addition in the presence of DBU and the product (**8.5**) was elaborated into **8.6**, so that at this stage both the 14-*R* (**7.7**) and 14-*S* (**8.6**) aldehydes were at hand. The 14-*R* isomer was elaborated first (Scheme 9).[7]

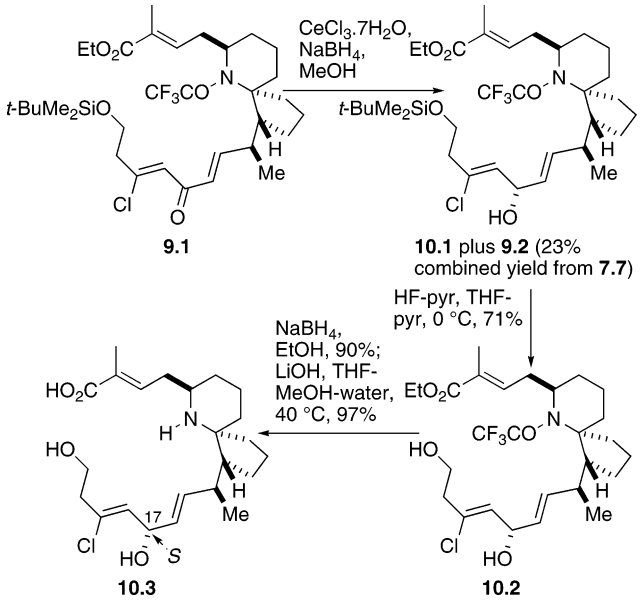
Olefination of aldehyde **7.7** with the known phosphonate **66.8**[23] (see Scheme 66 for preparation) was problematic as the reaction did not go to completion and separation of the desired product from starting aldehyde was difficult.[7] The mixture of **9.1** and **66.8** was reduced with Alpine-hydride[24] and, surprisingly, gave **9.2**, irrespective of whether the *R*- or *S*-hydride was used. At this stage **7.6** (formed by reduction of residual **7.7**) was separated, and **9.2** could be obtained in ca. 30% yield overall from **7.7**. Removal of the silyl group (**9.2** → **9.3**), deprotection of nitrogen, and ester hydrolysis gave **9.5** (arbitrarily shown in the nonzwitterionic form). This was eventually identified as natural pinnaic acid (**2**), but such an assignment had to await the outcome of considerably more experimental work. The high-field NMR spectrum of **9.5** was "quite similar" to that reported for the natural compound, but no reference sample was available for direct comparison, and it was not clear that even high-field NMR measurements would be capable of distinguishing isomers that differed only in stereochemistry at either or both of the centers C(14) and C(17). Progress toward a definite stereochemical assignment was facilitated by the observation that $NaBH_4$ reduction of **9.1** (Scheme 10) gave some of the C(17) isomer, ultimately identified as **10.1**. This was transformed, as in the 17-*R* series, into what was eventually identified as **10.3** (**10.1** → **10.2** → **10.3**[25]). The ^1H NMR spectrum of this pinnaic acid isomer differed from that of the natural compound. The observations thus far suggested that **9.5** represented natural pinnaic acid, but at this point the C(17) stereochemistry had not actually been determined—all that was known was that spectral comparisons favored **9.5** and excluded **10.3** as candidates for natural pinnaic acid. Corresponding 14-*R* compounds were also obviously needed for comparison purposes, and the 17-*R* assignment shown for **9.5** had to be established—the depiction given in Scheme 9 being based on hindsight.

Olefination of **8.6** with **66.8** (Scheme 11) again gave rise to a mixture of the desired product (**11.1**) and starting aldehyde, and as before, reduction afforded a separable mixture.[7] This sequence gave alcohols **11.2** [a 1.7:1 ratio of C(17) epimers] together with the alcohol derived from **8.6**. Alcohols **11.2** were indi-

Scheme 9

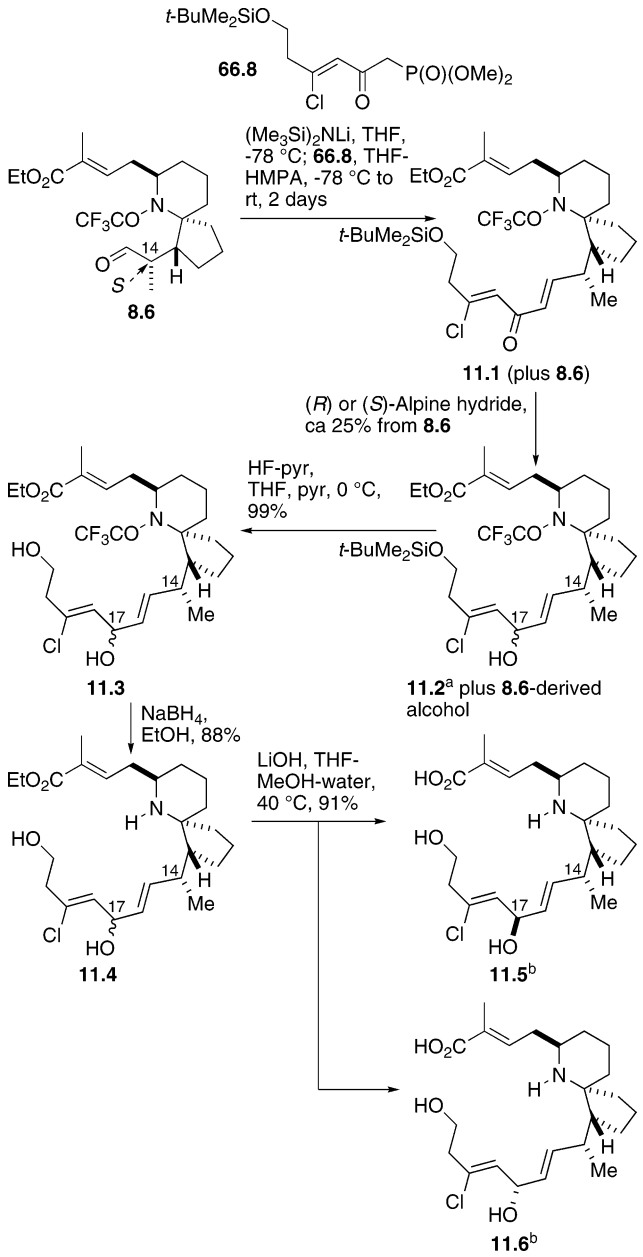


Scheme 10



vidually desilylated, deprotected on nitrogen, and finally hydrolyzed (**11.2** → **11.3** → **11.4** → **11.5**,[25] **11.6**[25]).[26] The stereochemistry at C(14) of the end products **11.5** and **11.6** follows, of course, from the stereochemistry of **8.6**, and the C(17) stereochemistry was established by a degradation discussed later (see Scheme 13).

Scheme 11



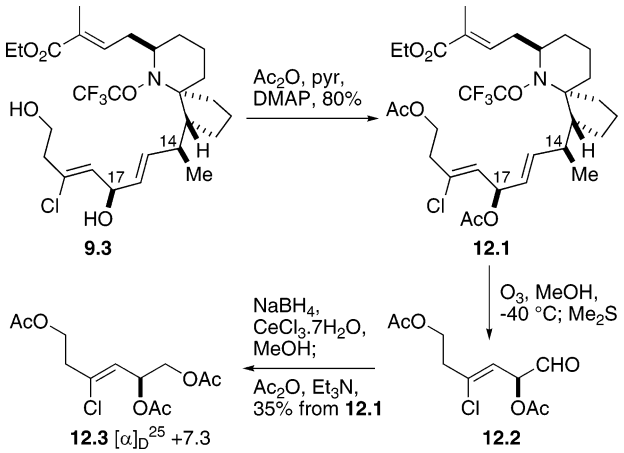
[a] 1.7:1 mixture of C(17) epimers. [b] Stereochemistry at C(17) is an arbitrary assignment.

With all four compounds (**9.5**, **10.3**, **11.5**, **11.6**) in hand that correspond to the stereochemical permutations at C(14) and C(17) it was possible to establish that only **9.5** has a ^{1}H NMR spectrum that corresponds to that published for natural pinnaic acid, and it remained only to establish the C(17) absolute configuration; this was achieved by degradation[7] (Scheme 12) of the synthetic intermediate **9.3**.

Acetylation and ozonolysis served to excise the requisite segment of the structure (**9.3** → **12.1** → **12.2** → **12.3**). Both **12.3** and its enantiomer had previously been made,[4] and direct comparison with those samples showed that **12.3** has the indicated absolute configuration, thereby establishing the 17-*R* configuration for pinnaic acid, as depicted in **9.5** (and **2**).

One of the alcohols represented by **11.3** (leading to **11.5**) was subjected to the same degradation

Scheme 12



sequence as shown in Scheme 12 and afforded a triacetate identical to **12.3**. This result serves to identify the C(17) stereochemistry of the pinnaic acid isomers **11.5** and **11.6**.

Reduction of **9.1** with Alpine borane—a large reducing agent—had given only **9.2**, with 17-*R* configuration, irrespective of the chirality of the borane; in the case of the C(14) epimer **11.1** the selectivity was only 1.7:1 in favor[27] of the 17-*R* alcohol **11.5**. Clearly, subtle conformational effects influence the facial accessibility of the C(17) carbonyl in the respective starting ketones.

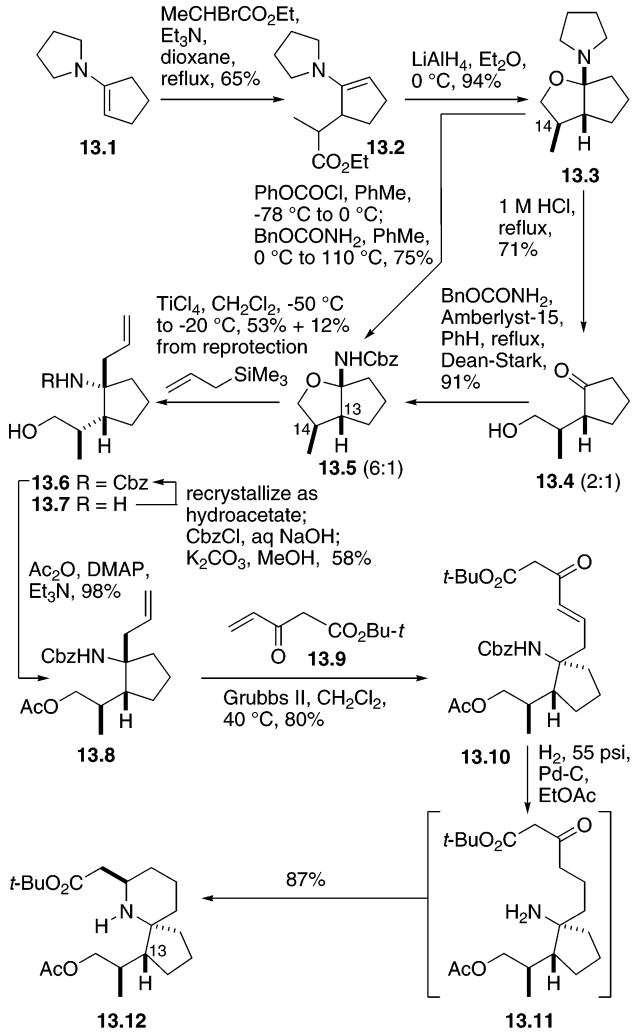
6. Studies in Heathcock's Laboratory

6.1. Total Synthesis of (±)-Halichlorine, (±)-Pinnaic Acid, and (±)-Tauropinnaic Acid[8]

The synthetic route reported[8] by Christie and Heathcock begins (Scheme 13) with the preparation of keto alcohol **13.4** as a 2:1 mixture of diastereoisomers, according to a published[28] procedure (**13.1** → **13.4**). Condensation with $BnOCONH_2$ provided the cis-fused bicyclic carbamates **13.5** as a 6:1 isomer mixture with the major component having the methyl substituent exo at C(14), as depicted. The same 6:1 mixture was obtained even when the keto alcohols **13.4** were processed individually, showing that epimerization occurs at C(13). The intermediate aminals **13.3** can be converted directly into **13.5** by successive reaction with PhOCOCl and $BnOCONH_2$. The carbamates **13.5** could be separated by HPLC, and X-ray analysis of the major isomer confirmed the structure shown. Treatment of **13.5** (as a 6:1 isomer mixture) with $TiCl_4$ and capture of the resulting iminium ions with allyltrimethylsilane then allowed isolation of **13.6** and **13.7**, each as a single isomer with the indicated stereochemistry. The latter compound was converted into the former by crystallization of its acetic acid salt, reprotection of the nitrogen (BnOCOCl, aqueous NaOH), and hydrolysis (K_2CO_3, MeOH) of the carbonate group that is formed. This recycling brought the overall yield of **13.6** to 65%.

At this point cross metathesis of **13.8** with the Nazarov ester **13.9**, using the Grubbs II catalyst, produced the *E*-olefin **13.10** in 80% yield. Hydrogenation of the double bond and hydrogenolytic removal

Scheme 13

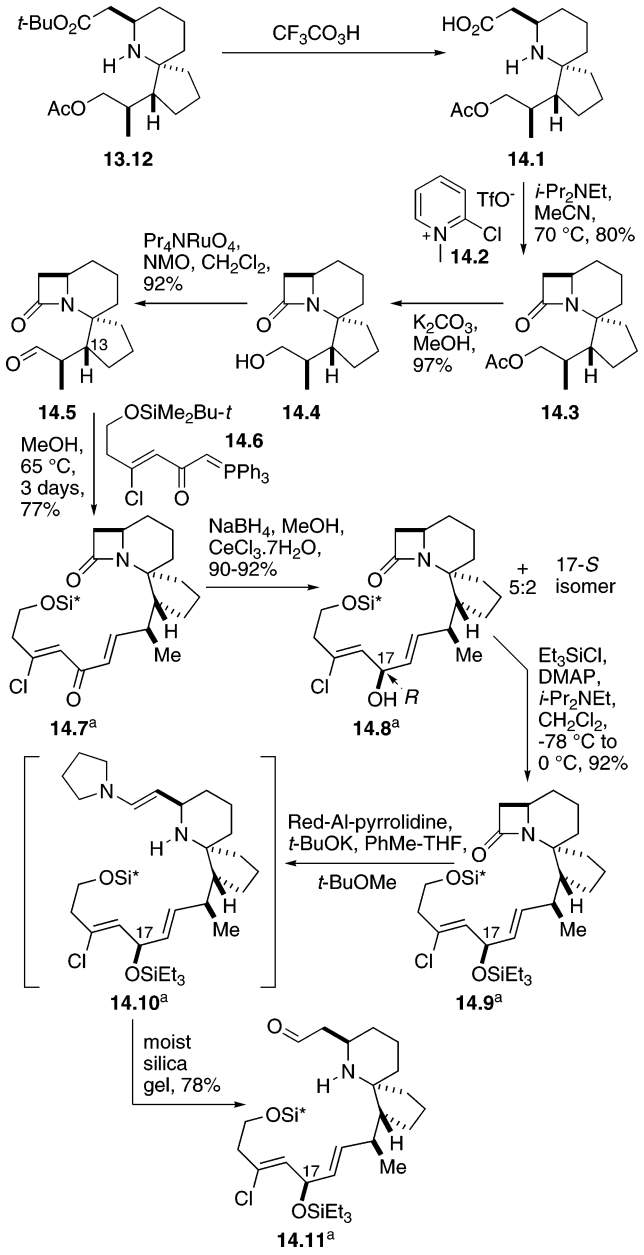


of the nitrogen protecting group then liberated the keto amine **13.11**, and this underwent spontaneous cyclization to **13.12**, as expected on the basis of a related[9,29] ring closure. Compound **13.12** represents a key advanced intermediate, which provided access to both halichlorine and the pinnaic acids.

At this stage the C(13) side chain was elaborated,[8] and in preparation for this, the nitrogen and the C(5) side chain were mutually protected as a lactam (Scheme 14), a choice that would avoid probable difficulties due to steric effects at nitrogen that might be anticipated for protection by intermolecular reactions.

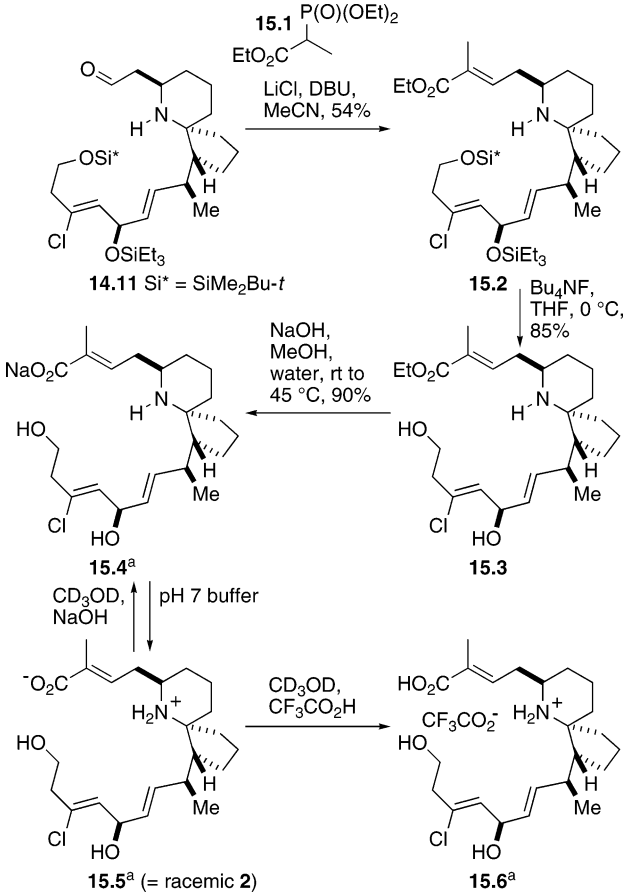
Removal of the *tert*-butyl group in the standard way gave amino acid **14.1**, and the derived β-lactam **14.3** was then formed in 80% yield by treatment with the pyridinium salt **14.2**. Acetate hydrolysis released the crystalline alcohol **14.4**, whose structure was confirmed by X-ray analysis. Oxidation with Pr_4NRuO_4 afforded aldehyde **14.5** and set the stage for elaboration of the C(13) side chain. Homologation with Weinreb's phosphonate **66.8** (see Scheme 66) was not very successful and gave at best about 25% yield of the condensation product **14.7**. However, the Wittig reagent **14.6**, which was easily made[30] from an intermediate (**66.6**) in the route to Weinreb's phosphonate (see later, Scheme 66), did react, al-

Scheme 14



[a] Si* = $SiMe_2Bu$-*t*.

Scheme 15



[a] Exchange of OH and NH hydrogens for deuterium arbitrarily ignored in these structures.

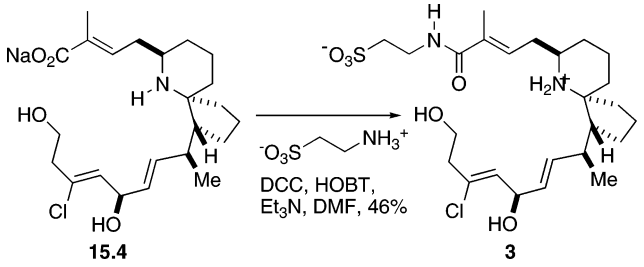
though slowly, to give **14.7** in acceptable yield (77%). Reduction of the ketone group (**14.7** → **14.8**) was best achieved by the action of $NaBH_4$–$CeCl_3{\cdot}7H_2O$. With this reagent combination the desired 17-*R* alcohol **14.8** was obtained as the major component of a 5:2 mixture of C(17) epimers, the stereochemical assignment being made by ultimate conversion to the natural products (whose stereochemistry had by now been established[6,7]). (Use of *S*-Alpine hydride[24] produced the undesired 17-*S* isomer[31] as the major (ca 2:1) alcohol.) Both the 17-*R* alcohol **14.8** and its 17-*S* epimer were silylated (Et_3SiCl), the latter product being converted into 17-*epi*-pinnaic acid (following the same route as used for the natural series).

The β-lactam was next cleaved by semireduction.[8] Use of DIBAL did give some of the desired aldehyde (**14.9** → **14.11**), but the process was inefficient as the corresponding alcohol as well as starting lactam were also obtained. Reduction with $LiBH_4$ followed by Pr_4NRuO_4 oxidation was a satisfactory way of making the aldehyde, but the most effective reagent was found to be Red-Al, modified by treatment with pyrrolidine and *t*-BuOK.[32] This reagent converted lactam **14.9** into the enamine **14.10**, from which point chromatography over moist silica gel afforded the desired aldehyde in 78% yield. This racemic aldehyde is at the branch point leading to the pinnaic acids and halichlorine.

6.2. Last Steps in the Total Synthesis of (±)-Pinnaic Acid[8]

Horner–Emmons–Wadsworth olefination of aldehyde **14.11** provided olefin **15.2** with high *E*/*Z* selectivity, although in only modest yield (54%) (Scheme 15). There remained now just the removal of the protecting groups. Desilylation was done first in order to defer as late as possible the experimental difficulties of handling amino acids. Treatment with Bu_4NF removed both the *t*-$BuMe_2Si$– and Et_3Si– groups, and the ester was then hydrolyzed with NaOH (**15.2** → **15.3** → **15.4**). The product of this hydrolysis was dissolved in pH 7 buffer and extracted into 1-butanol, so that purification could be effected by reverse-phase HPLC. A solution of the purified material (**15.5**) in CD_3OD was treated with NaOH, presumably forming the salt **15.4**. The ^1H NMR spectrum was the same as that measured on the initial hydrolysis product. Another sample of what

Scheme 16



was presumed to be zwitterion **15.5** was treated with CF_3CO_2H in CD_3OD to give, presumably, the salt **15.6**. Comparison of the ^1H NMR spectra of all three racemic species **15.4**, **15.5**,[33] and **15.6**[33] with the spectral data reported for the natural product suggested that the latter is most likely the zwitterion **15.5** or the carboxylate **15.4** or a mixture of both.[34]

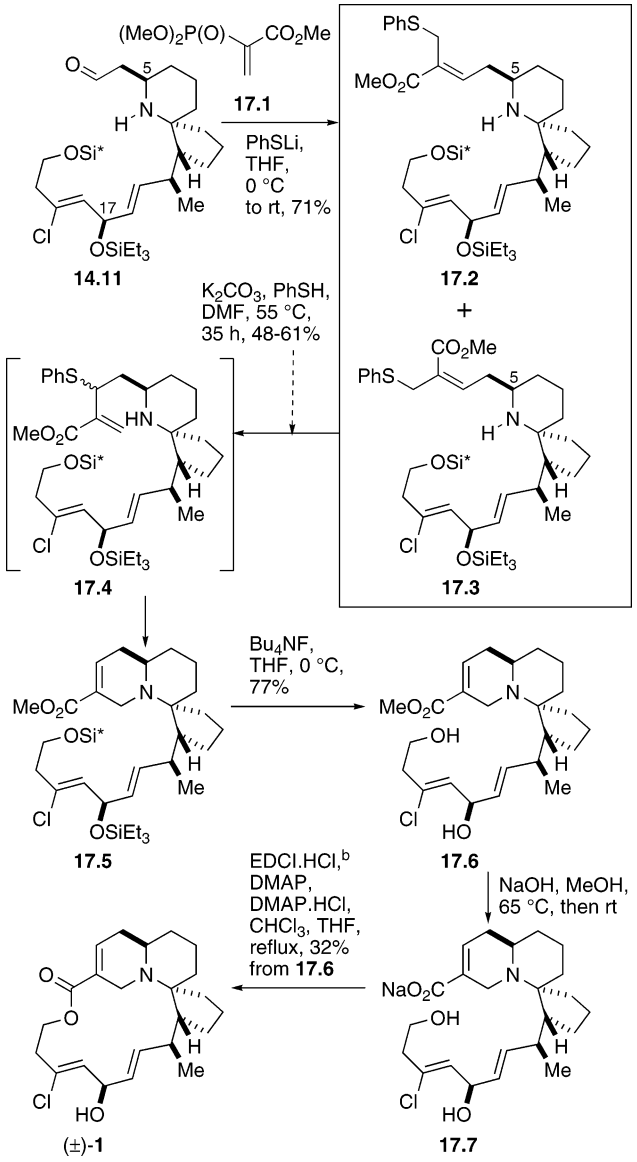
6.3. Last Step in the Total Synthesis of (±)-Tauropinnaic Acid[8]

The sodium salt of (±)-pinnaic acid (**15.4**) was coupled with taurine (Scheme 16) using DCC and HOBT to afford (46%) tauropinnaic acid (**3**).

6.4. Last Steps in the Total Synthesis of (±)-Halichlorine[8]

The aldehyde **14.11** was converted (Scheme 17) into a mixture of the two esters **17.2** and **17.3**, differing only in the double-bond geometry in the C(5) side chain, by reaction with trimethyl phosphonoacrylate (**17.1**) and PhSLi. The mixture of **17.2** and **17.3**, upon heating with PhSH and K_2CO_3, gave directly the dehydroquinolizidine **17.5**, presumably via the intermediacy of **17.4**. This cyclization method is related to that subsequently used in Clive's laboratory (see Scheme 35).[35] Cleavage of the silicon protecting groups in the standard manner (**17.5** → **17.6**) and saponification of the ester then brought the synthesis to within one step from the end. This last step—formation of the macrolactone—was achieved in 32% yield by use of the EDCI·HCl, DMAP, DMAP·HCl combination.[36] The Yamaguchi[37] method gave a lower yield, in part because of interference by the free secondary hydroxyl. The racemic halichlorine [(±)-**1**] was crystalline, and the first X-ray crystal structure of this alkaloid was obtained. The dehydroquinolizidine system does indeed have a cis ring fusion, as suggested by the NMR studies of the Danishefsky group, and the fact that all three natural products were obtained in the present work from the same advanced intermediate confirms that all have the same relative configuration.

Scheme 17



[a] Si* = $SiMe_2Bu$-*t*. [b] EDCI·HCl = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride.

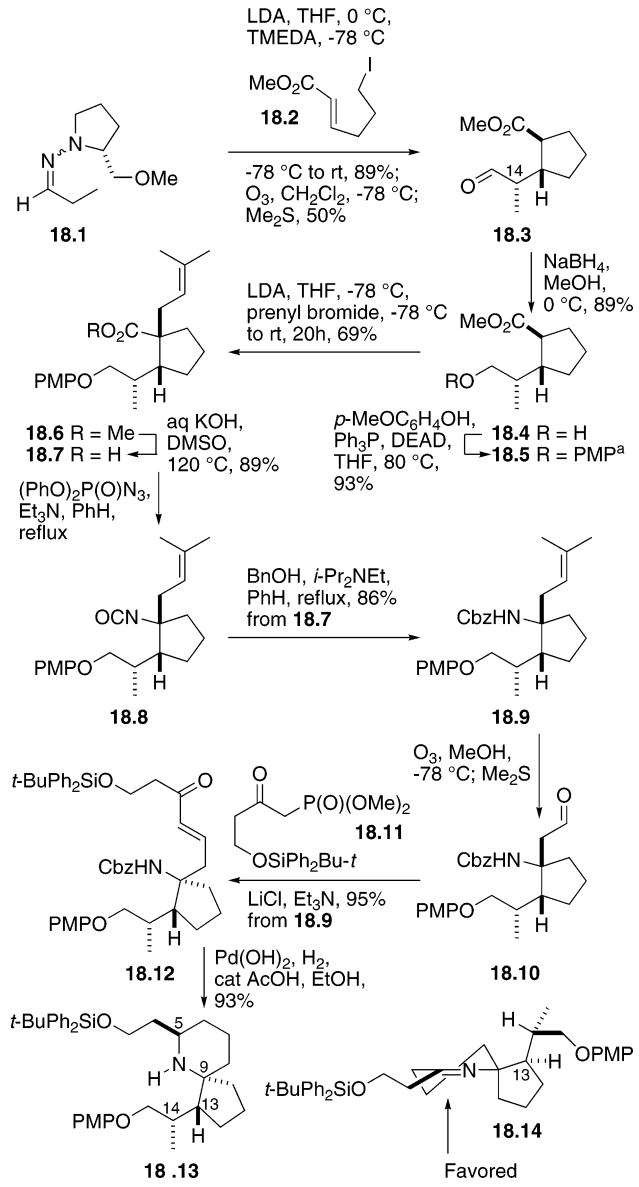
7. Studies in the Arimoto–Uemura Laboratories

7.1. Synthesis of an Azabicyclic Core Unit[29]

The SAMP hydrazone **18.1** was deprotonated and allowed to react with the Michael acceptor **18.2** (Scheme 18). As expected on the basis of close analogy,[38] conjugate addition and cyclization occurred, so that ozonolytic removal of the chiral auxiliary then released the aldehyde **18.3** as a single isomer of ≥97% ee. The aldehyde group was reduced ($NaBH_4$), and the resulting alcohol was protected as its *p*-methoxyphenyl ether (**18.5**) under Mitsunobu conditions. Next, facially selective alkylation with prenyl bromide gave **18.6**, whose stereochemistry was confirmed by chemical modification to a more rigid bicyclic derivative for which structurally convincing NOEs were observed. Ester hydrolysis (**18.6** → **18.7**) required harsh conditions, a fact that had necessitated protection of the hydroxyl in **18.4** by the robust PMP (*p*-methoxyphenyl) group. The acid **18.7** was subjected to standard Curtius rearrangement, and the resulting isocyanate was heated with BnOH to give the Cbz-protected amine **18.9**, all of these simple transformations occurring in good yield.

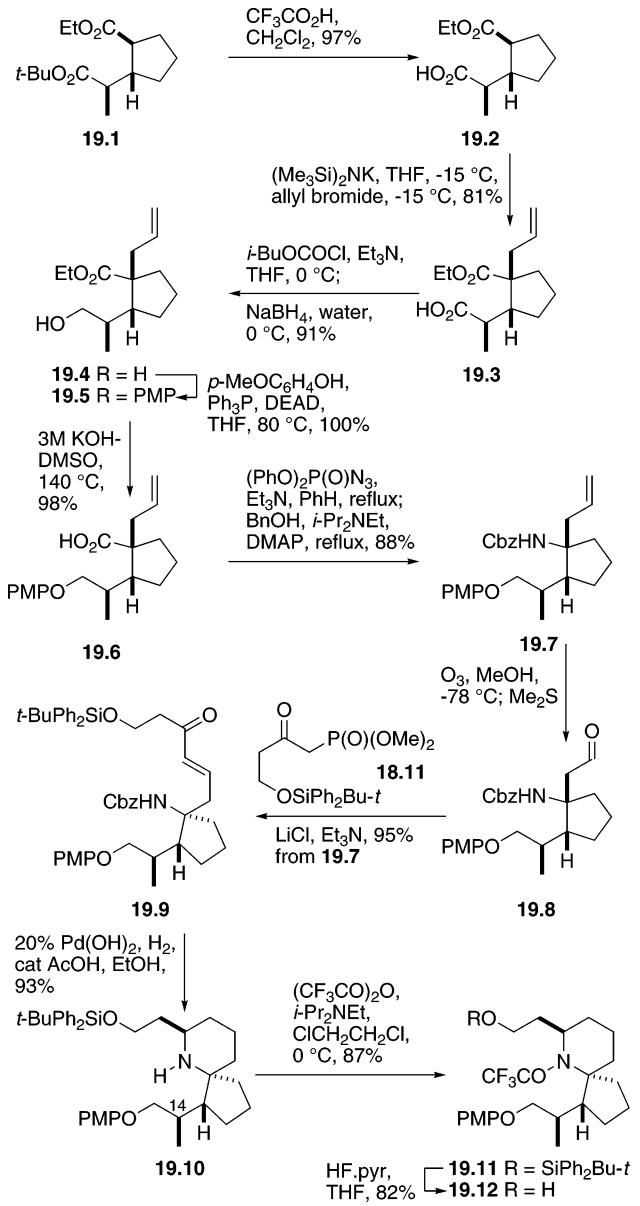
The double bond in the pendant side chain was cleaved by ozonolysis, giving aldehyde **18.10** (83%); surprisingly, the Lemieux–Johnson procedure afforded only a diol, which was not cleaved by $NaIO_4$ or $Pb(OAc)_4$. Horner–Emmons–Wadsworth olefina-

Scheme 18



[a] PMP = *p*-methoxyphenyl.

Scheme 19

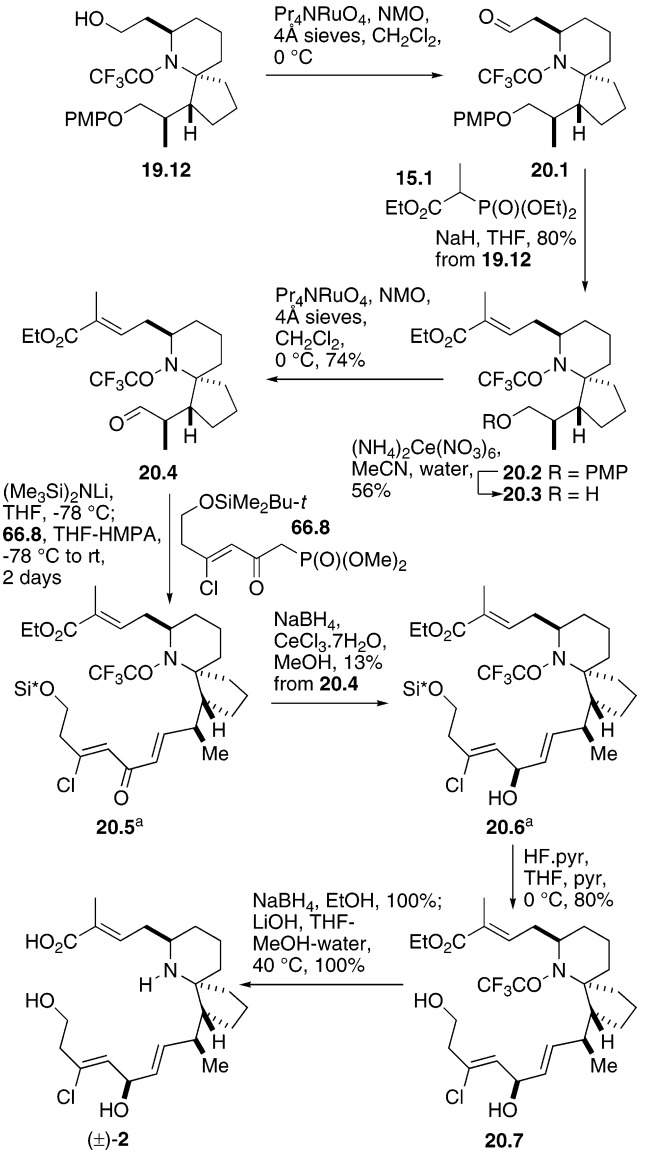


tion of the aldehyde (which was not purified) with the phosphonate **18.11** produced **18.12** in excellent overall yield (95%). Hydrogenation of the double bond and removal of the Cbz group, when done in the presence of a catalytic amount of AcOH, proceeded smoothly, and the intermediate imine (see **18.14**) was reduced in situ to give **18.13** directly and in high yield (93%). In the absence of acid and after treatment of the presumed imine intermediate with $NaCNBH_3$/AcOH, only a complex mixture was obtained. The stereochemical outcome of the hydrogenation is interpreted on the reasonable basis of preferential hydrogenation of the intermediate imine **18.14** from the face opposite to the C(13) substituent. The spirobicyclic amine **18.13** represents a portion of the pinnaic acid structure, although the C(14) stereochemistry corresponds to the initial[2] stereochemical assignment; later work[6,7] revealed that this assignment (which was based on research with very small quantities) should be reversed.

7.2. Synthesis of (±)-Pinnaic Acid by a Method that Merges with the Danishefsky Route[9]

The route of Scheme 18 was modified slightly in order to make racemic pinnaic acid.[9] The known racemic diester **19.1**[39] was treated with CF_3CO_2H (Scheme 19) to remove the *tert*-butyl group and then doubly deprotonated. Alkylation with allyl bromide gave largely (6:1) the isomer **19.3**. Reduction of the carboxyl, via its mixed anhydride, and protection of the resulting alcohol as its PMP (*p*-methoxyphenyl) ether took the route as far as **19.5**. From this point the reactions (Scheme 19) were modeled closely on the earlier route of Scheme 18 and gave, eventually, **19.10**, which corresponds to **18.13**, but has the natural stereochemistry at C(14). The nitrogen was protected as its trifluoroacetate, and the silicon group was then removed. Oxidation of the resulting alcohol (Scheme 20, **19.12** → **20.1**) and Horner−Emmons−Wadsworth olefination with phosphonate **15.1** gave **20.2**. *O*-Deprotection (CAN, 56%) and oxidation produced **20.4**, which is a racemic version of compound

Scheme 20



[a] Si* = $SiMe_2Bu$-*t*.

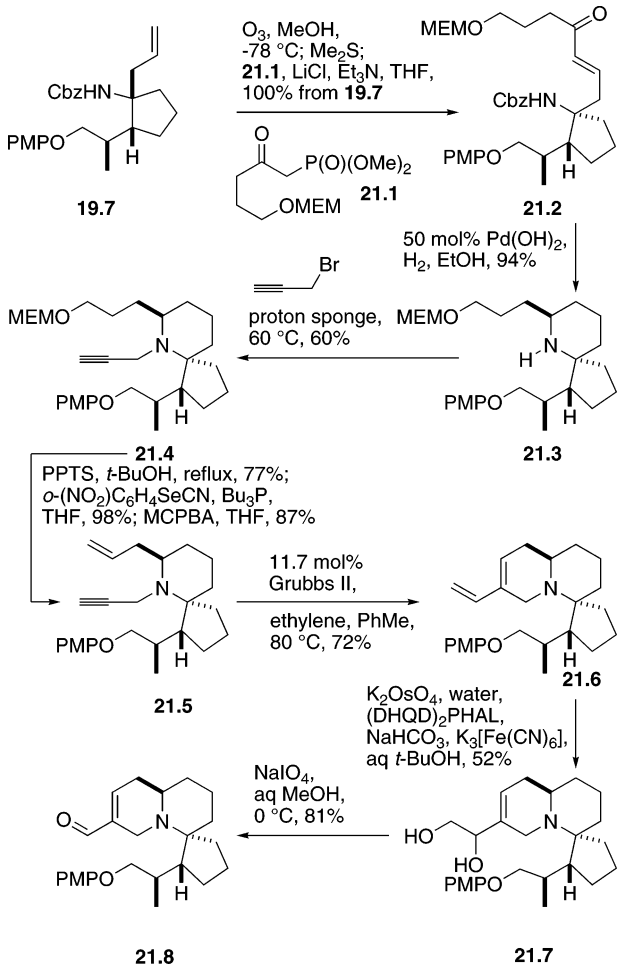
7.7 used in the Danishefsky synthesis,[6] and from this point that earlier synthesis was followed. Olefination with Weinreb's phosphonate (**66.8**) and Luche reduction ($NaBH_4$, $CeCl_3 \cdot 7H_2O$) allowed isolation of **20.6** in 13% yield. Desilylation, removal of the trifluoroacetyl group, and ester hydrolysis then completed the synthesis of (±)-pinnaic acid [**20.6** → **20.7** → (±)-**2**[25]]. The compound was converted into its sodium carboxylate. The zwitterionic[40] and sodium salt forms had very similar ^{1}H NMR spectra to those obtained with natural material; consequently, this synthesis confirms the stereochemical assignment made by the Danishefsky group.[6,7]

7.3. Synthesis of the Tricyclic Core of Halichlorine[41]

The racemic intermediate **19.7** from the pinnaic acid work was also elaborated (Scheme 21) into the tricyclic aldehyde **21.8**, which represents a significant portion of the halichlorine structure.

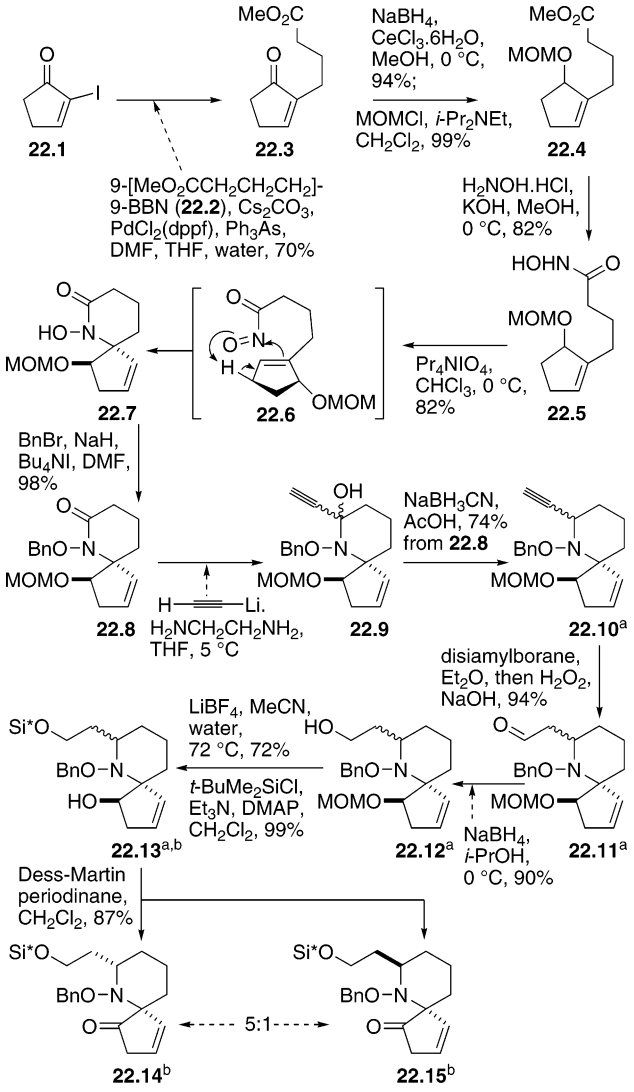
Ozonolysis and Horner−Emmons−Wadsworth olefination with the phosphonate **21.1** gave the *E*-olefin

Scheme 21



21.2. As in earlier work on pinnaic acid, hydrogenation caused a cascade of reactions: saturation of the double bond, removal of the nitrogen protecting group, and, finally, stereoselective reduction of the intermediate imine that is formed. In the present case large-scale reductions were best done in the absence of AcOH, an additive that was necessary[9] in the pinnaic acid series. A large amount of catalyst [50 mol %, 5% $Pd(OH)_2$/C from N. E. CHEMCAT Co., Tokyo] was needed for reproducible results. The nitrogen was next alkylated with propargyl bromide (**21.3** → **21.4**). This step also required extensive experimentation, but it was eventually established that the reaction works satisfactorily (60% yield) when Proton Sponge is used. Removal of the MEM group under mildly acidic conditions (PPTS) and formation of a terminal double bond by standard selenium chemistry (**21.4** → **21.5**) afforded the critical intermediate for ring-closing ene−yne metathesis.[42] When **21.5** was heated in the presence of Grubbs II catalyst (and in an ethylene atmosphere) the desired tricyclic system **21.6** was generated quite efficiently (72% yield). An unprotected tertiary amino group does not appear[43,44] to be compatible with the Grubbs catalysts, but evidently this feature did not suppress reaction in this case. To cleave the exocyclic double bond a bulky Sharpless osmium reagent was used first to effect dihydroxylation (**21.6** → **21.7**) since ozone gave a complex mixture, possibly because of poor selectivity between the double bonds and/or the

Scheme 22



[a] Isomer ratio = 5:1. [b] Si* = $SiMe_2Bu$-*t*.

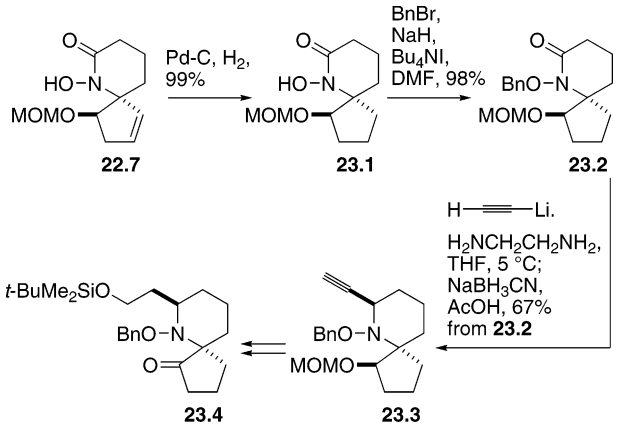
presence of the tertiary amino group. Finally, periodate cleavage yielded the target aldehyde **21.8**.

8. Studies in Kibayashi's Laboratory[45,46]

The azaspiro[4,5]decane core has been constructed by an intramolecular ene reaction of an acylnitroso compound (see **22.6**, Scheme 22). Suzuki−Miyaura coupling of the known iodoenone **22.1** with the borane **22.2** afforded enone **22.3** (70%).[45] The ketone carbonyl was reduced under Luche conditions, and the resulting alcohol was protected as its MOM ether (**22.3** → **22.4**). Treatment with H_2NOH in a basic medium then produced the hydroxamic acid **22.5**. Upon oxidation with Pr_4NIO_4 the desired acylnitroso species was generated, and it underwent spontaneous ene reaction (see **22.6**) at 0 °C to give directly the spiro compound **22.7** in good yield (82%). The structure was proven by X-ray analysis, and the stereochemical outcome is understandable on the basis that the niroso group approaches the less hindered face of the cyclopentene ring.

The next task was to introduce a two-carbon side chain at the eventual C(5) position. To this end, the

Scheme 23

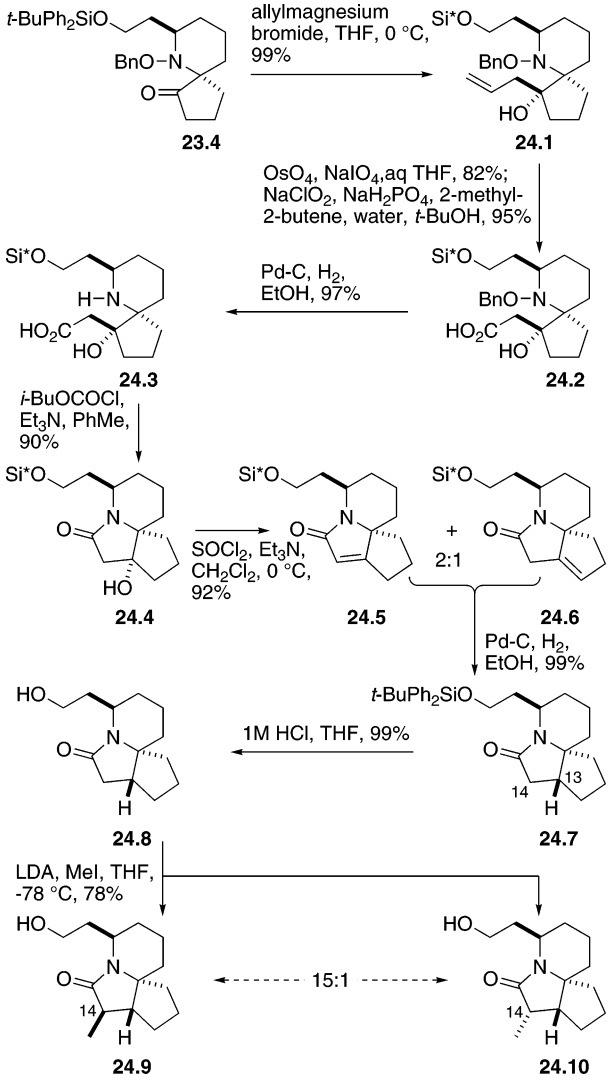


N-hydroxyl group was benzylated, and treatment with lithium acetylide−ethylenediamine complex served to introduce an alkynyl unit (**22.7** → **22.8** → **22.9**). Reduction in AcOH with $NaCNBH_3$ then gave the acetylenes **22.10** as a 5:1 mixture of epimers. The terminal acetylene was converted into a hydroxyethyl unit by hydroboration and reduction of the resulting aldehyde (**22.10** → **22.11** → **22.12**). Removal of the MOM group under acidic conditions did not work, but $LiBH_4$ in aqueous MeCN was successful; the silyl group was lost at the same time, and the resulting primary hydroxyl was then protected as its *tert*-butyldimethylsilyl ether (**22.12** → **22.13**). Dess−Martin oxidation now yielded the two separable epimers **22.14** and **22.15** as a 5:1 mixture, respectively.

The stereochemical outcome of the deoxygenation step **22.9** → **22.10** was interpreted on the basis of a conformational model which suggests that the proximal *vinyl* hydrogen of the five-membered ring blocked access of hydride from one face, so that the undesired isomer was the major product. It was found,[45] however, that saturation of the double bond removed this constraint. Catalytic hydrogenation of **22.7** (Scheme 23) and *O*-benzylation gave **23.2**. This was subjected to the same series of reactions used with **22.8**, leading eventually to **23.4**, free of the undesired epimer.

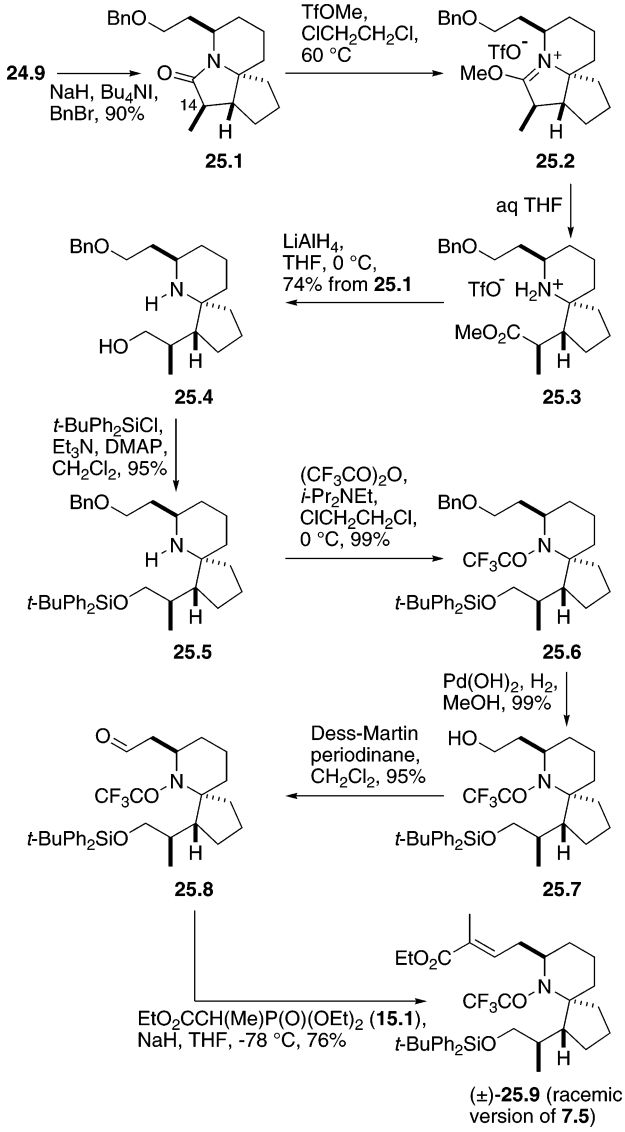
The (racemic) spirocyclic lactam **23.4** was converted[46] (Scheme 24) in almost quantitative yield into the tertiary alcohol **24.1** by treatment with allylmagnesium bromide, reaction occurring exclusively on the pro-*R* face of the carbonyl as the other face is obstructed by the benzyloxy group. The terminal double bond was next cleaved in the standard way with OsO_4 and $NaIO_4$, and the resulting aldehyde was oxidized ($NaClO_2$) to the corresponding acid. Removal of the benzyloxy group by hydrogenolysis (**24.2** → **24.3**) set the stage for construction of a third ring that would confer sufficient facial bias on the system to allow introduction of the C(14) methyl in the correct stereochemical sense. Ring formation was achieved by making a mixed anhydride with isobutyl chloroformate (**24.3** → **24.4**). Dehydration of the resulting alcohol ($SOCl_2$) gave a mixture of regioisomeric alkenes, both of which were equally useful, since catalytic hydrogenation of the mixture led in 99% yield to the single saturated tricycle **24.7**, having the required stereochemistry at C(13). At this stage

Scheme 24



[a] Si* = $SiPh_2Bu$-*t*.

Scheme 25



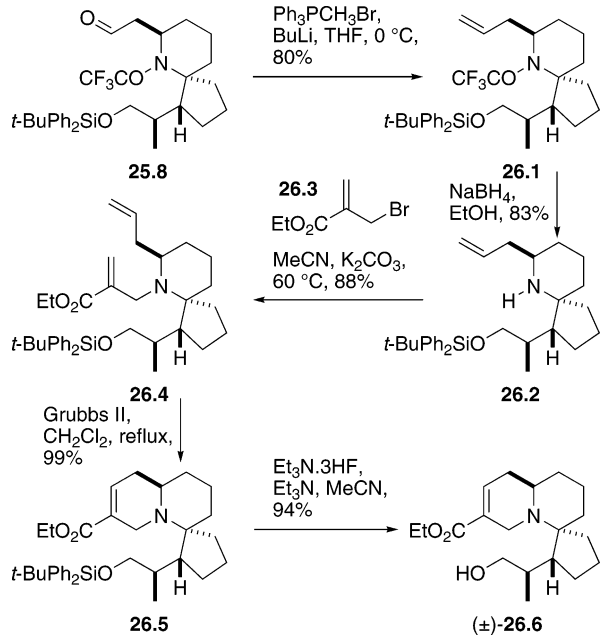
attempts to introduce a methyl group at C(14) were unpromising, but removal of the silyl protecting group gave an alcohol (**24.8**) that could be methylated easily α to the carbonyl, the reaction giving a mixture of C(14) epimers favoring (15:1) the desired epimer. Why the presence of the silyl group caused difficulties is not clear, although it should be noted that C(14) methylation of the corresponding triethylsilylated compound (Et_3Si instead of *t*-$BuPh_2Si$ in **24.7**) has been reported[47] under perfectly standard conditions.

The major product was protected on oxygen by benzylation (Scheme 25, **24.9** → **25.1**),[46] and attempts were then made to open the lactam. No reaction was observed with $LiNH_2BH_3$,[48] even though this reagent appears to be a general one for opening lactams,[49] and a substance corresponding to **25.1**, but having a triethylsilyl group instead of a benzyl group on oxygen, had been reported[47] to react satisfactorily (see Scheme 57, **57.13** → **57.14**). Even prolonged exposure (40 h) to refluxing aqueous KOH led to recovery of the lactam.[46] The corresponding *O*-methyl lactam (Me instead of Bn in **25.1**) was also not opened by heating in concentrated hydrochloric acid; only cleavage of the methoxy group was observed.[46] The authors of this review have also found that lactams related to **25.1** are difficult to open under conventional conditions (see Scheme 34, **34.4** → **34.5**). Lactam **25.1** was eventually opened by *O*-methylation with methyl triflate and hydrolysis of the intermediate iminium ion (**25.1** → **25.2** → **25.3**).

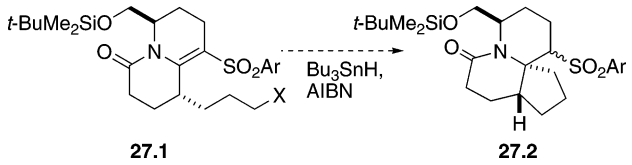
Reduction of the ester, silylation of the resulting alcohol, and acylation of the nitrogen gave **25.6** (**25.3** → **25.4** → **25.5** → **25.6**). Finally, hydrogenolysis of the *O*-benzyl group and Dess–Martin oxidization generated the key intermediate **25.8**. By the single step of Horner–Emmons–Wadsworth olefination with **15.1** this aldehyde was converted into the ester (±)-**25.9**, which is the racemic version of an intermediate (**7.5**) in the Danishefsky route[6,7] to pinnaic acid.

To tackle the problem of making (±)-halichlorine, aldehyde **25.8** was homologated[46] (Scheme 26) by Wittig methylenation (**25.8** → **26.1**) and the *N*-trifluoroacetyl group was removed by the action of $NaBH_4$. The liberated amine, though hindered, combined smoothly (88%) with the allylic bromide **26.3** in hot MeCN. Ring-closing metathesis (**26.4** → **26.5**) was almost quantitative with the Grubbs II catalyst, and desilylation afforded (±)-**26.6**; the corresponding

Scheme 26



Scheme 27



[a] Ar = C_6H_4Me-*p*.

optically pure *tert*-butyl ester is an intermediate in the Danishefsky route[5] to halichlorine.

It is noteworthy that the hindered nitrogen in **26.2** can be alkylated with a reactive allyl unit.

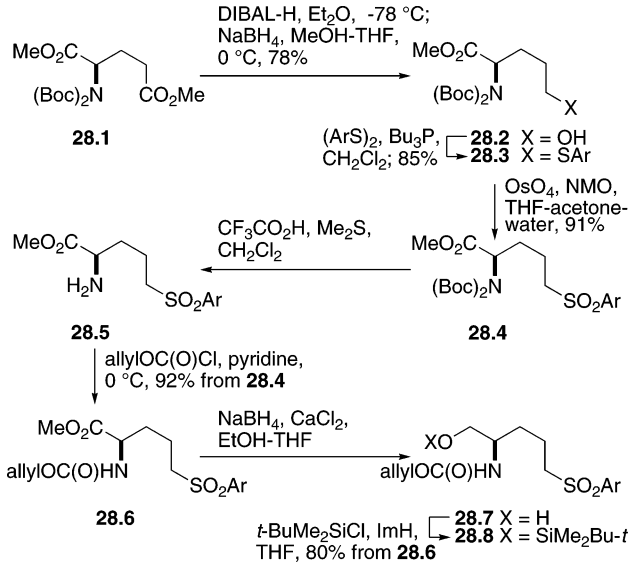
9. Studies in Clive's Laboratory[35,50−52]

Clive et al. reported a number of exploratory studies that lead to spiro compounds resembling the core structure of halichlorine and pinnaic acid. Their initial report[50] was based on the expectation that radical cyclization of **27.1** would lead to **27.2** (see Scheme 27). To test this concept **27.1** was assembled from two optically pure subunits, which were prepared as shown in Schemes 28 and 29.[50]

D-Glutamic acid was converted by a literature[53] procedure into the ester **28.1**. Reduction with DIBAL and then with $NaBH_4$ gave alcohol **28.2**, and the hydroxyl group was replaced in two steps by a sulfone, via the intermediate sulfide **28.3**. The Boc groups were removed and replaced by a single allyl carbamate unit (**28.4** → **28.5** → **28.6**). Finally, reduction ($NaBH_4$) of the remaining ester and protection of the resulting alcohol as a silyl ether afforded one of the required subunits (**28.8**).

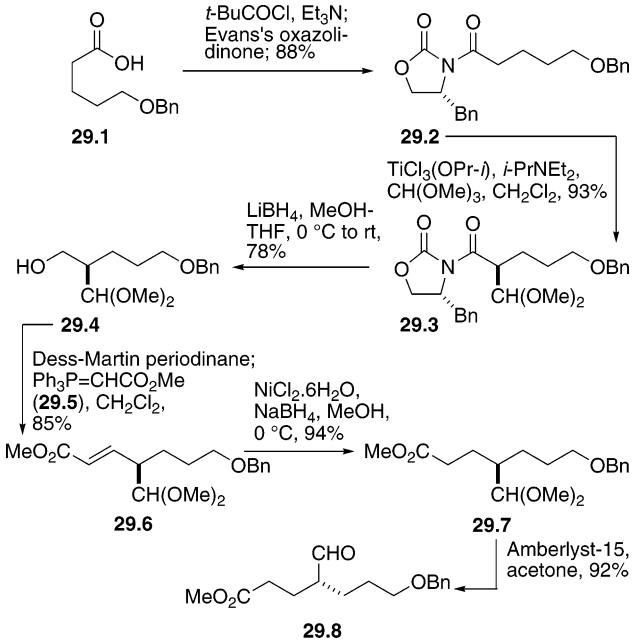
The other subunit (**29.8**) was prepared[50] by way of an asymmetric alkylation (Scheme 29). The oxazolidinone **29.2**, prepared in the standard way, was alkylated (**29.2** → **29.3**) with $HC(OMe)_3$ following a general literature procedure.[54] The stereochemistry was initially assigned by analogy with related alkylations but subsequently confirmed by X-ray analysis

Scheme 28



[a] Ar = C_6H_4Me-*p*.

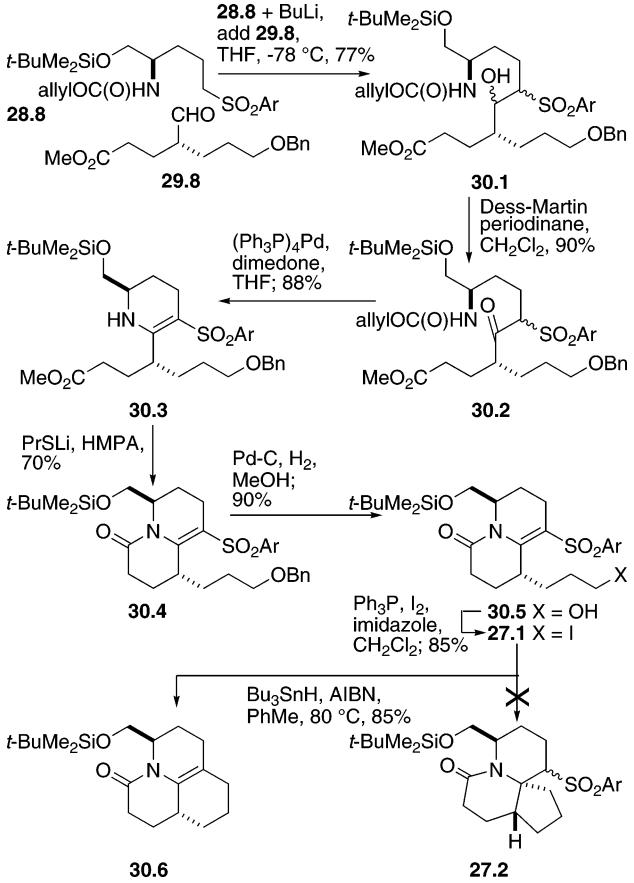
Scheme 29



of an advanced intermediate (**30.5**). Removal of the chiral auxiliary, Dess−Martin oxidation of the resulting alcohol, and Wittig olefination with $Ph_3P{=}CHCO_2Me$ completed the construction of the desired carbon skeleton (**29.3** → **29.6**). The double bond in **29.6** was saturated ($NaBH_4$, $NiCl_2{\cdot}6H_2O$), and the acetal was hydrolyzed under mildly acidic conditions that did not cause any epimerization (**29.6** → **29.7** → **29.8**).

At this point the two subunits were joined[50] (Scheme 30) by deprotonating the sulfone **28.8** with BuLi and allowing the resulting carbanion to react with aldehyde **29.8**. The required diastereoisomeric hydroxy sulfones were formed in 77% yield; they were easily oxidized to the corresponding ketone, and palladium-induced removal of the allyl carbamate resulted in direct formation of sulfone **30.3**. In accordance with the original plan, the lactam **30.4** was then generated by treating **30.3** with PrSLi in HMPA.[55] Hydrogenolysis now released alcohol **30.5**, whose structure

Scheme 30

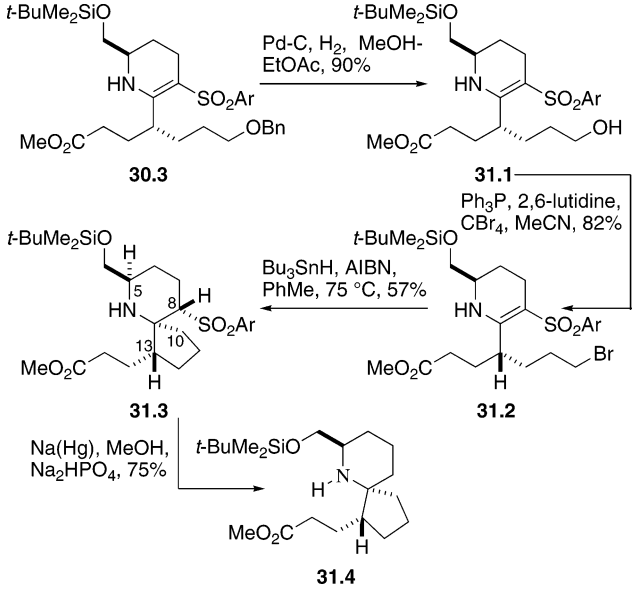


[a] Ar = C_6H_4Me-*p*.

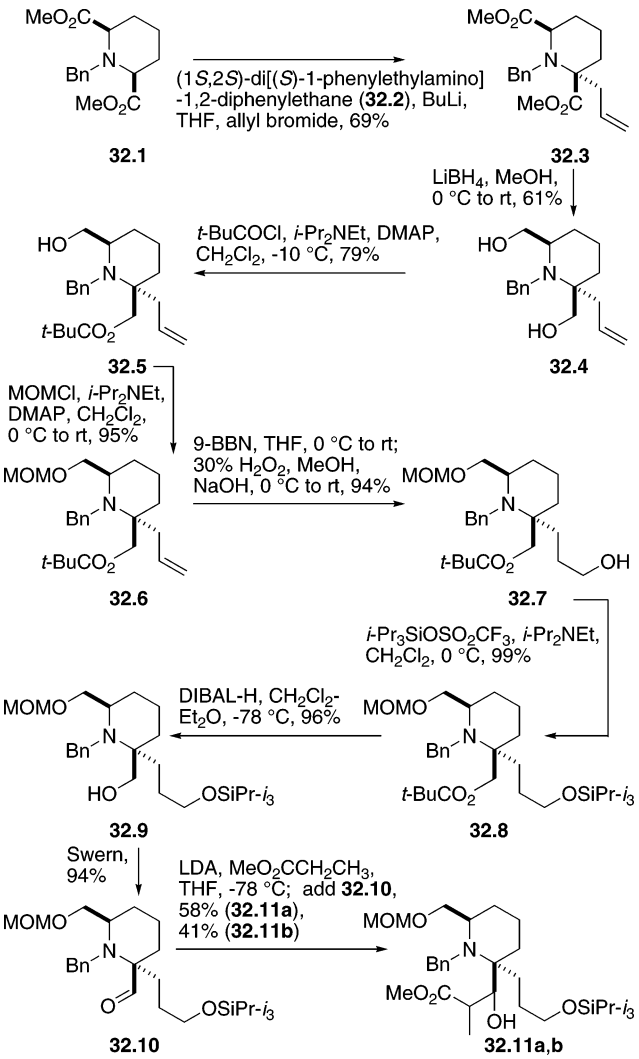
was confirmed by X-ray analysis. Formation of the corresponding iodide was uneventful, but attempts to perform the radical cyclization summarized in Scheme 27 did not work; the desired product (**27.2**) was not formed, and instead the tricycle **30.6**, arising by 6-endo closure, was isolated in high yield. Fortunately, the desired endo cyclization could be achieved[50] by moving the radical cyclization step to an earlier stage of the synthesis. To this end (see Scheme 31) the intermediate **30.3** was converted into bromide **31.2**. This bromide cyclized in the required fashion, although the yield was modest (57%), and a significant amount (30%) of the simple reduction product (Br replaced by H in **31.2**) was isolated. Finally, desulfonylation gave the target model spiro system **31.4**.

Another approach (Scheme 32) studied by the Clive group[51] was based on the readily available[56] piperidine bis-ester **32.1**. This compound was subjected to asymmetric allylation according to a literature procedure[57] using a chiral lithium amide base (**32.2**) for asymmetric deprotonation followed by quenching with allyl bromide. Although related alkylations have been accomplished with very high ee,[57] the present reaction gave a product with an ee of only 67%.[51,52] For exploratory purposes, this result was accepted, and **32.3** was reduced to the corresponding diol **32.4** with $LiBH_4$. The next step, acylation with *t*-BuCOCl, gave a most unexpected result, since the more hindered hydroxyl was selectively and efficiently (79%) acylated (**32.4** → **32.5**). Protection of the remaining hydroxyl as a MOM ether and hydroboration generated alcohol **32.7**, whose primary hydroxyl was then blocked by silylation (**32.5** → **32.6** → **32.7** → **32.8**). A number of compounds related to **32.8** were examined, but only **32.8** proved suitable

Scheme 31

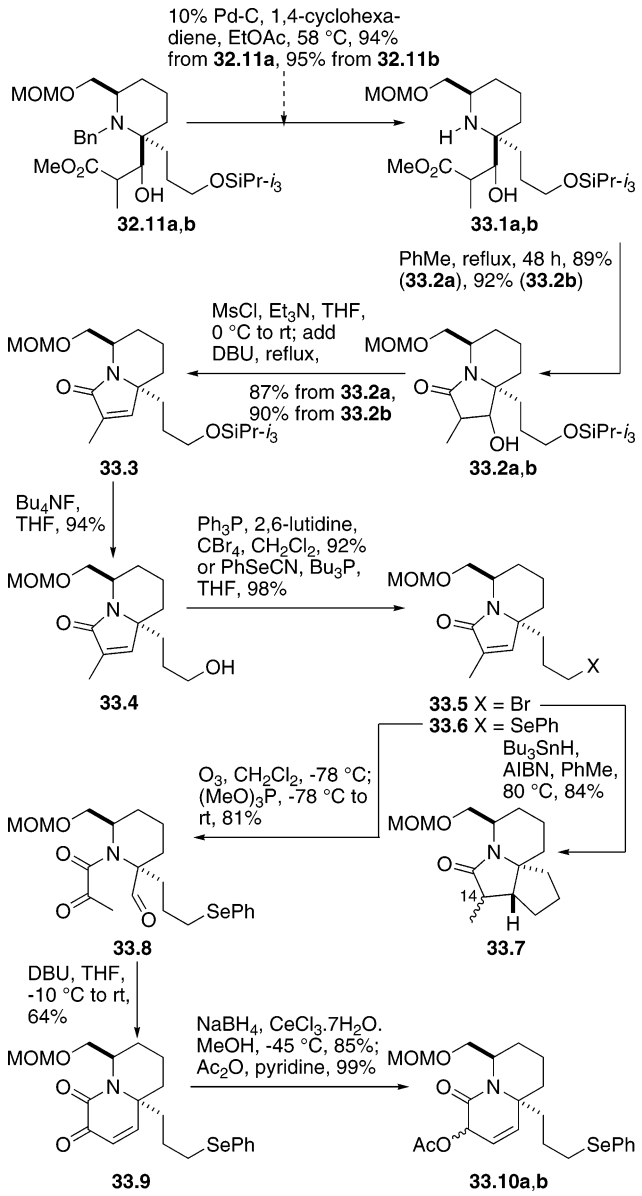


Scheme 32



[a] **32.11a** = less polar isomer; **32.11b** = more polar isomer.

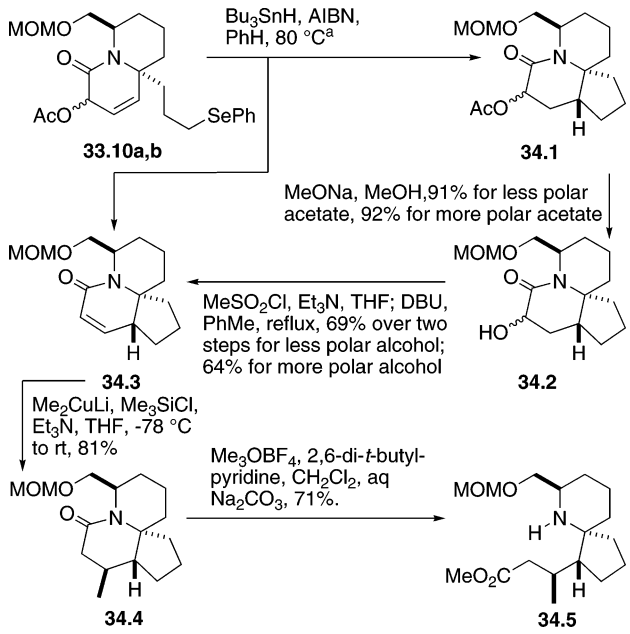
Scheme 33



for further elaboration. At this stage the pivaloyl group was removed (DIBAL), and Swern oxidation then afforded aldehyde **32.10**. This could be condensed with the anion made from methyl propionate, giving **32.11a**,**b** as a separable mixture of isomers.

The benzyl group was removed (ca 95% yield) by transfer hydrogenation (Scheme 33, **32.11a**,**b** → **33.1a**,**b**), at which point prolonged heating in PhMe caused the amino esters **33.1a**,**b** to cyclize to the lactams **33.2a**,**b**.[51] The resulting alcohols were dehydrated by mesylation and exposure to the action of DBU in refluxing THF, both series of compounds thereby converging to the single enone **33.3**. Desilylation released a primary hydroxyl, which was easily converted in the standard way into the corresponding bromide (**33.5**) and phenyl selenide (**33.6**). Radical cyclization using the bromide as starting material gave **33.7** as a 1:4 mixture epimeric at C(14) (halichlorine numbering), with the major isomer having the opposite relative stereochemistry to the natural product. Equilibration with *t*-BuOK−*t*-BuOH almost reversed the ratio, but the epimers were too difficult

Scheme 34

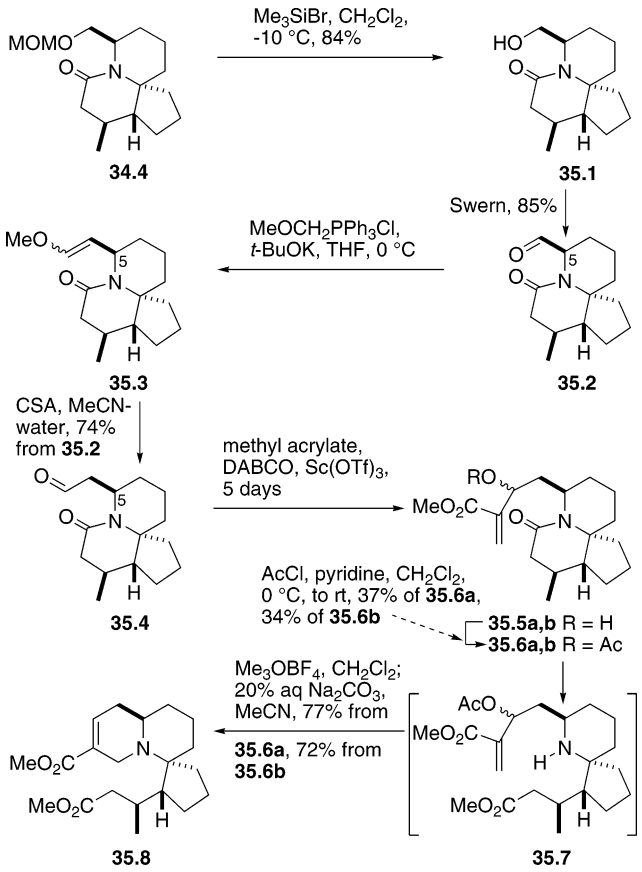


[a] The less polar isomer of **33.10a,b** gave **34.1** in 20% yield and **34.3** in 67% yield; the more polar isomer of **33.10a,b** gave **34.1** in 33% yield and **34.3** in 46% yield.

to separate for this route to be useful. Accordingly, the route was modified as follows to give better stereocontrol.

The selenide **33.6** was ozonized at a low temperature, and the cold ozonolysis mixture was treated with $(MeO)_3P$.[51] When the solution was allowed to warm to room temperature both the ozonide and intermediate selenoxides were reduced, so that it was possible to isolate the tricarbonyl compound **33.8**. This procedure is based on the fact that selenoxides do not normally fragment at a low temperature and that they are reduced by phosphites, the net result being that a PhSe group can survive ozonolysis conditions even though the selenide is temporarily oxidized. Intramolecular aldol condensation (**33.8** → **33.9**) mediated by DBU occurred smoothly with the selenide; not surprisingly, the same sequence with the corresponding bromide did not work. Unfortunately, radical cyclization of selenide **33.9** failed, and we assume that the enone system is reduced in preference to C−Se homolysis. To circumvent this behavior, the enone was reduced and the resulting alcohols were acetylated (**33.9** → **33.10a**,**b**). Now, radical cyclization did take place (Scheme 34) but was not straightforward. The less polar acetate **33.10a** gave **34.3** in 20% yield as well as **34.1** in 67% yield. The more polar acetate **33.10b** gave the corresponding products in 33% and 46% yields, respectively. In preparative experiments the acetates **34.1** were deacetylated (**34.1** → **34.2**) and mesylated. When the mesylates were treated with DBU they were smoothly converted into enone **34.3**, thereby serving to channel all the radical cyclization products to the same enone **34.3**. The required methyl group was now easily introduced (81%) by organocuprate addition in the presence of Me_3SiCl (**34.3** → **34.4**). The last step of the sequence—opening of the lactam—was initially very troublesome because semireduction with a variety of reagents was unsuccessful, the lactam being

Scheme 35



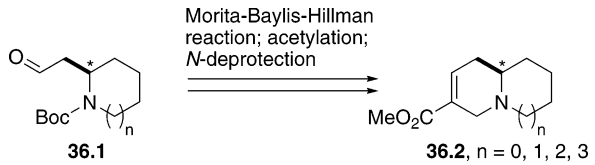
unusually prone to complete reduction to the tertiary amine, even with $LiNH_2BH_3$, which is normally an effective[47,49] reagent for semireduction of lactams. Eventually we found that reaction with the Meerwein reagent Me_3OBF_4 followed by basic aqueous workup gave **34.5** in satisfactory yield. The amino ester **34.5** showed no tendency to recyclize spontaneously to its parent lactam.

At this stage in the work the obvious next step was to convert **34.5** into a substance such as the dehydroquinolizidine **35.8**, and this was achieved[35] by the route summarized in Scheme 35.

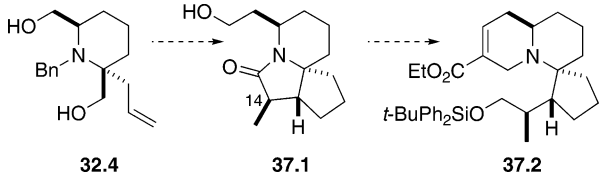
The MOM group of lactam **34.4** was removed by the action of Me_3SiBr, and Swern oxidation then gave aldehyde **35.2**. Wittig olefination converted the aldehyde into a mixture of enol ethers (**35.3**), which was hydrolyzed to the corresponding aldehyde **35.4**, these steps occurring without epimerization at C(5). Baylis−Hillman−Morita coupling of aldehyde **35.4** with methyl acrylate, in the presence of DABCO and $Sc(OTf)_3$, occurred slowly (5 days) but gave the expected alcohols **35.5a**,**b** in reasonable yield (71%). Acetylation of these alcohols and treatment with Me_3OBF_4, followed by exposure to aqueous Na_2CO_3, generated the amines **35.7**. These underwent spontaneous ring closure, affording the desired tricyclic dehydroquinolizidine **35.8** directly. This substance represents a significant portion of the halichlorine structure.

The method described above for making the dehydroquinolizidine, which resembles that used by Christie and Heathcock,[8] has been investigated in some detail.[35,58] The approach is general (see Scheme 36); it provides access to a number of related heterocycles (see **36.2**) and has been shown[35] to proceed with preservation of stereochemistry α to the nitrogen (see asterisked atoms in **36.1** and **36.2**).

Scheme 36



Scheme 37

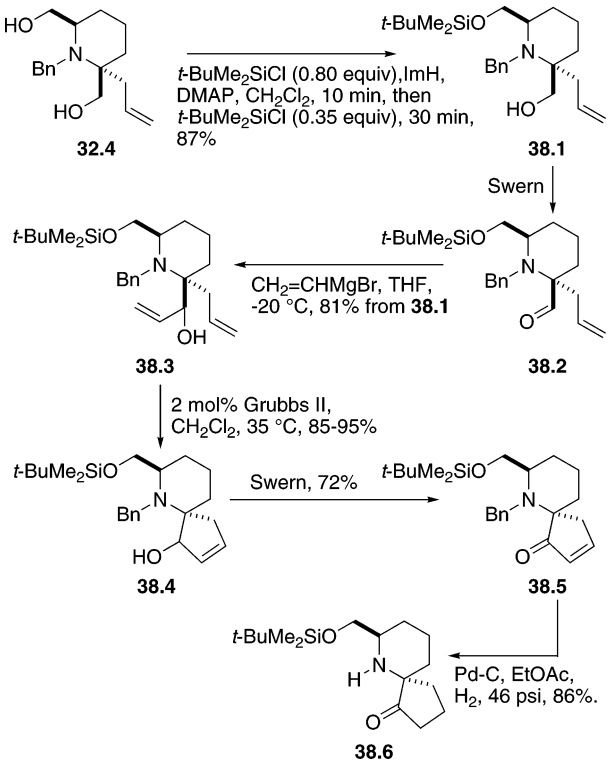


In a diversion (Scheme 37) from the main route (i.e., that summarized in Scheme 35), the tricycle **37.1** was also prepared.[52] This compound (in racemic form) had previously[46] been converted into the advanced intermediate (±)-**37.2**, whose relative stereochemistry is identical to that of halichlorine. The optically active *tert*-butyl ester corresponding to **37.2** is an intermediate in the Danishefsky synthesis of halichlorine (see **4.3**, Scheme 4), and (±)-**37.1** has also been elaborated[46] into the racemic version of an intermediate (see **7.5**, Scheme 7) in Danishefsky's route to pinnaic acid. The sequence of Scheme 37 was undertaken primarily because the previously reported[59] ketone **37.2** happened to be within very easy reach of intermediates already available in the group.

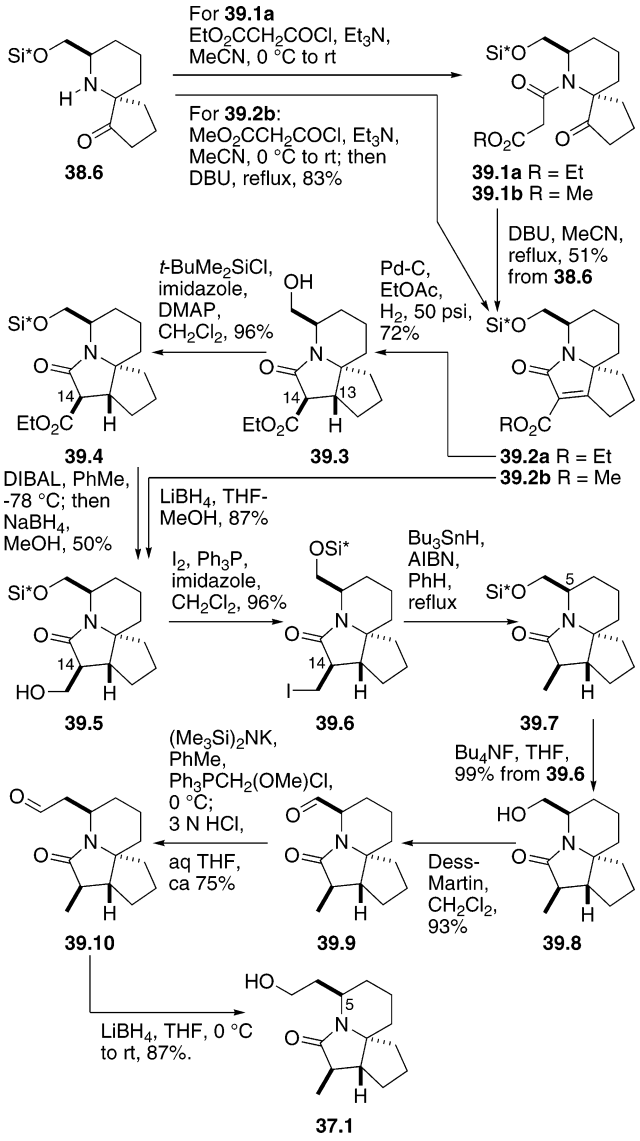
Diol **32.4** was silylated, and under the controlled conditions used (initial addition of a substoichiometric amount of *t*-$BuMe_2SiCl$ followed, after a short time, by addition of the remainder of the *t*-$BuMe_2SiCl$) a good yield of **38.1** was obtained (Scheme 38).[52] In contrast to the situation that prevailed with pivaloylation (cf. Scheme 32, **32.4** → **32.5**), the seemingly less hindered hydroxyl was protected. Swern oxidation gave the unstable aldehyde **38.2**, and the crude material reacted with vinylmagnesium bromide to afford a single alcohol **38.3** in quite good overall yield (81%). The stereochemistry of this alcohol was not established (but compare the related work of Simpkins shown in Scheme 58). Ring-closing metathesis with the Grubbs II catalyst in refluxing CH_2Cl_2 gave the cyclopentenol **38.4**, and oxidation and hydrogenolysis took the sequence as far as spiro ketone **38.6**.

The nitrogen of **38.6** is hindered and not easy to acylate, but it does react with EtO_2CH_2COCl (Scheme 39). The product (**39.1a**) can be cyclized (**39.1a** → **39.2a**) by heating with DBU, but a better overall yield (83% versus 51%) was obtained when the methyl ester MeO_2CH_2COCl (an arbitrary choice) was used and the DBU treatment performed without isolating the initial product (**39.1b**). Catalytic hydrogenation of **39.2a** was then carried out in the hope of adding both hydrogens from the β-face, so that the amide carbonyl carbon could eventually be converted into the methyl substituent at C(14) of halichlorine.

Scheme 38



Scheme 39



[a] Si* = $SiMe_2Bu$-*t*.

In the event the desired stereochemistry was indeed generated at C(13) (see **39.3**), but the product had the C(14) hydrogen on the α face. This undesired result thwarted the initial plans for which **39.2a** and **39.2b** had been made and prompted the diversion of the route to **37.1**. During hydrogenation the silyl group was removed and, therefore, had to be replaced (**39.3** → **39.4**). Reduction of the ester (DIBAL, followed by $NaBH_4$) gave alcohol **39.5** in only 50% yield, but the same compound was accessible directly from **39.2b** in 87% yield by the action of $LiBH_4$. Replacement of the hydroxyl by iodine and stannane reduction formed the α-methyl lactam **39.7**, at which point only homologation of the C(5) side chain remained in order to reach **37.1**. This was accomplished by deprotection (Bu_4NF) and Dess−Martin oxidation (**39.7** → **39.8** → **39.9**). Homologation to **39.10** was then done by Wittig reaction with $Ph_3P{=}CH(OMe)$ followed by mild acid hydrolysis. In the Wittig process strict temperature control at 0 °C was necessary in order to avoid epimerization at C(5). Finally, $LiBH_4$ reduction of aldehyde **39.10** completed the synthesis of **37.1**.

10. Studies in Feldman's Laboratory[60]

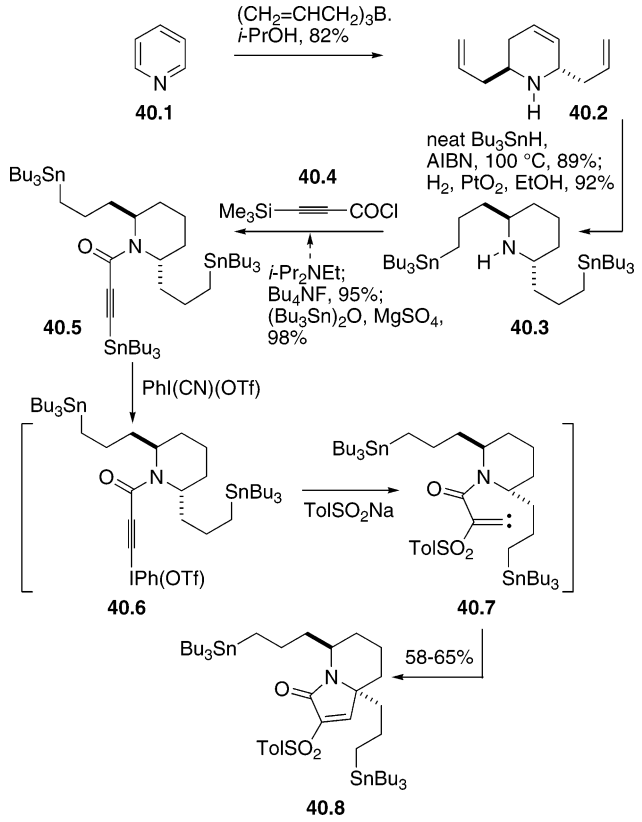
The Feldman approach is based on the ready generation of an alkylidene carbene and its selective insertion into a C−H bond of a tertiary carbon (Scheme 40, **40.6** → **40.7** → **40.8**).

The tetrahydropyridine **40.2**, readily accessible in a single step from pyridine itself, was subjected to radical hydrostannylation and then hydrogenation (**40.2** → **40.3**). The first of these steps was accomplished using a neat mixture of the stannane and the allylated tetrahydropyridine so as to avoid the intervention of radical cyclization pathways. The free amino group of **40.3** was next acylated with the acetylenic acid chloride **40.4**, and the silicon group was then exchanged for a tributyltin unit by successive reaction with Bu_4NF and $(Bu_3Sn)_2O$.

Treatment of the acetylenic stannane with Stang's reagent [PhI(CN)(OTf)] at a low temperature gave what was assumed to be the iodonium salt **40.6**. This reacted with *p*-$MeC_6H_4SO_2Na$ in refluxing DME to afford the product of carbene insertion (**40.8**) in yields that varied from 58% to 65%. The preparation of the sulfone **40.8** was easily conducted on a multigram scale.

At this point it was necessary to distinguish between the two stannyl groups; fortunately, this was easily achieved (Scheme 41). In the presence of a Lewis acid−$MgBr_2$ was best−the β position of the enone was sufficiently activated to be captured by the proximal C−Sn bond,[61] leading to the tricycle **41.1** (69%) of unestablished stereochemistry at the sulfur-substituted carbon. Reductive methylation, under carefully controlled conditions (lithium naphthalenide, MeI), served to install a methyl group with the desired stereochemistry (**41.1** → **41.2**).

Scheme 40



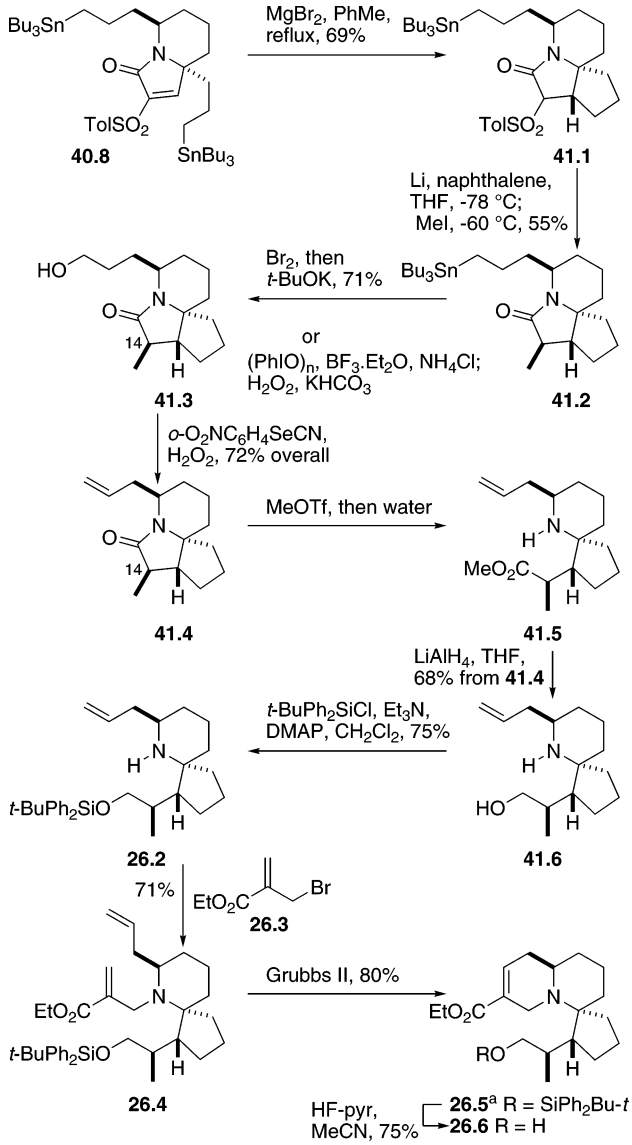
The next task was to convert the upper sidearm into an alkene. This was initially troublesome because it required discrimination between the three-carbon side chain and the butyl groups also attached to tin. Exhaustive bromination of **41.2**, followed by *tert*-butoxide-induced elimination of HBr, did generate the desired olefinic pendant, but at the same time the integrity of the C(14) stereochemistry was compromised, and a 2:1 mixture of C(14) isomers was formed. A much better approach involved conversion of **41.2** into its monochlorodibutyl derivative followed by a Tamao−Fleming oxidation—but applied to a tin rather than a silicon species (**41.2** → **41.3**). The resulting alcohol (**41.3**) was easily transformed into the corresponding alkene (**41.3** → **41.4**) by Grieco's standard selenoxide elimination method.

As others have found,[46,51] opening of the lactam ring was not easy but could be achieved by the method described by Kibayashi in his own work[46] on halichlorine and pinnaic acid synthesis. The lactam **41.4** was converted into an *O*-methyl iminium salt by treatment with $MeOSO_2CF_3$. Aqueous hydrolysis afforded the ester **41.5**, and this was reduced and protected (**41.5** → **41.6** → **26.2**). At this point the sequence overlaps with Kibayashi's route, and as in that work, the hindered amino group was alkylated with the reactive bromide **26.3**, and the stage was now set for intramolecular olefin metathesis, which was achieved with the Grubbs II catalyst (**26.4** → **26.5**). Finally, desilylation gave **26.6**, which had been reported[46] earlier by Kibayashi et al.

11. Studies in White's Laboratory[62]

The White group used the unusual approach of transannular cycloaddition to assemble a spirocyclic

Scheme 41

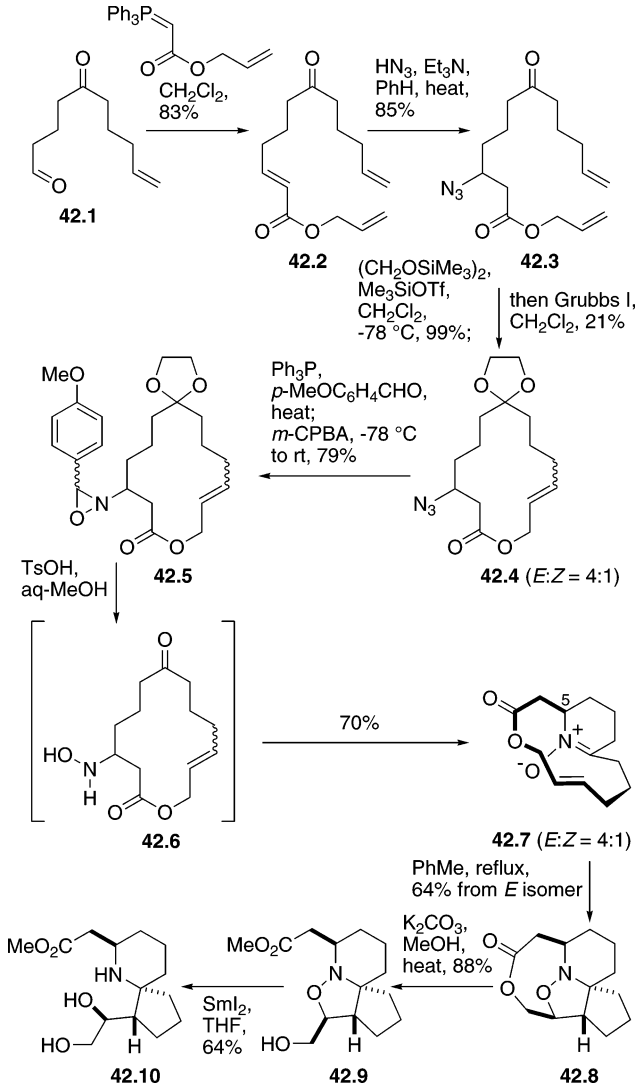


[a] This is the racemic version of **37.2**.

core unit of halichlorine and pinnaic acid. The key feature is addition of a nitrone to a double bond, and the work represents the first report of a transannular version of this process in which *both* the dipole and the olefin are within a ring. A consequence of having the termini of the nitrone and olefin tethered to one another is that a high degree of stereocontrol is observed.

The easily prepared keto aldehyde **42.1** was converted by Wittig reaction into the α,ω-unsaturated ester **42.2** (Scheme 42). Conjugate addition of azide, effected by treatment with HN_3 in the presence of Et_3N, gave the β-azido ester **42.3**. Ketalization of the ketone and ring-closing metathesis then afforded the 14-membered lactone **42.4**, although the yield in the ring closure was poor (21%) even with the Grubbs II catalyst. Lactone **42.4** was obtained as an inseparable 4:1 mixture of *E* and *Z* isomers. The azide was treated with Ph_3P, and condensation of the resulting iminophosphorane with anisaldehyde furnished an imine, which could be oxidized with *m*-CPBA to the oxaziridines **42.5**. These oxaziridines (a 3:2 mixture) were separated chromatographically, although this

Scheme 42



later turned out to be unnecessary. Treatment with TsOH in aqueous MeOH served to hydrolyze the ketal and generate the transient hydoxylamines **42.6**, which underwent spontaneous cyclization to nitrone **42.7**, as a 1:4 mixture of *Z* and *E* isomers. The minor isomer was removed by chromatography, and when the major isomer was heated in PhMe, the crystalline tetracycle **42.8** was isolated in 64% yield; its structure was confirmed by X-ray analysis. The macrocycle **42.7** is too small to allow the nitrone oxygen to pass through the ring, and so cyclization occurs only from one face of the molecule, determined by the C(5) stereochemistry of the ester pendant. Methanolysis (**42.8** → **42.9**) and cleavage of the isoxazolidine with SmI_2 gave the spirocyclic amine **42.10**.

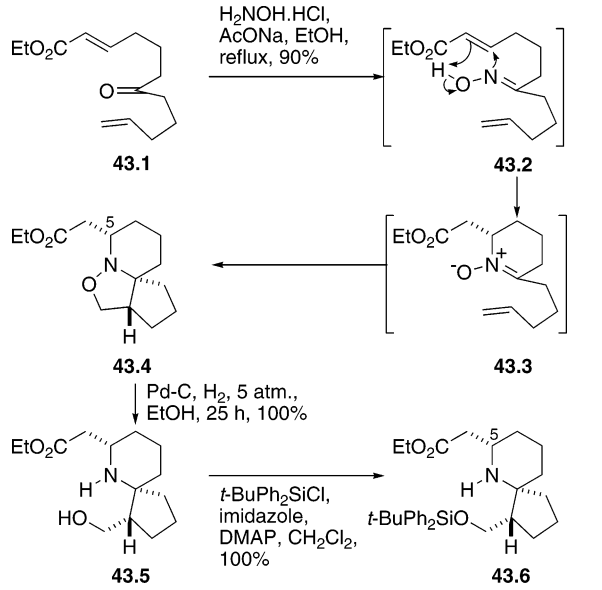
12. Studies in Shishido's and Itoh's Laboratories[63−65]

12.1. Studies in Shishido's Laboratory[63,64]

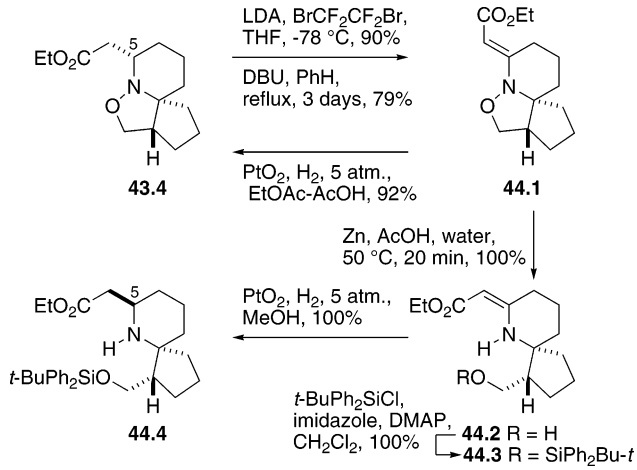
Another route based on intramolecular [3+2] cycloaddition was reported by the Shishido laboratory.[63]

The known keto ester **43.1**[66] (Scheme 43) was heated with $H_2NOH{\cdot}HCl$ in the presence of AcONa to afford (90%) the known spirocycle **43.4** via the

Scheme 43



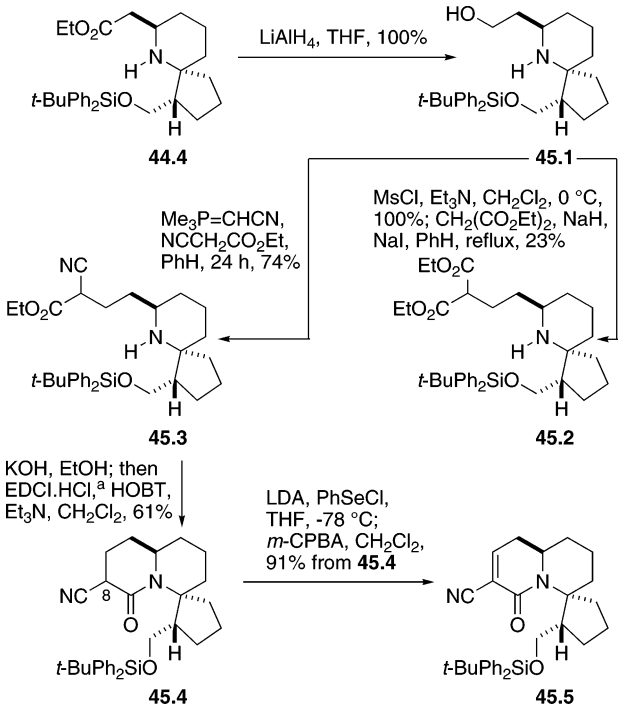
Scheme 44



mechanism shown (Scheme 43). The stereochemistry of **43.4** was confirmed by X-ray analysis of the hydrochloride of amine **43.6**, readily obtained by hydrogenolysis (**43.4** → **43.5**) and silylation. Attempts to invert the stereochemistry at C(5) in **43.6** were unsuccessful, and for example, the compound was recovered unchanged after exposure to the action of Et_3N at room temperature. Another approach—stereoselective hydrogenation of a double bond—was therefore examined to deal with the problem of the C(5) stereochemistry (Scheme 44).

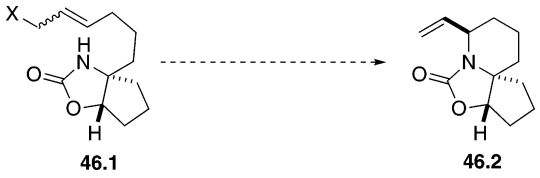
Bromination of the enolate derived from **43.4**, followed by dehydrobromination, gave the *E*-olefin **44.1**. Unfortunately, hydrogenation regenerated the undesired stereochemistry (**44.1** → **43.4**). However, a slight alteration to the plan overcame the problem. Cleavage of the N−O bond by reduction with Zn in AcOH released amino alcohol **44.2**, and this was found to give largely (2.6:1) the desired stereochemistry upon hydrogenation. Protection of the hydroxyl of **44.2** by silylation improved the stereochemical outcome significantly, and hydrogenation of **44.3** afforded the desired product **44.4** in quantitative yield. At this point the next task was to homologate

Scheme 45



[a] EDCl·HCl = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride.

Scheme 46

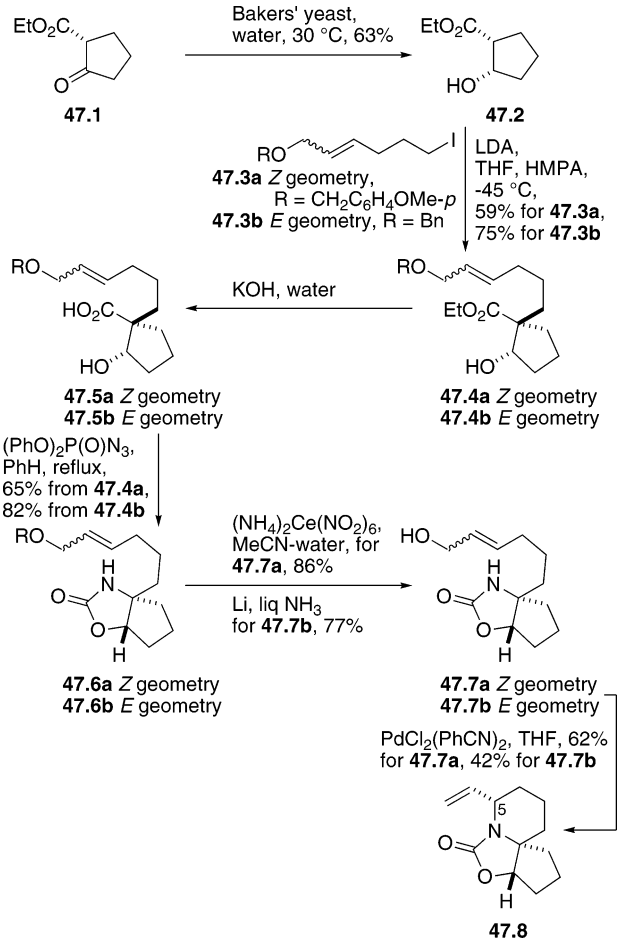


the C(5) appendage so as to be able to form the quinolizidine unit.

Ester **44.4** was reduced to the corresponding alcohol (**45.1**, Scheme 45), and several attempts were then made to extend the C(5) chain. Surprisingly, mesylation and treatment with $CH_2(CO_2Et)_2$ in the presence of NaH gave a very poor yield (23%) of the desired product (**45.2**). Eventually it was found that effective homologation (74%) could be achieved by reaction with $Me_3P{=}CHCN$ in the presence of $NCCH_2CO_2Et$,[67] a reagent combination that afforded **45.3**. Direct cyclization of the amino group onto the ester was unsuccessful; accordingly, the ester was hydrolyzed and the resulting carboxylic acid treated with EDCI·HCl [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride] and 1-hydroxybenzotriazole (HOBT) in the presence of Et_3N so as to effect cyclization (**45.3** → **45.4**). Finally, a double bond was introduced by the standard method of selenation and selenoxide fragmentation (**45.4** → **45.5**).

In a subsequent model study[64] Shishido and his group examined the possibility of making the tricycle **46.2** in optically pure form by a palladium-mediated cyclization of the type **46.1** → **46.2** (Scheme 46). To this end keto ester **47.1** was reduced (Scheme 47)[64] with Baker's yeast to the alcohol **47.2** (99% ee), and this was alkylated with the iodides **47.3a** and **47.3b**, reaction occurring exclusively from the face opposite the hydroxyl group. Ester hydrolysis and treatment

Scheme 47



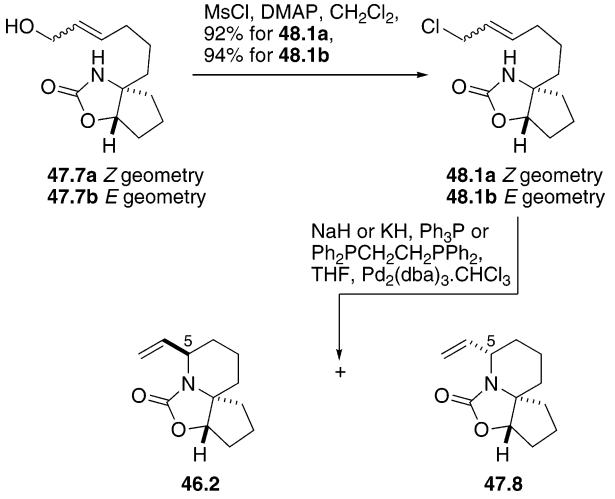
with $(PhO)_2P(O)PN_3$ in refluxing benzene then led directly to the cyclic carbamates **47.6a** and **47.6b**, respectively, at which point the protecting groups on the allylic oxygen were removed—in one case (**47.6a**) by oxidation and in the other by dissolving metal reduction. Treatment of the resulting alcohols with $PdCl_2(PhCN)_2$ in THF gave a cyclized product (**47.8**) having the undesired stereochemistry at C(5), a result that was established by X-ray analysis of a derivative. The corresponding experiment with a Pd(0) catalyst was slightly different but still unsatisfactory. The allylic alcohols **47.7a** and **47.7b** were individually converted into the corresponding chlorides (Scheme 48). In the presence of $Pd_2(dba)_3{\cdot}CHCl_3$, a base (NaH or KH), and a phosphine (Ph_3P or $Ph_2CH_2CH_2PPh_3$) some of the desired **46.2** was indeed formed from **48.1a** or **48.1b**, but the undesired stereochemistry was also generated, the ratio of **46.2** to **47.8** varying from 1:2 to 1:1 depending on the conditions.

Although, in principle, **47.8** might be amenable to epimerization at C(5) after further elaboration of the structure (cf. Scheme 54, **54.12** → **54.13**), investigations to examine this possibility have not been reported.

12.2. Biological Studies in the Itoh–Shishido Laboratories[65]

Although not specifically aimed at a halichlorine synthesis, a number of chemical transformations

Scheme 48



arising from synthetic work have been described briefly in flowchart form (Scheme 49) by Itoh and Shishido et al.,[65] and some of these intermediates have been evaluated for biological activity.

Earlier synthetic studies provided the alcohol **45.1** (Scheme 49). This was converted into the cyclic carbamate **49.1**, which was desilylated (**49.1** → **49.2**) with HF−pyridine. When the desilylation was done with Bu_4NF an isomeric carbamate (**49.3**) was formed. The original carbamate (**49.1**) afforded amide **49.4** on reaction with MeLi, and cyclization via an intermediate iodide generated the tricyclic lactam **49.5**, which was desilylated with Bu_4NF (**49.5** → **49.6**). The silylated lactam **49.5** was converted into the β-keto ester **49.7** and thereafter into the unsaturated ester **49.9**. Compound **49.7** was also desilylated (Bu_4NF, **49.7** → **49.8**). The ester group and the lactam carbonyl of **49.7** were then reduced (**49.7** → **49.10** → **49.11**). Finally, **45.5** was desilylated (**45.5** → **49.12**).

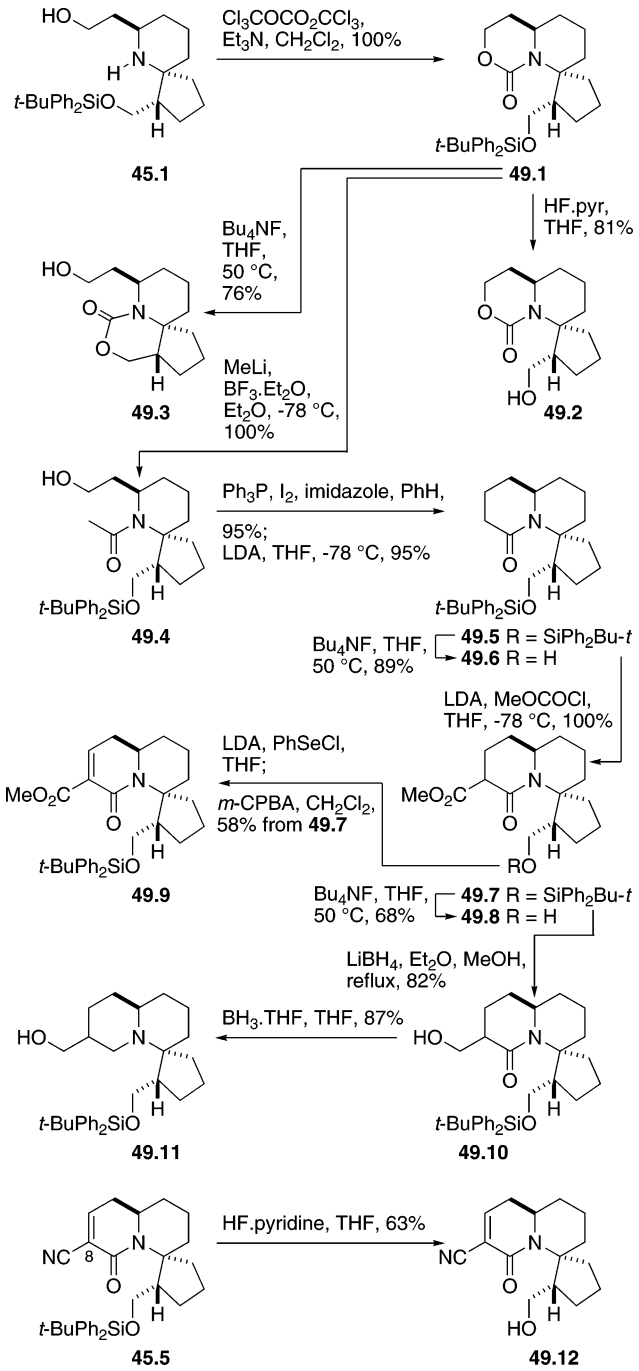
Compounds **43.4**, **44.2**, **44.3**, **44.4**, **45.1**, **49.1**, **49.2**, **49.3**, **49.4**, **49.5**, **49.6**, **49.7**, **49.8**, **49.9**, **49.10**, **49.11**, and **49.12** were subjected to a number of biological tests. Two (**45.1** and **49.9**) were found to have IC_{50} values (a decrease in cell viability by 50%) in the micromolar range (8.9 and 5.0 μM, respectively) toward an acute monocytic leukemia cell line. Some evidence was obtained to suggest that some of the compounds tested cause apoptosis.

13. Studies in Zhao's Laboratory[68,69]

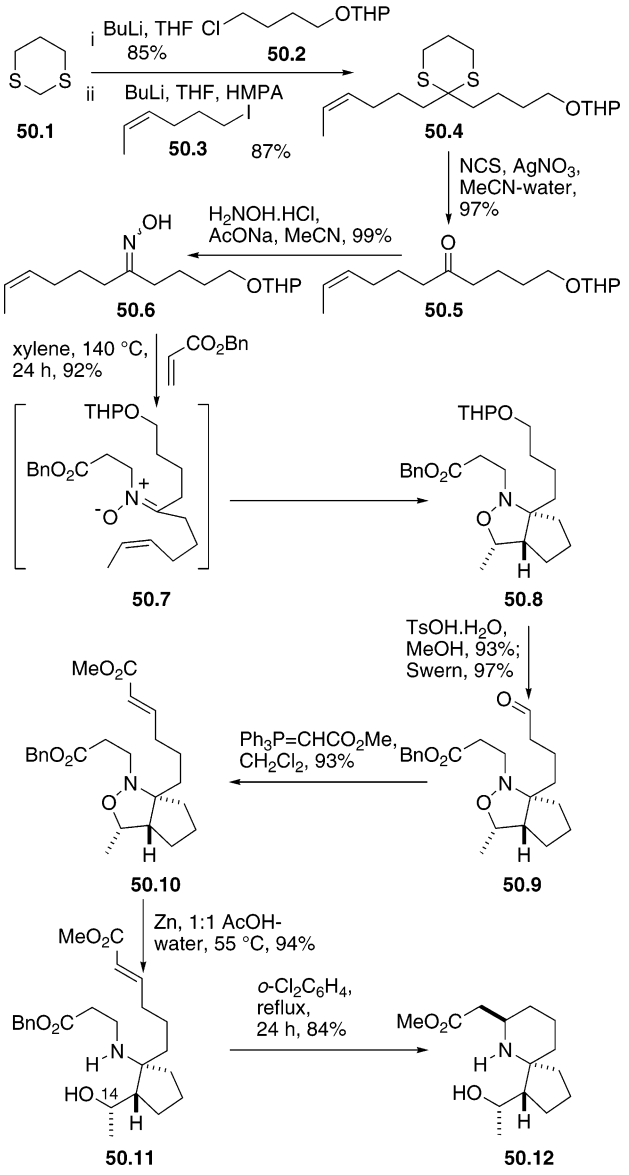
Zhao and Lee also used nitrone cycloaddition to construct a spirocyclic model compound, but unlike the White approach, only one terminus of the nitrone was tethered to the acceptor alkene.[68,69]

Dithiane **50.1** was readily converted into the substituted derivative **50.4** by double alkylation with **50.2** and then with **50.3** (Scheme 50).[68] Release of the ketonic carbonyl (**50.4** → **50.5**) and reaction with hydroxylamine gave the oxime **50.6** as an ca. 1:1 mixture of geometric isomers. When this mixture was heated at 140 °C with benzyl acrylate, the cycloaddition product **50.8** was isolated as a single isomer in excellent yield (92%). The nitrone **50.7** is, of course, an intermediate is generated by Michael reaction with the acrylate, such nitrone formation and cycloaddition being well precedented.[70] Removal of the THP group, Swern oxidation of the resulting alcohol, and Wittig homologation took the route as far as **50.10**. The N−O bond was next cleaved with Zn in aqueous AcOH to give amino alcohol **50.11**. On heating in *o*-dichlorobenzene for 24 h, this was transformed efficiently into the desired spiro system **50.12**. Formation of **50.12** follows the pathway summarized in Scheme 51, as indicated by isolation of intermediates **51.1** and **51.2**. Evidently the stereochemistry of the ester side chain in **50.12** is thermodynamically favored, so that reversible Michael addition (**51.3** → **50.12**) delivers the desired product. Computer modeling revealed a 3.8 kcal/mol energy difference between **51.2** and **50.12**, representing an equilibrium ratio of >100:1 in favor of **50.12**.

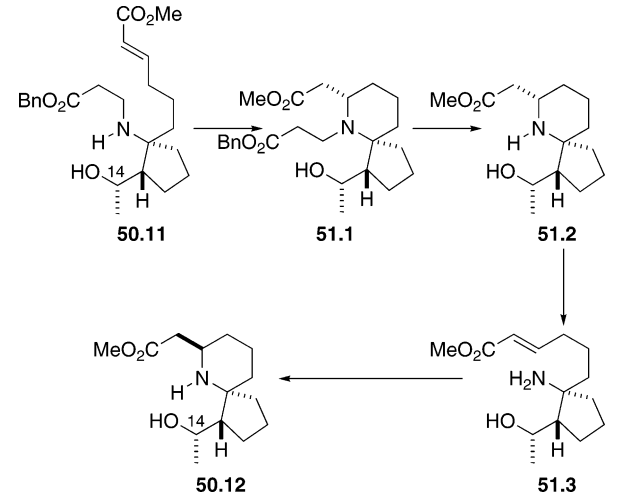
Scheme 49



Scheme 50

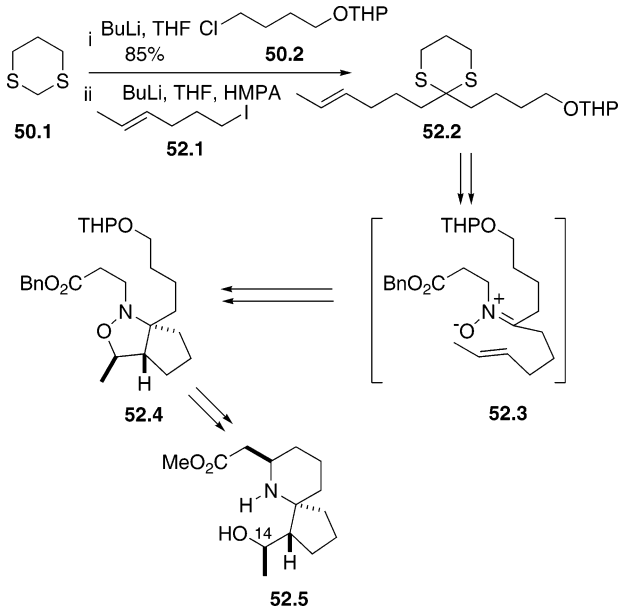


Scheme 51

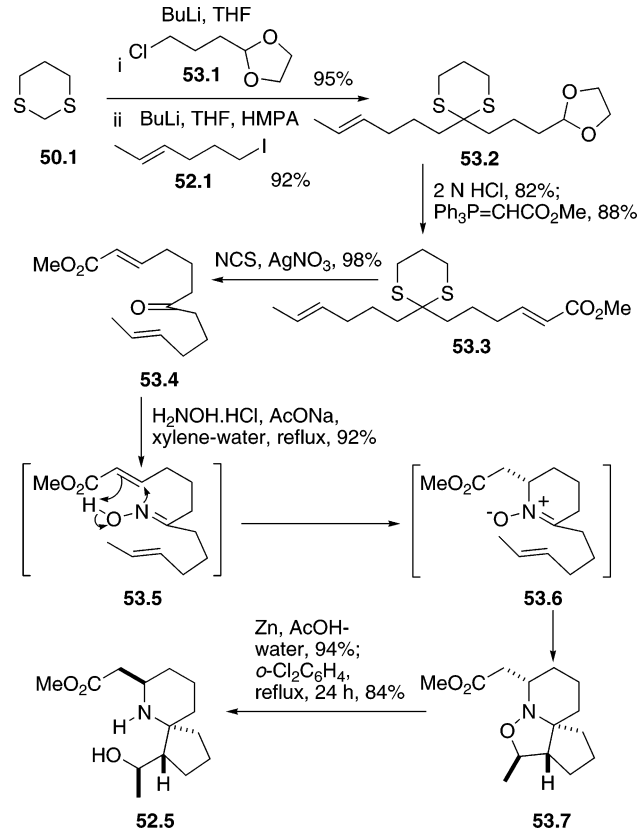


The sequence of Scheme 50 was then repeated[68] (see Scheme 52, full experimental details not yet available) with **52.1**, the *E*-isomer of alkyl iodide **50.3**, so as to obtain **52.5**, with the natural stereochemistry

Scheme 52



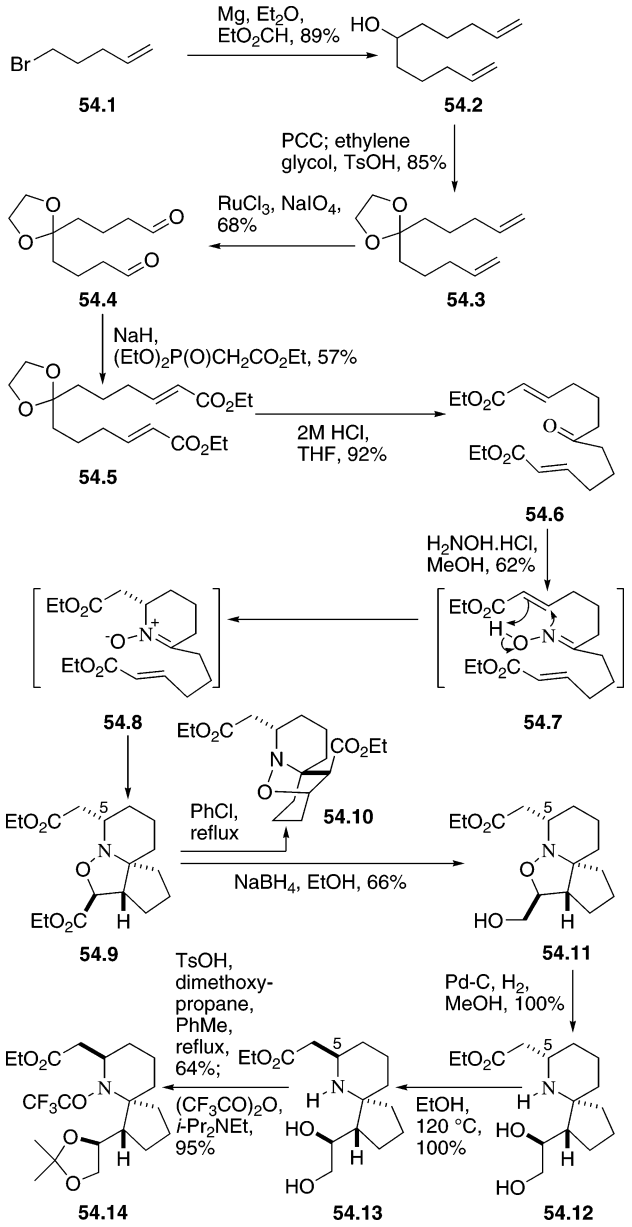
Scheme 53



at C(14), through the sequence **52.2** → **52.3** → **52.4** → **52.5**.

A slightly modified route was also developed (Scheme 53).[69] The substituted dithiane **53.2** was prepared in the conventional manner as shown, and the ketal was hydrolyzed and subjected to Wittig homologation (**53.2** → **53.3**). Removal of the dithioketal unit then gave ketone **53.4**, and this was heated with H_2NOH to afford directly the tetracycle **53.7** via the sequence **53.4** → **53.5** → **53.6** → **53.7**. Formation of the intermediate **53.6** by the process depicted in

Scheme 54



53.5 is well precedented.[66] Reduction and thermal isomerization generated **52.5**.

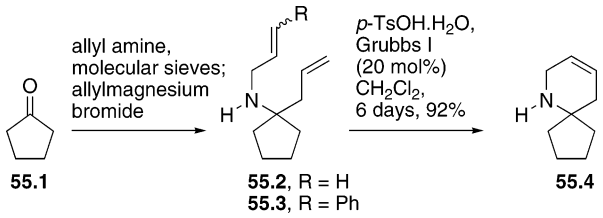
The sequence of Scheme 53 was then repeated with the *Z*-alkyl iodide **50.3** (shown in Scheme 50) so as to obtain **50.12** [with the unnatural stereochemistry at C(14)].

14. Studies in Stockman's Laboratory[71]

The symmetrical bis-ester **54.6** was assembled by standard methods from ethyl formate (Scheme 54). Reaction of EtOCHO with the Grignard reagent derived from 5-bromo-1-pentene (**54.1**) gave alcohol **54.2**, which was oxidized and protected as its ketal.

The terminal double bonds were cleaved (**54.3** → **54.4**), a process best achieved in this case with the $RuCl_3$–$NaIO_4$ system rather than by the Lemieux–Johnson procedure, and then Horner–Emmons–Wadsworth homologation of the resulting bis-aldehyde followed by deprotection produced the key symmetrical ketone **54.6**. On conversion into its

Scheme 55



oxime (**54.6** → **54.7**), spontaneous Michael addition, 1,4-prototropic shift, and regioselective [3+2] cycloaddition occurred to afford the tricycle **54.9** (62%). This cascade of steps is similar to that used in other laboratories.[62,68,69]

In an attempt to invert the C(5) stereochemistry to that required for the natural targets, compound **54.9** was heated in PhCl in the hope of effecting a retro-Michael addition followed by Michael addition. However, this approach was unsuccessful; the starting material was largely recovered, and a poor yield (39%) of **54.10** was obtained. Presumably, this product arises by [3+2] cycloreversion to **54.8**, followed by the opposite regiochemical [3+2] cycloaddition. The ester group in **54.9** was reduced with $NaBH_4$, and the N–O bond was cleaved by hydrogenolysis (**54.9** → **54.11** → **54.12**). When **54.12** was heated in a sealed tube in EtOH at 120 °C it underwent the desired epimerization at C(5) (**54.12** → **54.13**). Finally, the two hydroxyls were protected as a ketal and the nitrogen as a trifluoroacetate (**54.13** → **54.14**).

As presently developed, the above approach gives a racemic product.

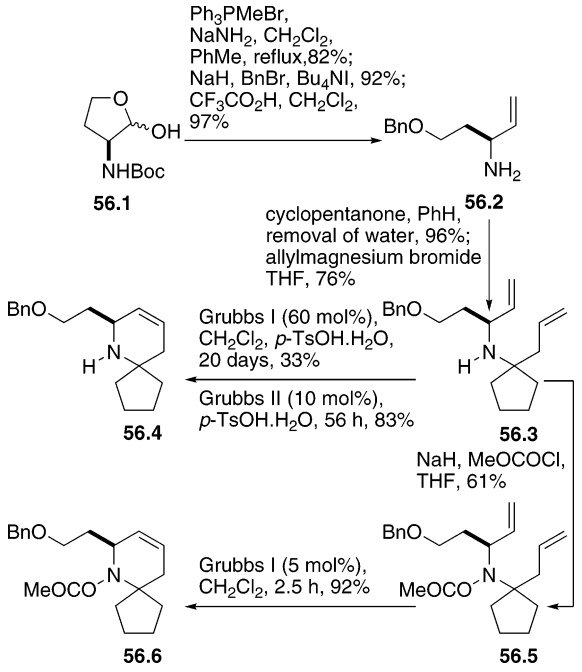
15. Studies in Wright's Laboratory[72]

A general method has been developed by the Wright group for constructing simple spiro compounds that resemble the core of halichlorine and pinnaic acid. The method is based on a ring-closing metathesis that forms the six-membered ring (Scheme 55).

In a typical example (Scheme 55), cyclopentanone was converted into an imine by warming with allylamine in the presence of molecular sieves, and then treatment with allylmagnesium bromide gave amine **55.2**, ready for ring-closing metathesis. Free amines are usually unsuitable substrates for this reaction[43,44] because the basic nitrogen attacks the catalyst. However, formation of an ammonium salt can avoid this problem,[43,44] and the ring-closing metathesis of **55.2** worked when done in the presence of *p*-TsOH. The reaction was slow, however, and significant amounts of catalyst (20–30 mol % in all) were required. Little improvement was achieved using the phenyl-substituted analogue **55.3**, even though such substitution has been of benefit in other cyclizations.[44] Examination of several related examples quickly showed that the sequence is general. The reaction rate could be raised and the catalyst loading decreased by protecting the nitrogen as a carbamate.

A closer model to what would be required for synthesis of halichlorine was then made along the lines summarized in Scheme 56.

Scheme 56



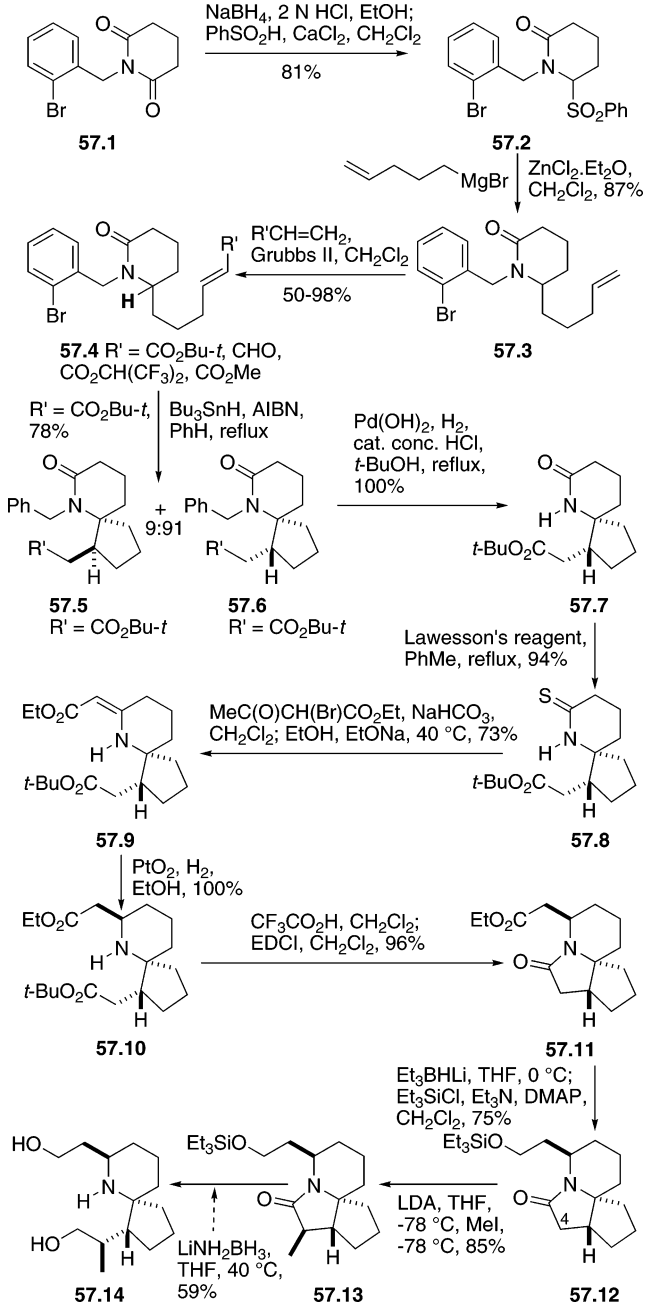
The lactols **56.1**, readily obtained by DIBAL-H reduction of the known corresponding lactone,[73] were converted by Wittig olefination, *O*-benzylation, and *N*-deprotection into amine **56.2**. Condensation with cyclopentanone and reaction with allylmagnesium bromide produced the ring-closing metathesis substrate **56.3**. The ring closure (in the presence of *p*-TsOH.H_2O) was very slow (20 days), even when 60 mol % of Grubbs I catalyst was used, and the yield was only 33%. Poisoning of the catalyst by the protonated nitrogen together with the additional steric factors introduced by the presence of the side chain were presumably responsible for this poor result. However, acylation of the nitrogen (**56.3** → **56.5**) now allowed the ring-closing metathesis (**56.5** → **56.6**) to work very well (92%).

Finally, the effect of using the Grubbs II catalyst was examined, and with this change, **56.3** was converted into **56.4** in high yield at a modest catalyst loading (10 mol %) and with a much shorter reaction time (15 h versus 20 days). Protonation of the nitrogen was still necessary however.

16. Studies in Ihara's Laboratory—Synthesis of the Azabicyclic Core of Halichlorine and Pinnaic Acid[47]

Radical translocation has been used in an unusual approach to the spirocyclic core of halichlorine and pinnaic acid.[47] The *N*-substituted glutarimide **57.1**, readily available (91%) by alkylation of glutarimide with 2-bromobenzyl bromide (Scheme 57), was reduced with $NaBH_4$ and treated with $PhSO_2H$ to yield the sulfone **57.2**. Reaction with 4-pentenylmagnesium bromide in the presence of $ZnCl_2$ gave the piperidinone **57.3**. This served as the starting material for a range of compounds (**57.4**) that were made by cross metathesis with olefins R′CH=CH_2 [R′ = CO_2Bu-*t*, CHO, $CO_2CH(CF_3)_2$, CO_2Me] using the Grubbs II catalyst. Each of the products **57.4** was

Scheme 57



treated with Bu_3SnH and AIBN in refluxing benzene so as to generate an aryl radical. In some cases a small amount of simple reduction product (H replacing Br in **57.4**) was isolated, but the main products[74] (**57.5** and **57.6**) arose by intramolecular transfer of hydrogen (see **57.4** bold H) and 5-exo trigonal cyclization of the resulting radical. Stereoselectivity (91:9) in favor of the desired **57.6** was greatest for R′ = CO_2Bu-*t,* and the yield was also acceptable (78%); consequently, this product was taken further.

Debenzylation of **57.6** by hydrogenolysis in the presence of acid released the lactam **57.7**, which was converted into the corresponding thiolactam **57.8**, and then into the vinylogous carbamate **57.9** by Eschenmoser sulfide contraction.[75] This last step involved alkylation of the thiolactam with 2-bromoacetoacetate followed by deacetylation with EtO-Na. Catalytic hydrogenation of **57.9** occurred stereo-

selectively, giving exclusively the ester **57.10**, the stereochemical outcome of the process being the same as observed previously[63] for a related compound (see Scheme 44, **44.3** → **44.4**).

Stereoselective introduction of the C(14) methyl group was unsuccessful with **57.10** and required formation of a rigid concave structure. To this end, standard conditions were applied to remove the *tert*-butyl group and cyclize the resulting amino acid (**57.10** → **57.11**). Next, the ethyl ester was reduced with Et_3BHLi under controlled conditions (0 °C), and silylation gave **57.12**. At this point alkylation with MeI was completely selective for the desired β-methyl derivative **57.13**, which was obtained in good yield (85%). Opening of the lactam ring was, apparently, difficult, but use of $LiNH_2BH_3$[48,49,76] afforded **57.14** in acceptable yield (59%), the silyl group also being removed in the process.

17. Studies in Keck's Laboratory[77]

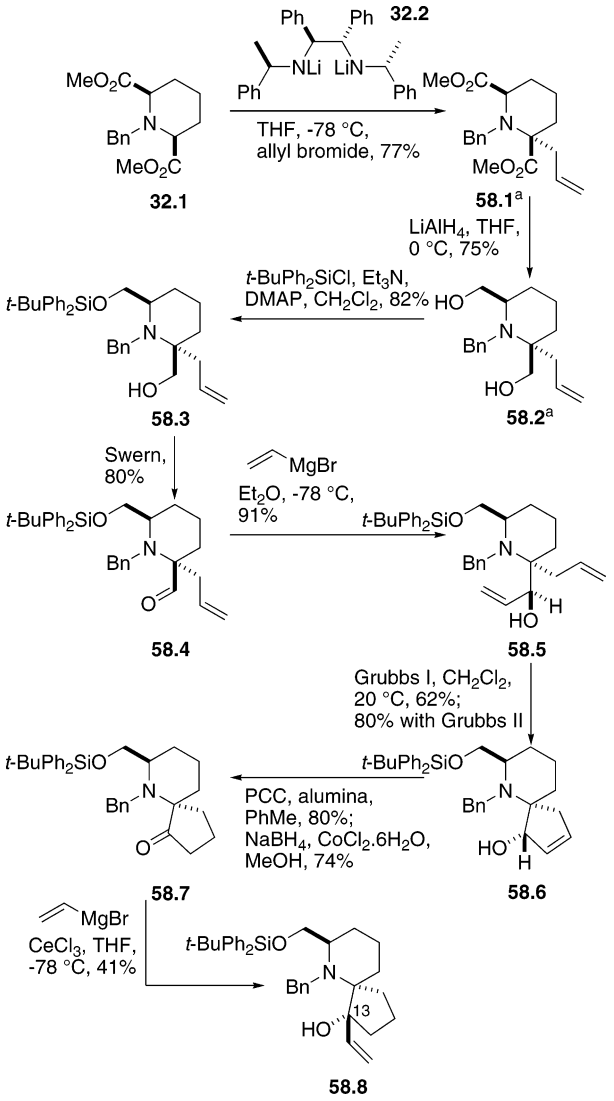
An approach that uses radical cyclization to form the five-membered ring of halichlorine has been reported[77] by Keck and Dalton at an ACS Meeting, but full details are not yet available.

18. Studies in Simpkins's Laboratory[78]

Allylation of the known and readily available[56] bis-ester **32.1**, using chiral base **32.2**, gave the optically enriched product **58.1** with an ee of 90−95% (Scheme 58). This type of asymmetric alkylation has been studied in some detail;[57] with BnBr the ee is ≥98%, and similar levels of stereocontrol were observed with MeI and cinnamyl chloride.[57] The authors of this review have also found that the ee is somewhat lower (ca 67%) with allyl bromide (see Scheme 32 and associated text). Reduction ($LiAlH_4$) of both ester groups, monosilylation of the less hindered hydroxyl, and Swern oxidation of the other hydroxyl provided the hindered aldehyde **58.4** (**58.1** → **58.2** → **58.3** → **58.4**), all the steps working in good yield. The aldehyde reacted stereoselectively with vinylmagnesium bromide to give the single alcohol **58.5.** This was properly set up for ring-closing metathesis, and treatment at room temperature with the Grubbs I catalyst resulted in the cyclopentenol **58.6** (62%). With the Grubbs II catalyst the yield was 80%. PCC oxidation and reduction of the conjugated double bond, using $NaBH_4-CoCl_2{\cdot}6H_2O$, afforded the saturated spiro ketone **58.7**, which reacted with vinylmagnesium bromide, again stereoselectively, to generate alcohol **58.8**. This stereochemical outcome does not at all preclude elaboration to halichlorine or pinnaic acid as a compound with the same stereochemistry at C(13) has actually been so elaborated (see Scheme 24 and associated text).[46]

Aldehyde **58.4** was processed in another way as well.[78] The ester **59.1** (Scheme 59) was prepared by Peterson olefination, and then DIBAL-H reduction gave allylic alcohol **59.2**. This was subjected to Johnson ortho ester rearrangement (**59.2** → **59.3** → **59.4**), which produced a 4:1 mixture of **59.4** and its C(13) epimer. Finally, ring-closing metathesis completed assembly of the azaspiro structure **59.5**. Again, the stereochemistry at C(13) is not the natural stereochemistry, but there exists the possibility of inverting that center by a dehydrogenation−hydrogenation or a double-bond migration−hydrogenation sequence; however, such transformations have not yet been reported.

Scheme 58

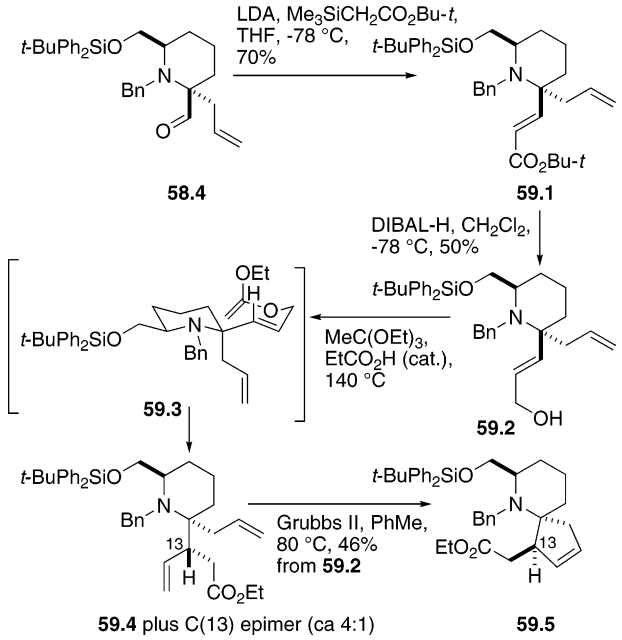


[a] These compounds have the same structures as the corresponding compounds in Scheme 38 but different ee's.

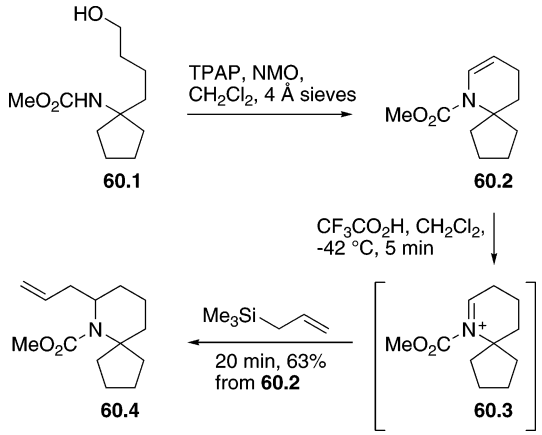
19. Studies in Forsyth's Laboratory[79]

Two models have been reported by Koviach and Forsyth.[79] The carbamate **60.1**[80] (Scheme 60) was converted into the spirocycle **60.2** by Pr_4NRuO_4 oxidation in the presence of molecular sieves, during which the intermediate aldehyde underwent spontaneous cyclization and dehydration. Treatment of the enamine **60.2** with CF_3CO_2H at a low temperature served to generate the iminium ion **60.3**; this was then captured by allyltrimethylsilane, affording **60.4** in 63% yield overall from **60.2**. This simple model does not provide information on the stereochemical outcome of the allylation, and a more complex model was studied next in order to examine that point.

Scheme 59



Scheme 60



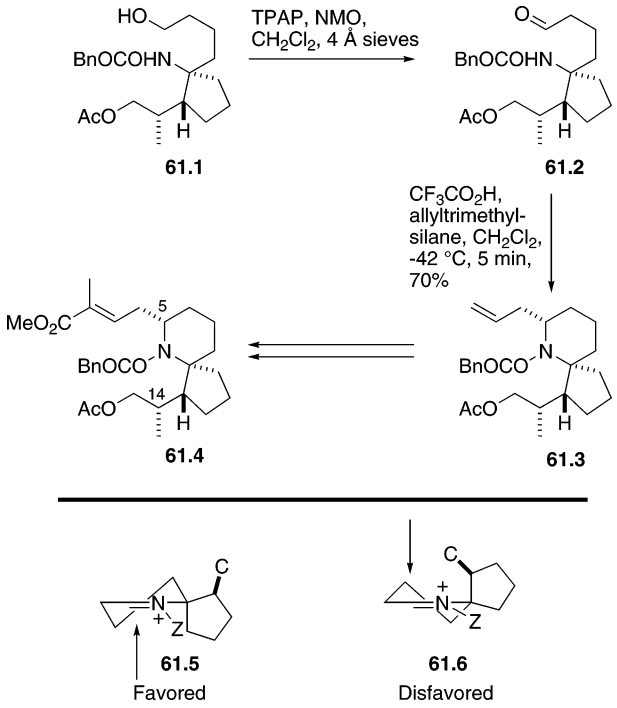
The racemic alcohol **61.1**[81] was oxidized as before (Scheme 61), but this time cyclization and dehydration were not spontaneous. Fortunately, however, treatment of the crude aldehyde **61.2** with CF_3CO_2H led to formation of the desired iminium ion, which reacted with allyltrimethylsilane to give **61.3** in 70% yield overall from **61.2**. Oxidative cleavage of the double bond and Wittig olefination (details not provided) took the route as far as **61.4.** NOE measurements established the stereochemistry, which is understandable on the basis of allylation from the direction shown in **61.5** as opposed to reaction according to approach **61.6**.

20. Studies in Dake's Laboratory[82]

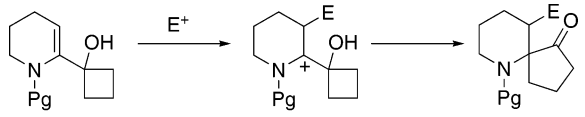
Dake and co-workers developed[82] a method for making azaspirocyclic systems that is based on the ring-expansion process summarized in Scheme 62.

In the simplest model study (Scheme 63) the *N*-tosyl lactam **63.1** was transformed, by way of the corresponding enol triflate **63.2**, into vinyl stannane **63.3**. Further conversion into a vinyl Grignard reagent and reaction with cyclobutanone gave the

Scheme 61

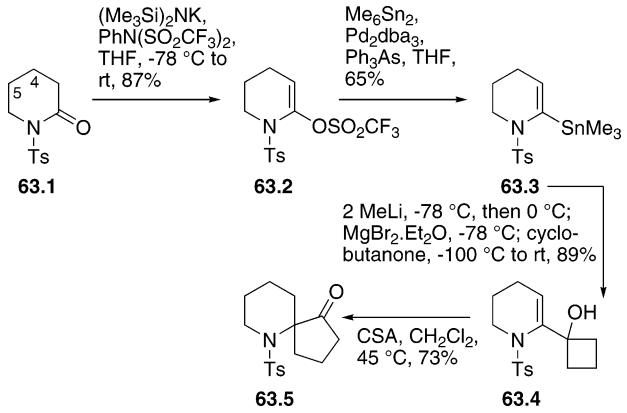


Scheme 62



[a] Pg = protecting group. [b] E^+ = electrophile.

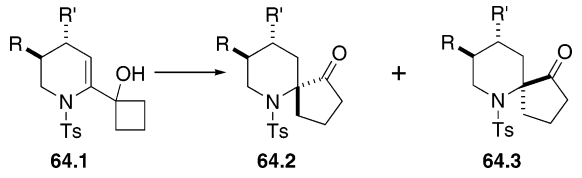
Scheme 63



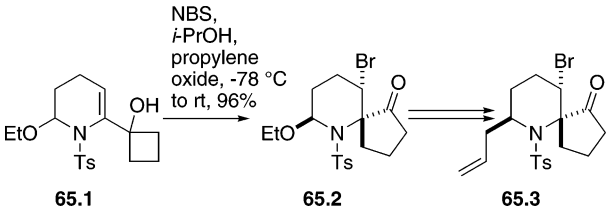
substrate for the ring expansion (**63.3** → **63.4**). When **63.4** was exposed to the prolonged action (13 h) of camphorsulfonic acid at 45 °C it rearranged to the spiro compound **63.5**. Shorter reaction times (2 h) were acceptable (67% yield) with 1.1 equiv of concentrated hydrochloric acid.

A brief study (see Scheme 64) was also made of the diastereoselectivity when the original lactam tosylate carried substituents at positions C(4) and C(5). Selectivities ranging from ca. 3:1 to 14:1 were found using protic acids, but it was then discovered that NBS sometimes gave much better results and the tosyl lactam **65.1** (Scheme 65), for example, yielded a single diastereoisomer (**65.1** → **65.2**). The substrate **65.1** was of importance because the rearrangement

Scheme 64



Scheme 65



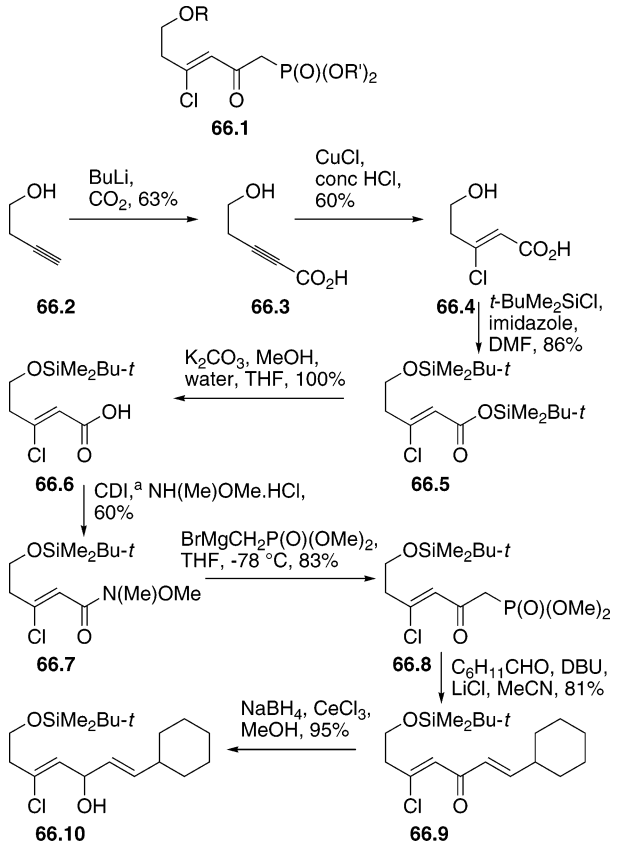
product was amenable to elaboration that installed an allyl side chain (**65.2** → **65.3**) that would be needed to reach the halichlorine structure.

21. Studies in Weinreb's Laboratory[23]

With a view to introducing the C(15)−C(21) subunit by Horner−Emmons−Wadsworth reaction, Keen and Weinreb considered the use of phosphonates of the general type **66.1**. Such reagents would be expected[83] to react with an aldehyde to generate the required *E* geometry for the C(15)−C(16) double bond, although it was appreciated that **66.1** might be prone to elimination of HCl and/or ROH and might also be subject to 1,4-addition−elimination.[84] In the event a representative of this compound class was easily prepared (Scheme 66) and found to be well behaved.

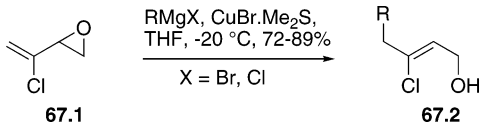
The commercially available acetylene **66.2** was readily carboxylated, and the resulting acetylenic acid, on treatment with concentrated hydrochloric acid in the presence of CuCl, gave the *Z* vinyl chloride **66.4**. The anti addition of HCl was a known but little-used process; it appears to be general. Global silylation and release of the carboxyl group (**66.4** → **66.5** → **66.6**) provided the required subunit for attachment of the phosphonate segment. This was achieved by converting the acid into its Weinreb amide followed by treatment with $BrMgCH_2P(O)(OMe)_2$ to afford **66.8**. Use of the magnesium salt is critical; when the experiment was tried with the lithium analogue, an inseparable mixture of **66.8** and the corresponding acetylene, resulting from loss of HCl, was obtained. Furthermore, the desired product was the minor component of the mixture (ca. 2:3). Fortunately, the magnesium salt, which was readily obtained from the lithium compound by metal exchange, behaved well and gave **66.8** in 83% yield. By way of demonstrating the intended use of **66.8**, the compound was condensed with cyclohexanecarbaldehyde in the presence of DBU and LiCl. The product (**66.9**) had exclusively the desired *Z*,*E*-geometry. The carbonyl group of **66.9** was easily reduced by the Luche method, and it was found that alcohol **66.10**, which is a model for the divinyl alcohol chain of halichlorine and the pinnaic acids, is an easily handled compound, amenable to chromatography.

Scheme 66



[a] CDI = 1,1′-carbonyldiimidazole.

Scheme 67



22. Studies in Taber's Laboratory[85]

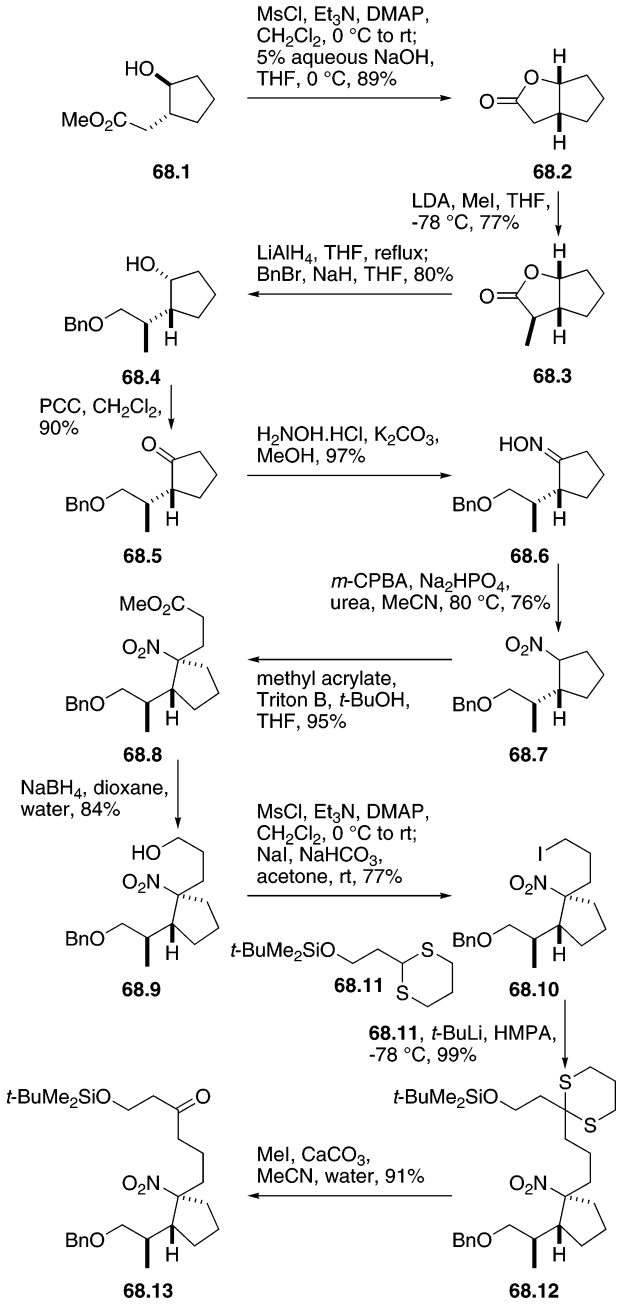
A general method for making (*Z*)-3-chloroallylic alcohols, a subunit of halichlorine and the pinnaic acids, is available using simple reagents. The chloro epoxide **67.1** was found to undergo efficient conjugate addition with organocuprates, generated in situ by addition of Grignard reagents to a THF solution of the epoxide in the presence of $CuBr{\cdot}Me_2S$ complex (Scheme 67). The *Z*:*E* ratios were usually higher than 10:1, and the reaction worked for both aliphatic and aromatic Grignard reagents.

23. Developments Published after Submission of the Manuscript

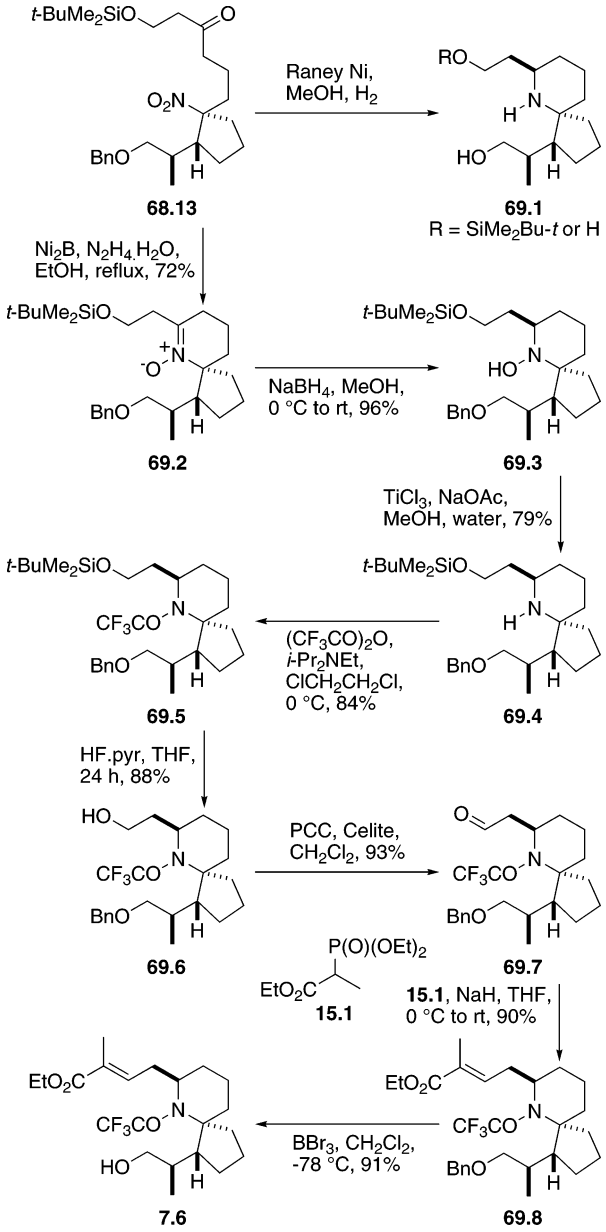
23.1. Studies in the Zhao and Ding Laboratories—Formal Synthesis of Pinnaic Acid by a Method That Merges with the Danishefsky Route, and Synthesis of the Azabicyclic Core of Halichlorine.[86]

The optically pure hydroxy ester **68.1** (Scheme 68), obtained enzymatically from the corresponding racemic acetates, was converted into lactone **68.2**, which was methylated stereoselectively from the exo face (**68.1** → **68.2** → **68.3**). At that point a number of

Scheme 68



Scheme 69



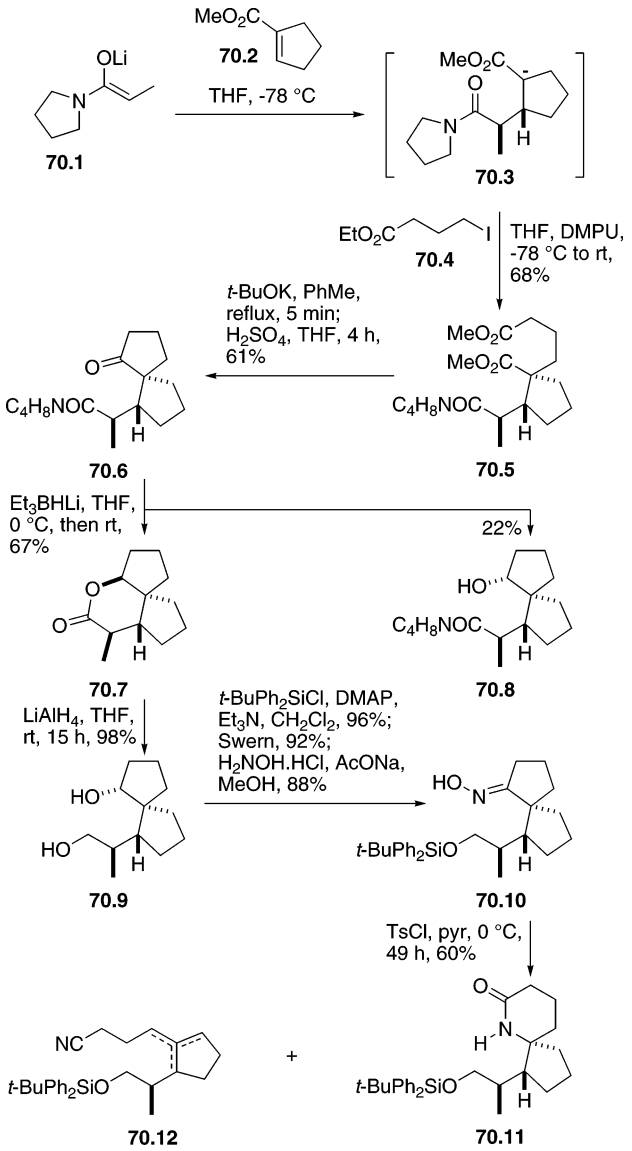
simple functional group modifications led to oxime **68.6**. Oxidation with *m*-CPBA then gave the nitro compound **68.7**, which underwent very efficient and stereoselective Michael addition to methyl acrylate (**68.7** → **68.8**). The ester group was converted into an iodide (**68.8** → **68.9** → **68.10**) under standard conditions, and the iodide was coupled with the dithiane **68.11**. Hydrolysis of the thioketal (**68.12** → **68.13**) released the key intermediate **68.13**, from which the spiro system would be generated.

To this end, the nitro group was reduced[86] using the Ni_2B−hydrazine combination to afford the nitrone **69.2** and not the expected amine **69.4** (Scheme 69). The nitro group in **68.13** was inert to hydrogenation over Pd/C, and while hydrogenation over Raney nickel did generate the piperidine system (**68.13** → **69.1**), some loss of the silyl group was observed. For these reasons the Ni_2B method was used, and the product (**69.2**) was converted into the desired piperidine **69.4** by successive further reduction with $NaBH_4$ and $TiCl_3$. The cyclization **68.13** → **69.2** is related to the corresponding steps shown in Schemes 13,[8] 18,[29] and 19.[9]

With **69.4** in hand, the amino group was protected as its trifluoroacetate and the silicon group was removed (**69.4** → **69.5** → **69.6**). The final product of these reactions (**69.6**) is similar to an intermediate in the Danishefsky route to halichlorine (compare **69.6** and **3.14**). Another closely related intermediate is alcohol **25.7** made during Kibayashi's studies on halichlorine.

Oxidation of **69.6** and Horner−Emmons−Wadsworth olefination, using **15.1**, gave **69.8**. Finally, debenzylation with BBr_3 produced the same alcohol (**7.6**), which was an intermediate in the Danishefsky synthesis of pinnaic acid.

Scheme 70



23.2. Studies in Pilli's Laboratory[87]

Stereoselective Michael addition of the *Z*-enolate **70.1** to the unsaturated ester **70.2** and in situ trapping with iodide **70.4**, using similar conditions to those established in another study,[88] gave the bis-ester **70.5** as the major product (68% yield, Scheme 70). Dieckmann cyclization and decarboxylation then produced the expected spiro ketone amide **70.6**, but the required next step—amide hydrolysis—could not be done directly as the amide group in **70.6** was resistant to hydrolysis. Fortunately, the required hydrolysis was easily achieved using intramolecular assistance. To this end, the ketone group in **70.6** was reduced and the resulting major alkoxide cyclized onto the amide carbonyl to generate lactone **70.7** (67%). The minor alkoxide afforded alcohol **70.8** (22%) on workup. In principle, it should be possible to recycle **70.8**, but this has not yet been reported. Lactone **70.7** was then easily converted into oxime **70.10** by standard operations (**70.7** → **70.9** → **70.10**). Finally, Beckmann rearrangement under carefully controlled conditions (TsCl in pyridine at 0 °C) gave the spirocyclic core unit **70.11** (60%) together with a small amount (15% yield) of a mixture of nitriles (**70.12**), arising by competitive fragmentation. The route to the core unit **70.11** should also provide access to optically active material, as there is good precedent for an asymmetric version of the initial Michael addition used in the present work.[89]

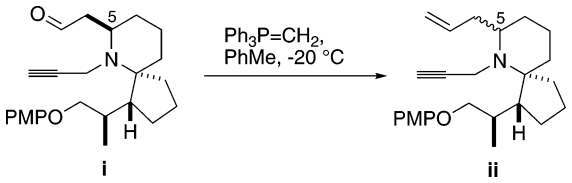
24. Acknowledgments

We thank NSERC for financial support and Dr. Bodhuri Prabhudas for assistance in the preparation of the manuscript. M.Y. holds a Province of Alberta Graduate Fellowship.

25. References

(1) Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867−3870.
(2) Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3871−3874.
(3) This sponge is also a source of okadaic acid (an inhibitor of phosphatases 1 and 2A) and halichondrins (antitumor agents) (ref 1).
(4) Arimoto, H.; Hayakawa, I.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett*. **1998**, *39*, 861−862.
(5) Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed*. **1999**, *38*, 3542−3545.
(6) Carson, M. W.; Kim, G.; Hentemann, M. F.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4450−4452.
(7) Carson, M. W.; Kim, G.; Danishefsky, S. J. *Angew. Chem., Int. Ed*. **2001**, *40*, 4453−4456.
(8) Christie, H. S.; Heathcock, C. H. *Proc. Nat. Acad. Sci*. **2004**, *101*, 12079−12084.
(9) Hayakawa, I.; Arimoto, H.; Uemura, D. *Heterocycles* **2003**, *59*, 441−444.
(10) Cf. Kobayashi, J.; Ishibashi, M. *Chem. Rev*. **1993**, *93*, 1753−1769.
(11) (a) Springer, T. A. *Cell* **1994**, *76*, 301−314. (b) Carlos, T. M.; Harlan, J. M. *Blood* **1994**, *84*, 2068−2101.
(12) Foster, C. A. *J. Allergy Clin. Immunol*. **1996**, S270−S277.
(13) Postigo, A. A.; Teixidó, J.; Sánchez-Madrid, F. *Res. Immunol*. **1993**, *144*, 723−735.
(14) 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. Nat. Acad. Sci. U.S.A*. **2000**, *97*, 734−739.
(15) (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.
(16) Trauner, D.; Danishefsky, S. J. *Tetrahedron Lett*. **1999**, *40*, 6513−6516.
(17) Trauner, D.; Churchill, D. G.; Danishefsky, S. J. *Helv. Chim. Acta* **2000**, *83*, 2344−2351.
(18) Cf. Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc*. **1991**, *113*, 9858−9859.
(19) Godfrey, A. G.; Ganem, B. *Tetrahedron Lett*. **1992**, *33*, 7461−7464.
(20) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem*. **1979**, *44*, 4997−4998.
(21) (a) Soai, K.; Niwa, S. *Chem. Rev*. **1992**, *92*, 833−856. (b) Soai, K.; Takahashi, K. *J. Chem. Soc., Perkin Trans. 1* **1994** 1257−1258.
(22) For conformational studies on quinolizidine, see: (a) Prokai-Tatrai, K.; Zoltewicz, J. A.; Kem. W. R. *Tetrahedron* **1994**, *50*, 9909−9918. (b) McIntosh, J. M.; Matassa, L. C. *J. Org. Chem*. **1988**, *53*, 4452−4457. (c) Gössinger, E. *Monatsh. Chem*. **1980**, *111*, 143−158. (d) Wenkert, E.; Chauncy, B.; Dave, K, G.; Jeffcoat, A. R.; Schell, F. M.; Schenk, H. P. *J. Am. Chem. Soc*. **1973**, *95*, 8427−8436.
(23) Keen, S. P.; Weinreb, S. M. *J. Org. Chem*. **1998**, *63*, 6739−6741.
(24) Krishnamurthy, S.; Vogel, F.; Brown, H. C. *J. Org. Chem*. **1977**, *42*, 2534−2536.
(25) Arbitrarily shown in nonzwitterionic form.
(26) It is not clear from our reading of the manuscript if the yields shown in Scheme 11 refer to one of the C(17) epimers or if identical yields were obtained for each epimer. We note that the manuscript states that the alcohols **11.2** were separable, but the associated scheme indicates they were inseparable. In any event, two stereoisomers of pinnaic acid were eventually obtained.
(27) From our reading of the manuscript it seems that the 17-*R* isomer is the major one, but this is not clearly stated, only implied. What is not in doubt is that the reaction is not highly stereoselective when C(14) has the *R*-configuration, as in **11.1**.

(28) Carlsson, S.; El-Barbary, A. A.; Lawesson, S.-O. *Bull. Chim. Belg*. **1980**, *89*, 643−649.
(29) Arimoto, H.; Asano, S.; Uemura, D. *Tetrahedron Lett*. **1999**, *40*, 3583−3586.
(30) By reaction of **66.6** with pivaloyl chloride and $Ph_3P{=}CH_2$ (66%).
(31) It is a curious fact that in a related case (see ref 7) Danishefsky observed that the stereochemical outcome was independent of whether *S*- or *R*-Alpine hydride was used and that the 17-*R* isomer **9.2** was the major alcohol.
(32) Abe, T.; Haga, T.; Negi, S.; Morita, Y.; Takayanagi, K.; Hamamura, K. *Tetrahedron* **2001**, *57*, 2701−2710.
(33) The ^{1}H NMR spectra of these species had been reported (see ref 9).
(34) A table in ref 9 indicates that a characteristic signal occurs in the CD_3OD ^{1}H NMR spectrum at δ 6.36 (t, J = 7.2 Hz) for the naturally derived sodium salt, at δ 6.35 (t, J = 7.2 Hz) for the synthetic carboxylate, and at δ 6.56 (m) for the "free synthetic carboxylic acid" (it is not clear to the authors of the present review whether this is the trifluoroacetate salt or corresponds to the zwitterion **15.5**). The Supporting Information for ref 8 gives δ ca. 6.35 for the synthetic material presumed to be the zwitterionic form, δ 6.49 for the synthetic sodium salt, and δ 6.70 for the synthetic TFA salt. Professor Arimoto has informed one of us (D.L.J.C.) that the ^{1}H NMR spectrum of pinnaic acid is very sensitive to pH.
(35) Clive, D. L. J.; Yu, M.; Li, Z. *Chem. Commun*. **2005**, 906−908.
(36) Boden, E. P.; Keck, G. E. *J. Org. Chem*. **1985**, *50*, 2394−2395.
(37) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 1989−1993.
(38) Enders, D.; Scherer, H. J.; Runsink, J. *Chem. Ber*. **1993**, *126*, 1929−1944.
(39) Yamaguchi, M.; Tsukamoto, M.; Hirao, I. *Tetrahedron Lett*. **1985**, *26*, 1723−1726.
(40) It is not clear from our reading of the paper (ref 9) if the free acid (i.e., zwitterionic form) or its trifluoroacetate salt was generated.
(41) Hayakawa, I.; Arimoto, H.; Uemura, D. *J. Chem. Soc, Chem. Commun*. **2004**, 1222−1223.
(42) This method for constructing the allyl pendant at C(5) was used because the following more obvious approach led to extensive epimerization at C(5).



i ii

(43) Fu, G. C.; Nguyen, S. B.; Grubbs, R. H. *J. Am. Chem. Soc*. **1993**, *115*, 9856−9857.
(44) Kirkland, T. A.; Lynn, D. M.; Grubbs, R. H. *J. Org. Chem*. **1998**, *63*, 9904−9909.
(45) Matsumura, Y.; Aoyagi, S.; Kibayashi, C. *Org. Lett*. **2003**, *5*, 3249−3252.
(46) Matsumura, Y.; Aoyagi, S.; Kibayashi, C. *Org. Lett*. **2004**, *6*, 965−968.
(47) Takasu, K.; Ohsato, H.; Ihara, M. *Org. Lett*. **2003**, *5*, 3017−3020.
(48) (a) Meyers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron* Lett. **1996**, *37*, 3623−3626. (b) Godjoian, G.; Fisher, G. B.; Goralski, C. T.; Singaram, B. *Reductions in Organic Synthesis. Recent Advances and Practical Applications*; Abdel-Magid, A. F., Ed.; ACS Symposium Series 641; American Checmial Society: Washington, DC; 1996, pp 153−166.
(49) (a) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc*. **2000**, *122*, 4583−4592. (b) Itoh, T.; Yamazaki, N.; Kibayashi, C. *Org. Lett*. **2002**, *4*, 2469−2472.
(50) Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett*. **1999**, *40*, 8503−8507.
(51) Yu, M.; Clive, D. L. J.; Yeh, V. S. C.; Kang, S.; Wang, J. *Tetrahedron Lett*. **2004**, *45*, 2879−2881.
(52) Clive, D. L. J.; Wang, J.; Yu, M. *Tetrahedron Lett*. **2005**, *46*, 2853−2855.
(53) Cf. Kokotos, G.; Padrón, J. M.; Martín, T.; Gibbons, W. A.; Martín, V. S. *J. Org. Chem*. **1998**, *63*, 3741−3744.
(54) Evans, D. A.; Urpí, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc*. **1990**, *112*, 8215−8216.
(55) (a) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett*. **1970**, 4459−4462. (b) Hale, K. J.; Cai, J. *Tetrahedron Lett*. **1996**, *37*, 4233−4236.
(56) Chênevert, R.; Dickman, M. *J. Org. Chem*. **1996**, *61*, 3332−3341.
(57) Goldspink, N. J.; Simpkins, N. S.; Beckmann, M. *Synlett* **1999**, 1292−1294.
(58) Clive, D. L. J.; Yu, M.; Li, Z. Unpublished observations.
(59) Strictly speaking, not previously known, as our compound is optically enriched, while the prior report dealt with racemic material.
(60) Feldman, K. S.; Perkins, A. L.; Masters, K. M. *J. Org. Chem*. **2004**, *69*, 7928−7932.
(61) Macdonald, T. L.; Mahalingam, S. *J. Am. Chem. Soc*. **1980**, *102*, 2113−2115.
(62) White, J. D.; Blakemore, P. R.; Korf, E. A.; Yokochi, A. F. T. *Org. Lett*. **2001**, *3*, 413−415.
(63) Shindo, M.; Fukuda, Y.; Shishido, K. *Tetrahedron Lett*. **2000**, *41*, 929−932.
(64) Yokota, W.; Shindo, M.; Shishido, K. *Heterocycles* **2001**, *54*, 871−885.
(65) Itoh, M.; Kuwahara, J.; Itoh, K.; Fukuda, Y.; Kohya, M.; Shindo, M.; Shishido, K. *Bioorg. Med. Chem. Lett*. **2002**, *12*, 2069−2072.
(66) Grigg, R.; Markandu, J.; Surendrakumar, S.; Thornton-Pett, M.; Warnock, W. *Tetrahedron* **1992**, *48*, 10399−10422.
(67) Tsunoda, T.; Nagino, C.; Oguri, M.; Itô, S. *Tetrahedron Lett*. **1996**, *37*, 2459−2462.
(68) Lee, S.; Zhao, Z. (S.) *Org. Lett.* **1999**, *1*, 681−683.
(69) Lee, S.; Zhao, Z. (S.) *Tetrahedron Lett*. **1999**, *40*, 7921−7924.
(70) Grigg, R.; Markandu, J.; Perrior, T.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 6929−6952.
(71) Arini, L. G.; Szeto, P.; Hughes, D. L.; Stockman, R. A. *Tetrahedron Lett*. **2004**, *45*, 8371−8374.
(72) Wright, D. L.; Schulte, J. P., II; Page, M. A. *Org. Lett*. **2000**, *2*, 1847−1850.
(73) (a) Baldwin, J. E.; Flinn, A. *Tetrahedron Lett*. **1987**, *28*, 3605−3608. (b) Pattenden, G.; Reynolds, S. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 379−385.
(74) For R′ = CHO, only a trace amount of **57.4** was detected.
(75) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710−734.
(76) Lactams of type **57.13** are difficult to open, and the ammonia−borane reagents do not always work (see ref 51).
(77) Keck, G.; Dalton, S. A. *Abstracts of Papers*; 226th ACS National Meeting, New York, Sept 7−11, 2003; American Chemical Society: Washington, DC, 2003, ORGN-187.
(78) Huxford, T.; Simpkins, N. S. *Synlett* **2004**, 2295−2298.
(79) Koviach, J. L.; Forsyth, C. J. *Tetrahedron Lett*. **1999**, *40*, 8529−8532.
(80) The synthesis of **60.1** is not reported in ref 79.
(81) Details of the preparation have not been reported except in a Ph.D. Thesis (which we have not examined): Koviach, J. L. Thesis, University of Minnesota, Minneapolis, MN, 1999.
(82) Dake, G. R.; Fenster, M. D. B.; Hurley, P. B.; Patrick, B. O. *J. Org. Chem.* **2004**, *69*, 5668−5675. Cf. Dake, G. R.; Fenster, M. D. B.; Fleury, M.; Patrick, B. O. *J. Org. Chem.* **2004**, *69*, 5676−5683.
(83) Cf. Friesen, R. W.; Blouin, M. *J. Org. Chem*. **1996**, *61*, 7202−7206.
(84) Cf. Vedejs, E.; Bershas, J. P. *Tetrahedron Lett*. **1975**, 1359−1362.
(85) Taber, D. F.; Mitten, J. V. *J. Org. Chem.* **2002**, *67*, 3847−3851.
(86) Zhang, H.-L.; Zhao, G.; Ding, Y.; Wu, B. *J. Org. Chem*. **2005**, *70*, 4954−4961.
(87) de Sousa, A. L.; Pilli, R. A. *Org. Lett*. **2005**, *7*, 1617−1619.
(88) Heathcock, C. A.; Stafford, J. A.; Clark, D. A. *J. Org. Chem*. **1992**, *57*, 2575−2585.
(89) Heathcock, C. A.; Stafford, J. A. *J. Org. Chem*. **1992**, *57*, 2566−2574.

CR0406209