JOC Article
pubs.acs.org/joc

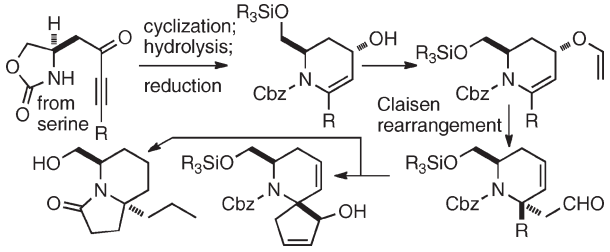
2,6-Disubstituted and 2,2,6-Trisubstituted Piperidines from Serine: Asymmetric Synthesis and Further Elaboration

Hukum P. Acharya and Derrick L. J. Clive*

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

derrick.clive@ualberta.ca

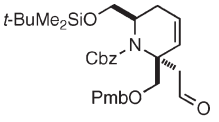
Received May 23, 2010



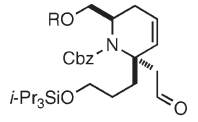
4-Hydroxy-3,4-dihydro-2*H*-pyridine-1-carboxylic acid benzyl esters, which are readily prepared from serine and terminal acetylenes, undergo Claisen rearrangement to piperidine derivatives when heated with butyl vinyl ether in the presence of $Hg(OAc)_2$ and Et_3N. This route to optically pure piperidines having substituents α to nitrogen is general, and the rearrangement products are versatile intermediates for making a broad range of amines containing a substituted piperidine subunit.

Introduction

During studies on the total synthesis of the marine alkaloid halichlorine,[1] a method was developed in this laboratory for constructing optically pure piperidines with a quaternary center adjacent to nitrogen. The method was used to make aldehyde **1**, which was elaborated further for the halichlorine project, but the related compounds **2** and **3** were also prepared as evidence that the approach is general. Substituted piperidines[2] are important in medicinal chemical research[3] and also feature in many natural products;[4] therefore, we have made a more extensive study of this piperidine synthesis, and the results are reported here, together with a number of further transformations that lead to azaspiro compounds and the indolizidine skeleton.



1



2 R = *t*-BuMe$_2$Si
3 R = Cbz

Results and Discussion

Our route to piperidines starts with the construction of dihydropyridinones of type **4**. Stereoselective reduction of the carbonyl group gives the tetrahydropyridinol **5**, which forms a vinyl ether that undergoes Claisen rearrangement[5] (**5**→**6**→**7**) when heated in butyl vinyl ether in the presence of $Hg(OAc)_2$ and Et_3N (Scheme 1).

A number of routes to the starting dihydropyridinones **4** are known,[6] but the method of Turunen and Georg[7] seemed most appropriate and, with some modification, proved to be

(1) Liu, D.; Acharya, H. P.; Yu, M.; Wang, J.; Yeh, V. S. C.; Kang, S.; Chiruta, C.; Jachak, S. M.; Clive, D. L. J. *J. Org. Chem.* **2009**, *74*, 7417–7428.

(2) Synthesis of piperidines. Reviews: (a) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729. (b) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693–3712. (c) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953–2989. (d) Bates, R. W.; Sa-Ei, K. *Tetrahedron* **2002**, *58*, 5957–5978. (e) Enders, D.; Thiebes, C. *Pure Appl. Chem.* **2001**, *73*, 573–578. (f) Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383–394. (g) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781–1813. (h) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238. (i) Rubiralta, M.; Giralt, E.; Diez, A. *Piperidines, Structure, Preparation, Reactivity, and Synthetic Applications of Piperidine and its Derivatives*; Elsevier: Amsterdam, 1991. Routes to non-racemic piperidines: (j) Coombs, T. C.; Zhang, Y.; Garnier-Amblard, E. C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2009**, *131*, 876–877. (k) Lebold, T. P.; Leduc, A. B.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 3770–3772. (l) Abrunhosa-Thomas, I.; Roy, O.; Barra, M.; Besset, T.; Chalard, P.; Troin, Y. *Synlett* **2007**, 1613–1615. (m) Adriaenssens, L. V.; Hartley, R. C. *J. Org. Chem.* **2007**, *72*, 10287–10290. (n) Gotchev, D. B.; Comins, D. L. *J. Org. Chem.* **2006**, *71*, 9393–9402. (o) Back, T. G.; Nakajima, K. *J. Org. Chem.* **1998**, *63*, 6566–6571. (p) Waldmann, H.; Braun, M.; Dräger, M. *Angew. Chem., Int. Ed.* **1990**, *29*, 1468–1471. (q) Kunz, H.; Pfrengle, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1067–1068.

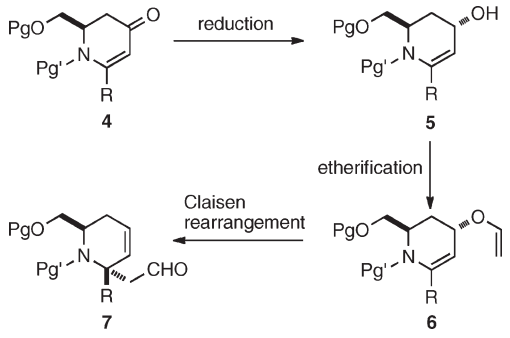
(3) For comments on the pharmaceutical significance of piperidines, see: Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679–3681.

(4) See, for example: Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556–1575.

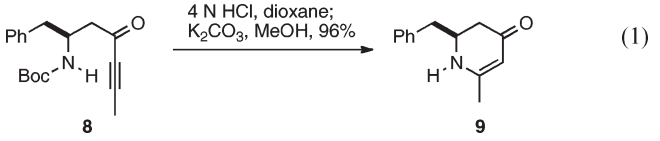
(5) Review of the Claisen rearrangement: Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939–3002.

DOI: 10.1021/jo101010c Published on Web 06/30/2010

SCHEME 1. General Plan



ideal for our purpose. A key example of their work is shown in eq 1, the product **9** being formed with an ee of >90%.



(1)

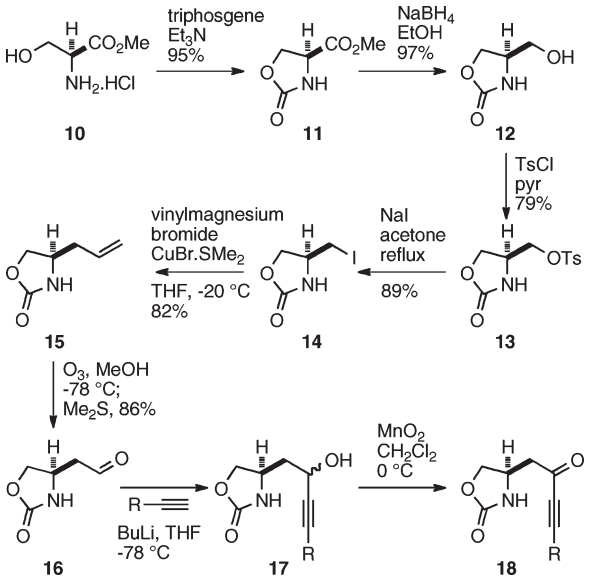
The initial requirements in the context of our route to halichlorine were suggestive of serine as a starting material for making the dihydropyridinones of type **4**, and such a route was readily developed,[1] as summarized in Scheme 2. In principle, amino acids with other subunits besides the CH_2OH of serine should also be appropriate starting materials, but we have not investigated this possibility.

Following a literature procedure,[8] serine methyl ester hydrochloride was converted into the oxazolidinone **11**, which was treated successively with $NaBH_4$ and TsCl (**11** → **12** → **13**). The tosyloxy group was then displaced by a Finkelstein reaction using NaI, and the resulting iodide **14** was treated with vinylmagnesium bromide in the presence of $CuBr \cdot SMe_2$. These operations gave the allyl-substituted oxazolidinone **15**,[9] and ozonolysis then provided the key aldehyde **16** that was used for much of our work. All of the yields in the steps leading to **16** were satisfactory (>79%).

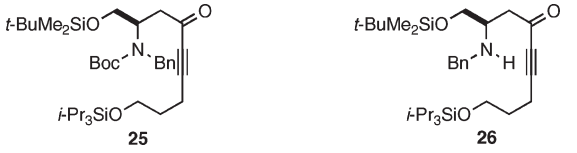
The aldehyde reacted efficiently with a range of lithium salts derived from terminal acetylenes to afford the expected propargylic alcohols (**16** → **17**), which were oxidized with MnO_2 to generate ketones of type **18**. These ketones were then converted into the corresponding dihydropyridinones **4**, as described later. Most of the acetylenic alcohols (of type **17**) and ketones (of type **18**) that we made are listed in Table 1, which also includes the two examples[1] (entries i, ii) investigated during the synthesis of halichlorine.

Choice of Nitrogen Protecting Groups. Table 1 shows our optimized approach, which is discussed in detail below; however, we first examined the acetylenic ketone **25**, whose

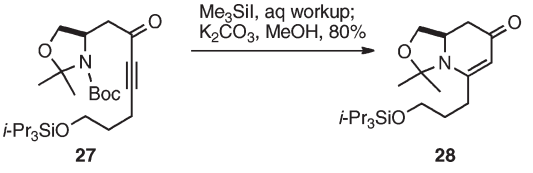
SCHEME 2. Route to Acetylenic Ketones



structure seemed appropriate for the halichlorine synthesis. When it was subjected to the first step of the reported conditions for cyclization to a dihydropyridinone (4 N HCl in dioxane, or Me_3SiI in CH_2Cl_2)[7] only a complex mixture was obtained. Removal of the Boc group could be achieved, however, with $ZnBr_2$ to release the *N*-benzyl amine **26**, which was unstable and did not appear to cyclize under the conditions we tried (K_2CO_3, MeOH; Na_2CO_3, DMF), our impression being that it underwent loss of benzylamine.



We next evaluated a different set of protecting groups by making the acetylenic ketone **27**. This compound did cyclize to **28** (80%) when treated with Me_3SiI, followed by workup with aqueous $NaHCO_3$ and then treatment with K_2CO_3 in MeOH for 1 h at room temp, but the two attempts we made to remove the isopropylidene group ($FeCl_3 \cdot SiO_2$;[10] $CuCl_2 \cdot 2H_2O$[11]) were unsuccessful.



(2)

At the same time as these experiments were underway, we also prepared the acetylene **29** and found that it could be cyclized to **30** in good yield (84%) by a seemingly small but crucial modification of the conditions reported by Turunen

(6) For two powerful modern methods, see: (a) Back, T. G. *Can. J. Chem.* **2009**, *87*, 1657–1674. (b) Back, T. G.; Hamilton, M. D.; Lim, V. J. J.; Parvez, M. *J. Org. Chem.* **2005**, *70*, 967–972. (c) Comins, D. L. *J. Heterocycl. Chem.* **1999**, *36*, 1491–1500. (d) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719–4728. (e) Comins, D. L; Hong, H.; Salvador, J. M. *J. Org. Chem.* **1991**, *56*, 7197–7199.

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

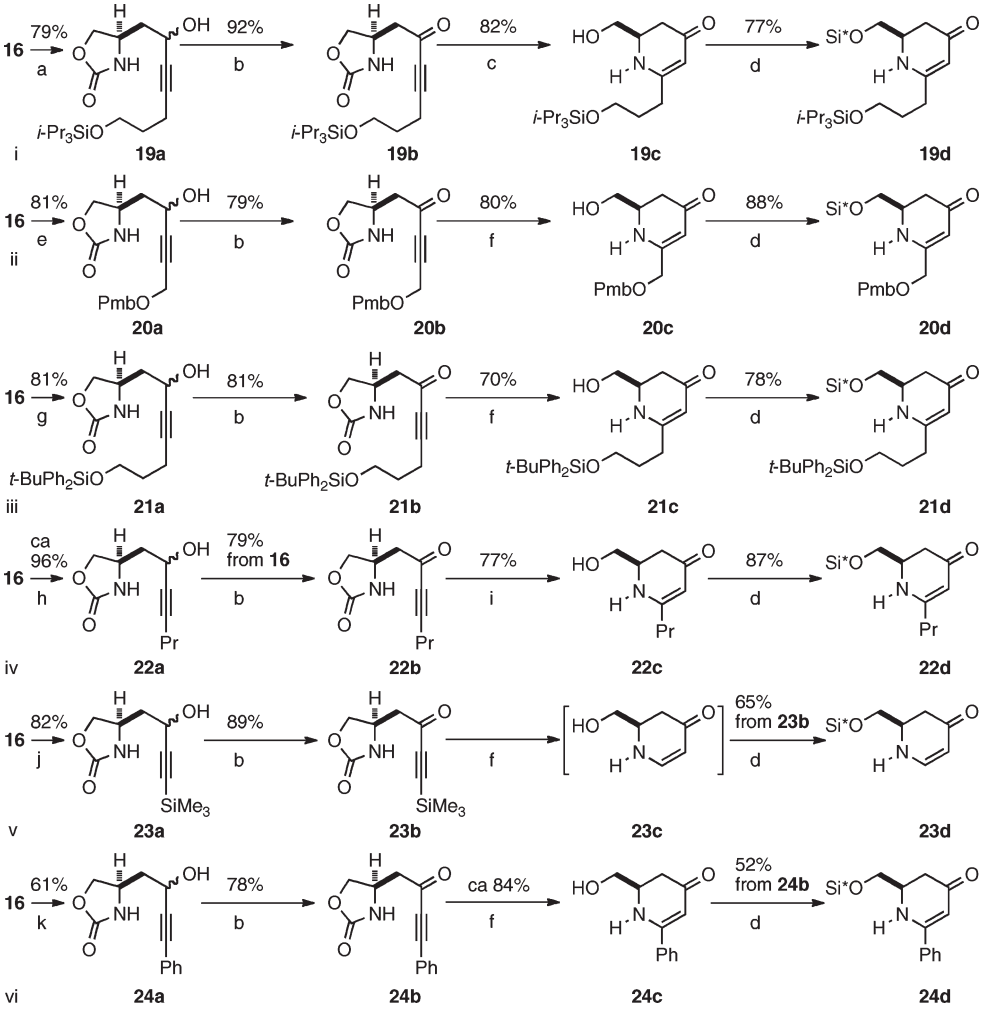
(8) Sibi, M. P.; Rutherford, D.; Renhowe, P. A.; Li, B. *J. Am. Chem. Soc.* **1999**, *121*, 7509–7516.

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

(10) Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem.* **1996**, *51*, 404–407.

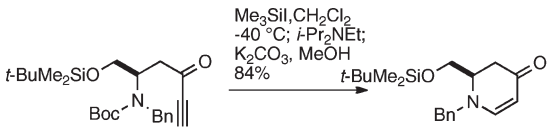
(11) Saravanan., P.; Chandrasekhar, M.; Anand, R. V.; Singh, V. K. *Tetrahedron Lett.* **1998**, *39*, 3091–3092.

TABLE 1. Cyclization to Dihydropyridinones[a]



[a]Reagents and conditions: (a) Tris(1-methylethyl)(4-pentynyloxy)silane, BuLi, THF, −78 °C. (b) MnO_2, CH_2Cl_2. (c) Cs_2CO_3, MeOH, 65 °C, 12 h. (d) *t*-$BuMe_2SiCl$, Et_3N, DMAP, CH_2Cl_2. (e) 1-Methoxy-4-[(2-propyn-1-yl-oxy)methyl]benzene, BuLi, THF, −78 °C. (f) Cs_2CO_3, MeOH, 80 °C, 6 h. (g) (1,1-Dimethylethyl)(4-pentynyloxy)diphenylsilane, BuLi, THF, −78 °C. (h) 1-Pentyne, BuLi, THF, −78 °C. (i) Cs_2CO_3, MeOH, 80 °C, 5 h. (j) Trimethylsilylacetylene, BuLi, THF, −78 °C. (k) Ethynylbenzene, BuLi, THF, −78 °C.

and Georg. This modification involved operating at a lower temperature (−15 to −40 °C) and introducing *i*-$PrNEt_2$ after the initial treatment (30 min at −15 to −40 °C) with Me_3SiI.

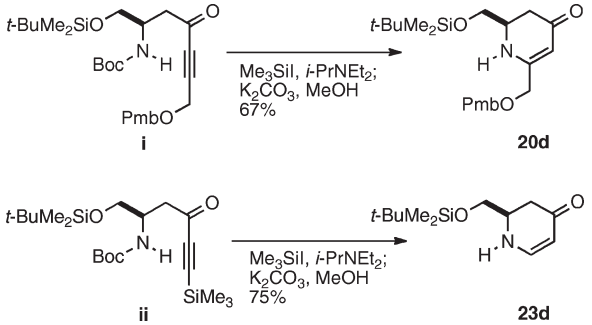


(3)

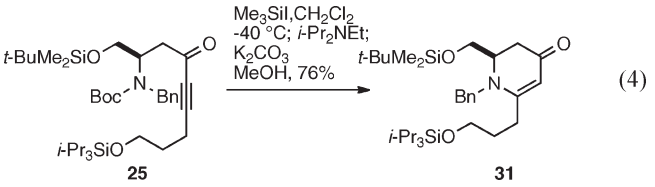
In the absence of Hünig's base only a trace of **30** was detected after warming the mixture to room temperature, removing volatile material, and treating the residue with K_2CO_3 in MeOH. The inclusion of Hünig's base is part of a standard method for making vinyl iodides.[12,13] Once satisfactory conditions for cyclization of **29** had been found, we reexamined the acetylene **25**. In the event, this compound underwent cyclization satisfactorily (76%) using the modified procedure but, unfortunately, attempts to reduce the carbonyl group (DIBALH; $NaBH_4$−$CeCl_3 \cdot 7H_2O$;

(12) (a) Jasperse, C. P.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 5601–5609. (b) Cheon, S. H.; Christ, W. J.; Hawkins, L. D.; Jin, H.; Kishi, Y.; Taniguchi, M. *Tetrahedron Lett.* **1986**, *27*, 4759–4762.

(13) The same modified procedure also worked for conversion of **i** into **20d** and **ii** into **23d**, but we measured the ee (> 99%) only for **20d**.



DIBALH-[4-methyl-2,6-di(*tert*-butyl)phenol]; $LiAlH_4$; Red-Al) of the product (**31**) were not successful. Related dihydropyridinones in which the nitrogen is protected as a carbamate have been reduced,[14] and so our next approach was to prepare the cyclic carbamate **19b** (Scheme 3), expecting that it might afford **32**. This expectation was not realized, as we obtained **19c** from the cyclization, which was done using Cs_2CO_3−MeOH at reflux. The initial choice of Cs_2CO_3 was arbitrary, but a subsequent brief optimization survey, using **20b**, showed that the Cs_2CO_3−MeOH combination is one of the best conditions we examined (Table 2). The liberation of the hydroxyl and amino groups (as in **19c**) was of no consequence, as each could be reprotected.



(4)

SCHEME 3. Cyclization and Hydrolysis of Oxazolidinone

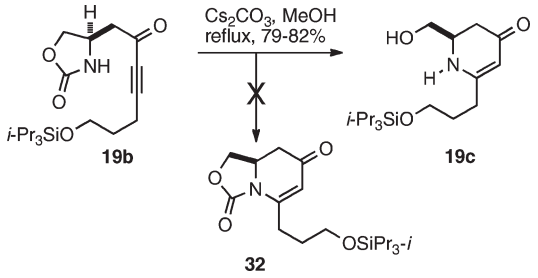
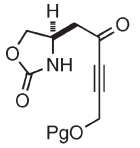


TABLE 2. Optimization Studies

	base	solvent/ additive	bath temp (°C)	time (h)	yield (%)
i	Cs_2CO_3	MeOH	80	5	79
ii	K_2CO_3	MeOH	80	6	80
iii	Cs_2CO_3	CH_2Cl_2−H_2O	80	6	no reaction
iv	K_2CO_3	CH_2Cl_2−H_2O	80	5	no reaction
v	K_2CO_3	PhMe	80	5	no reaction
vi	Cs_2CO_3	MeCN	80	5	**20b** + trace **20c**
vii	Cs_2CO_3	PhMe, Aliquat	rt	12	decomp of **20b**, no **20c**
viii	Cs_2CO_3	PhMe, Aliquat	0	5	decomp of **20b**, no **20c**

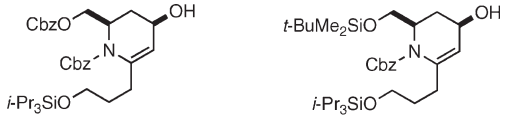
The conditions used (see Scheme 3) to make **19c** were applied to all the other ketones listed in Table 1 to afford the unprotected hydroxy amines **20c**−**24c**, respectively. We did find one restriction on the structure of the starting acetylenic ketones: attempts to apply our standard cyclization conditions to **33** and **34** showed that neither silicon protecting group survived, and so we used other forms of protection for the pendant originating from the terminal acetylene. In contrast, other compounds in which an *i*-Pr_3SiO or *t*-$BuPh_2SiO$ group was present on a *three*-carbon chain (as in **19a** and **21a**) were not desilylated.



33 Pg = $SiPh_2Bu$-*t*
34 Pg = $SiMe_2Bu$-*t*

The hydroxyl group of the cyclized products from **19c**−**24c** was protected, usually by silylation (Table 1), and the nitrogen was converted into a carbamate (Table 3) by reaction with CbzCl or Boc_2O, except for one case (Table 3, entry iv, **19c** → **19n**), where triphosgene was used to mutually protect the hydroxyl and amino functions. Introduction of the Cbz group was done by deprotonation with BuLi, followed by reaction with CbzCl. The same procedure with Boc_2O appeared to be unsuccessful (at least with **19d**), but the Boc group was easily introduced in all cases by a more conventional procedure (Boc_2O, DMAP, MeCN). Attempts to protect the hydroxyl of **19c** as a MOM ether were unsuccessful and the MOM group was not examined with any of our other substrates.

Reduction of the Carbonyl Group. The fully protected dihydropyridinones shown in Table 3 could be reduced stereoselectively to the indicated α-alcohols, using $NaBH_4$−$CeCl_3 \cdot 7H_2O$ at a low temperature (−40 °C), the yield generally being > 80%. In the case of **24e**, reduction gave 8.5% of the undesired *β* epimer and 71% of the desired α isomer. The stereochemical outcome for the reductions **19e** → **19f** (Table 3, entry i) and **19k** → **19l** (Table 3, entry iii) was established by comparison of the ^1H NMR spectra with those of the C-4 epimeric alcohols **35** and **36**, respectively, obtained by use of DIBALH-[4-methyl-2,6-di(*tert*-butyl)phenol],[14b,15] it being known[14b] that reduction of related dihyropyridinones with $NaBH_4$−$CeCl_3 \cdot 7H_2O$ and di-isopropylaluminum hydride-[4-methyl-2,6-di(*tert*-butyl)phenol] (we used DIABLH-[4-methyl-2,6-di(*tert*-butyl)phenol][15]) gives opposite stereochemical results. As expected for the α alcohol **19f**,

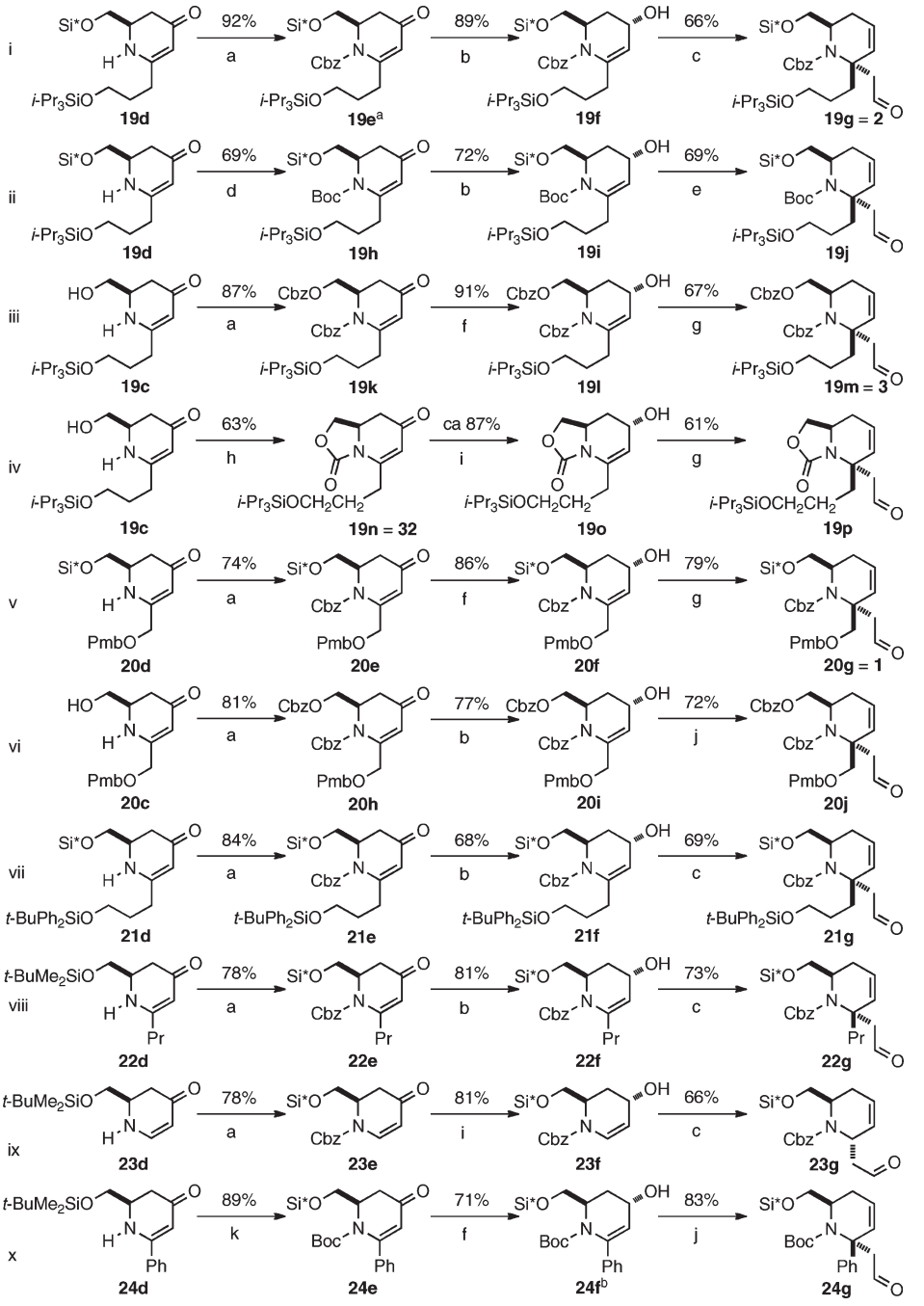


TROESY measurements showed an NOE enhancement between the carbinyl hydrogen (C**H**OH) and the CH_2 of the CH_2OCbz side chain. The stereochemical assignment could not be made on the basis of coupling constants because the presence of rotamers broadened the key signals. The chemical shifts of the carbinyl hydrogen C**H**OH of the α and *β* isomers are distinctly different. Access to the *β* alcohol **35** via Mitsunobu inversion (we did not try to make **36** in this

(14) (a) Comins, D. L.; Foley, M. A. *Tetrahedron Lett.* **1988**, *29*, 6711–6714. (b) Comins, D. L.; Kuethe, J. T.; Miller, T. M.; Février, F. C.; Brooks, C. A. *J. Org. Chem.* **2005**, *70*, 5221–5234.

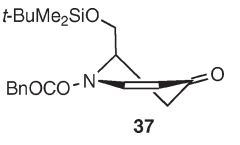
(15) Iguchi, S.; Nakai, H.; Hayashi, M.; Yamamoto, H.; Maruoka, K. *Bull. Chem. Soc. Jpn.* **1981**, *64*, 3033–3041.

TABLE 3. Claisen Rearrangement



[a]Si* = *t*-BuMe$_2$Si. Reagents and conditions: (a) BuLi, CbzCl, THF, −78 °C. (b) NaBH$_4$, CeCl$_3\cdot$7H$_2$O, MeOH, −40 C, 30 min. (c) Hg(OAc)$_2$, Et$_3$N, *n*-butyl vinyl ether, 80 °C, 36 h. (d) (Boc)$_2$O, DMAP, MeCN, 6 h. (e) Hg(OAc)$_2$, Et$_3$N, *n*-butyl vinyl ether, 110 °C, 38 h. (f) NaBH$_4$, CeCl$_3\cdot$7H$_2$O, MeOH, −40 C, 45 min. (g) Hg(OAc)$_2$, Et$_3$N, *n*-butyl vinyl ether, 110 °C, 36 h. (h) BuLi, triphosgene, THF, −78 °C. (i) NaBH$_4$, CeCl$_3\cdot$7H$_2$O, MeOH, −40 C, 1 h. (j) Hg(OAc)$_2$, Et$_3$N, *n*-butyl vinyl ether, 110 °C, 48 h. (k) (Boc)$_2$O, DMAP, MeCN, 5 h. [b]8.5% of *β*-alcohol also isolated.

way) was not successful because of the instability of the intermediate ester, but reduction of **19k** with DIBALH-[4-methyl-2,6-di(*tert*-butyl)phenol] was satisfactory, although the yield was lower than that obtained in the reduction with NaBH$_4$−CeCl$_3\cdot$7H$_2$O leading to the isomeric α alcohol **19l**. We assume that all of the Luche reductions involve the conformation **37**, which is adopted to alleviate A^{1,3} strain. If complexation of the carbonyl occurs anti to the silyloxy substituent, then hydride delivery would occur axially (*syn* to the silyloxy substituent.



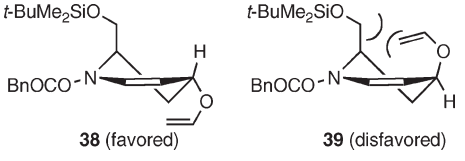
37

Optical Purity of 20d and 19d. As described in our publication on the synthesis of halichlorine,[1] the optical purity of

20d was measured by *N*-acylation with (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride to give a product with a vinyl signal in the ^{1}H NMR spectrum (400 MHz) at 5.93 ppm. Acylation of **20d** with the enantiomeric reagent gave a signal at 5.88 ppm; this signal is absent in the spectrum of the derivative made with the *S*-reagent and so **20d** must be a single enantiomer. The same procedure was used to establish[1] that **19d** had an ee of > 99%, and we assume that the other dihydropyridinones are likewise formed without compromising the stereochemical purity of the starting serine. We also hydrolyzed the cyclic carbamate **19n** (derived from serine with ee of 97%) back to the parent dihydropyridinone **19c** using the conditions we employed for the original cyclization **19b** → **19c** and showed (using the above Mosher amide procedure, after *O*-silylation) that there was no loss of optical purity.

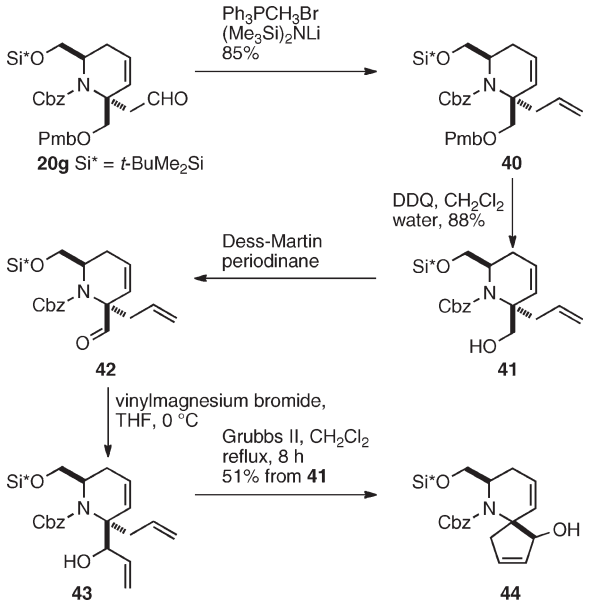
Claisen Rearrangement. The tetrahydropyridinols listed in Table 3 (third column of structures) reacted with butyl vinyl ether on heating for ca. 36 h in the presence of $Hg(OAc)_2$ and Et_3N to afford the product of Claisen rearrangement. Obviously, an intermediate vinyl ether is generated and rearranges in situ (cf. **5** → **6** → **7**). Our attempts to isolate such an intermediate, using **19l**, were unsuccessful, as the compound appeared (^{1}H NMR) to suffer elimination of the vinyloxy group during chromatography. The formation and rearrangement of the vinyl ethers were all conducted by heating the substrate alcohol in butyl vinyl ether (bp 94 °C) as solvent, using a Teflon-sealed thick-walled tube partially immersed in an oil bath set at 100−115 °C. When the reaction was attempted with **19f** in refluxing butyl vinyl ether under Ar, but at 1 atm, some of the derived vinyl ether remained (^{1}H NMR) after the normal reaction time of 40 h (but could not be isolated). We did try a higher-boiling vinyl ether (cyclohexyl vinyl ether, bp 147 °C) at a bath temperature of 140 °C to avoid the use of a sealed vessel, but the reaction, at least with **19f** and **20f**, was slower and this protocol did not appear to offer any advantage. The use of Et_3N in the Claisen rearrangement was simply a precaution suggested by prior observations with $Pd(OCOCF_3)_2$-mediated Claisen rearrangements;[16] in a single experiment done at a somewhat lower temperature without the amine, the yield was significantly lower.

The alcohol stereochemistry is important and the α-alcohol must be used; tests with the *β*-alcohols **35** and **36** were unsuccessful, presumably because Claisen rearrangement requires two substituents to adopt an axial conformation, whereas only one substituent need be axial for rearrangement of the vinyl ether derived from the α-alcohol. This situation is illustrated in diagrams **38** and **39**. The restriction to α-alcohols means that a careful choice must be made for the substituent on the acetylene used in constructing the dihydropyridinones of type **4** (group R) so that, after the Claisen rearrangement, the appendages on the fully substituted carbon α to the nitrogen can be modified in the desired way.



Use of the Ireland Ester Enolate Rearrangement. Using **19l** as a test substrate, we examined the possibility of applying the Ireland ester enolate rearrangement instead of the Claisen rearrangement. An acyclic version of a related Ireland ester enolate rearrangement has been reported,[17] and it was noted that the intermediate esters are unstable to chromatography. In the acyclic series the diastereoselectivity was usually in the range 2:1 to 3:2 (with one exception, 95:5).

SCHEME 4. Formation of an Azaspiro[4,5]decadiene

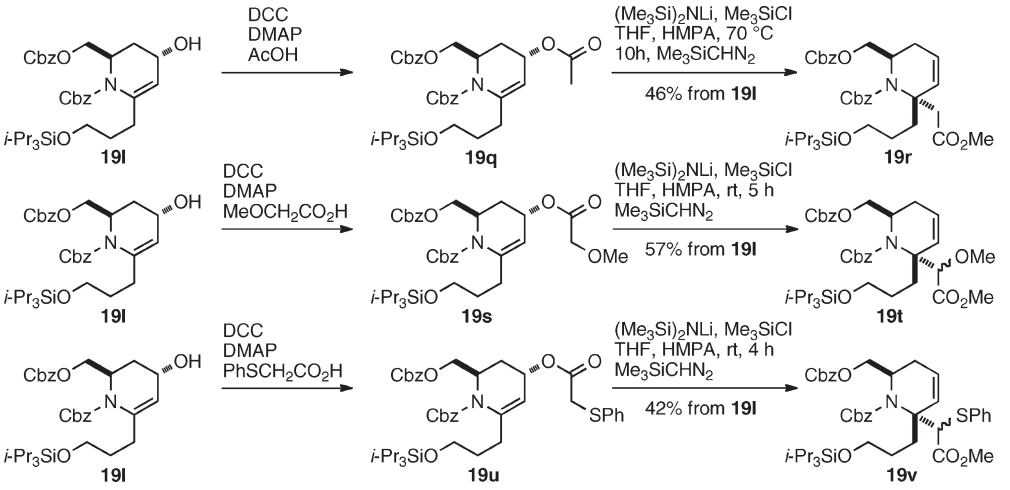


Alcohol **19l** was converted into its acetate **19q** by DCC-mediated coupling; acylation using Ac_2O/Et_3N was unsuccessful because the derived acetate decomposed in situ. The material could not be purified because of its instability to silica chromatography, but it did rearrange on treatment with $(Me_3Si)_2NLi$ in the presence of Me_3SiCl and HMPA in THF (−78 to +70 °C). The yield of ester obtained by methylation of the resulting acid was only 46%. Use of $(Me_3Si)_2NNa$ under the same conditions gave a comparable yield of ester (43%). Corresponding experiments were done with the methoxy acetate **19s** and the (phenylthio)acetate **19u**, each made by DCC coupling, but yields of the derived esters **19t** and **19v** were always below 60%; consequently, this route was not investigated further, even though the products do have functionality that is potentially useful for further elaboration.

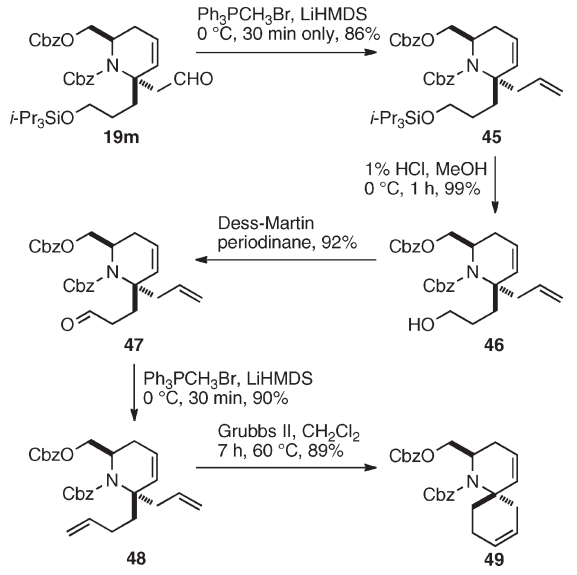
Elaboration of the Claisen Rearrangement Products. Most of the Claisen rearrangements shown in Table 3 afford compounds with two pendant functionalized chains α to nitrogen. These chains should be modifiable in a number of ways, and we have illustrated a few of the possibilities. Wittig homologation of **20g** with methylenetriphenylphosphorane gave **40** (Scheme 4), and the PMB group was then removed. Oxidation of the resulting alcohol to the unstable aldehyde **42** and reaction with vinylmagnesium bromide generated dienyl alcohol **43**, which was obtained as a single isomer whose stereochemistry at the hydroxyl-bearing carbon was not established. Ring-closing metathesis (Grubbs II) gave the azaspirocycle **44** in just over 50% yield overall from **41**.

(16) Wei, X.; Lorenz, J. C.; Kapadia, S.; Saha, A.; Haddad, N.; Busacca, C. A.; Senanayake, C. H. *J. Org. Chem.* **2007**, *72*, 4250–4253.
(17) Ylioja, P. M.; Mosley, A. D.; Charlot, C. E.; Carbery, D. R. *Tetrahedron Lett.* **2008**, *49*, 1111–1114.

TABLE 4. Ireland Ester Enolate Rearrangement



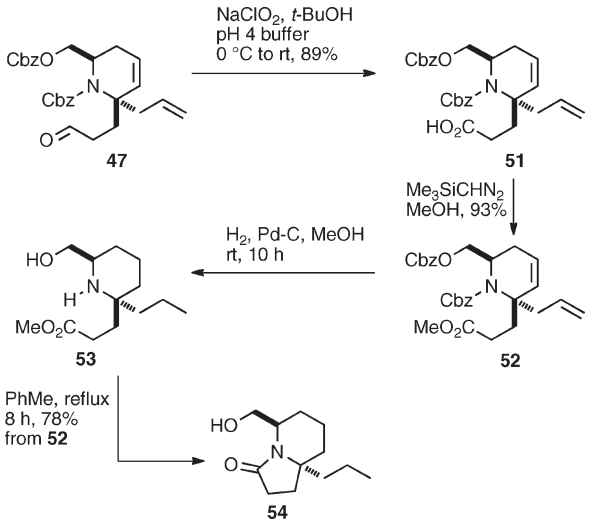
SCHEME 5. Preparation of an Azaspiro[5,5]undecadiene



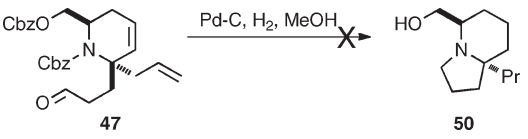
As summarized in Scheme 5 the related azaspirocycle **49** was accessible from **19m**, again using conventional procedures. Wittig homologation of **19m** (**19m** → **45**), followed by deprotection, oxidation, and Wittig homologation of the siloxypropyl side arm (**45** → **46** → **47** → **48**) set the stage for ring-closing metathesis, which proceeded in high yield (89%) to afford the spirocycle **49**. We found that both Wittig reactions must be done at a low temperature and for 30 min only, in order to avoid loss of the Cbz groups.

Finally, we converted the olefinic aldehyde **47** into the simple indolizidine **54** (Scheme 6). Our expectation (eq 5) was that simple hydrogenation of **47** would serve to saturate the carbon−carbon double bonds, remove the Cbz groups, and allow the nitrogen to cyclize onto the pendant aldehyde group;

SCHEME 6. Formation of an Indolizidine



the resulting imine would then undergo hydrogenation (**47** → **50**). To our surprise, an experiment along these lines (eq 5) failed to afford the indolizidine and gave only a complex mixture, but the indolizidine structure could be reached by the steps summarized in Scheme 6. Pinnick oxidation of the aldehyde group (**47** → **51**) and methylation of the resulting ester gave **52**, and at that point the Cbz groups were removed by hydrogenolysis. Finally, the required cyclization to generate the indolizidine[18] skeleton was induced by heating amine **53** in PhMe.

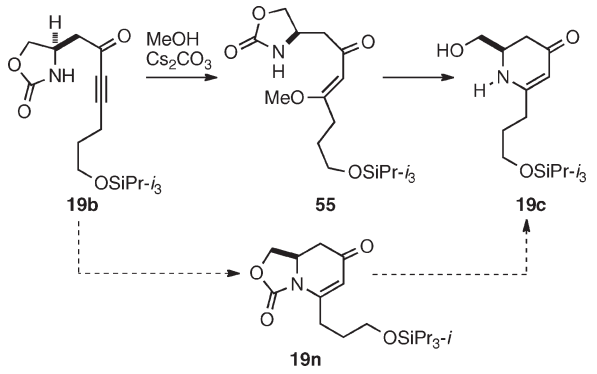


(5)

Mechanistic Studies. As described in the full report on the synthesis of halichlorine,[1] a brief mechanistic study indicated, at least for the test example (**19b**), that the pathway

(18) For recent approaches to indolizidines, see, for example: (a) Reference 6a. (b) Friedman, R. K.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10775–10782. (c) Barbe, G.; Pelletier, G.; Charette, A. B. *Org. Lett.* **2009**, *11*, 3398–3401. (d) Reviews: Perreault, S.; Rovis, T. *Chem. Soc. Rev.* **2009**, *38*, 3149–3159. (e) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139–165.

SCHEME 7. Attempted Isolation of Intermediates



probably was via **55** (arbitrary double bond geometry shown), and although we could not specify the timing of the oxazolidinone hydrolysis, we suspect it happens after cyclization because **19n** gave **19c** on exposure to the cyclization conditions, but the reference model **15** (see Scheme 2) was largely unchanged under these conditions; **19n** is an imide, whereas **15** is a carbamate, and we would expect the hydrolytic stability of **15** to accurately reflect the hydrolytic stability of **19b**, while an imide would be more sensitive to hydrolysis. When **55** was subjected to the cyclization conditions, but only for 1.5 h, so that some **55** remained, only **19c** and **55** were detectable in the mixture (^{1}H NMR), apart from obviously minor impurities.

Conclusion

Heating readily available and optically pure 4-hydroxy-3,4-dihydro-2*H*-pyridine-1-carboxylic acid benzyl esters in butyl vinyl ether is a general method for preparing piperidine derivatives having a quaternary center adjacent to nitrogen. The method, which was developed specifically for the synthesis of the complex marine alkaloid halichlorine, involves Claisen rearrangement of a vinyl ether that is generated in situ. Corresponding Ireland ester enolate rearrangements are much less efficient. The substituted piperidines can be elaborated in a number of ways, and several possibilities were illustrated in the present work by making two spiro compounds and an indolizidine.

Experimental Section

(4*R*)-4-[7-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-hydroxy-3-heptyn-1-yl]-2-oxazolidinone (21a). *n*-BuLi (2.5 M in THF, 1.02 mL, 2.56 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of (1,1-dimethylethyl)(4-pentynyloxy)-diphenylsilane[19] (0.753 g, 2.33 mmol) in THF (8 mL). Stirring at −78 °C was continued for 30 min, and a solution of **16** (0.148 g, 1.15 mmol) in THF (2 mL plus 1 mL as a rinse) was added dropwise. Stirring at −78 °C was continued for 2 h, and then saturated aqueous NH_4Cl (10 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 10 cm), using 1:5 EtOAc−hexane, gave **21a** (0.427 g, 81%) as an oil which was a mixture of two isomers: FTIR ($CHCl_3$ cast) 3448, 3317, 2210, 1748 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (s, 9 H), 1.71−2.02 (m, 5 H), 2.33−2.41 (m, 2 H), 3.73 (t, J = 6.0 Hz, 2 H), 3.97−4.23 (m, 2 H), 4.43−4.60 (m, 2 H), 5.47−5.57 (m, 1 H), 7.34−7.48 (m, 6 H), 7.62−7.70 (m, 4 H); exact mass (electrospray) m/z calcd for $C_{26}H_{33}NNaO_4Si$ (M + Na) 474.2071, found 474.2071.

(4*R*)-4-[7-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-oxo-3-heptyn-1-yl]-2-oxazolidinone (21b). Activated MnO_2 (0.578 g, 6.67 mmol) was added to a stirred solution of **21a** (0.31 g, 0.69 mmol) in CH_2Cl_2 (8 mL). Stirring was continued for 1.5 h, and the slurry was filtered through a short pad of Celite (3 × 3 cm), using EtOAc (3 × 10 mL) as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 12 cm), using 1:5 EtOAc−hexane, gave **21b** (0.253 g, 81% yield) as a colorless oil: $[\alpha]^{25}_D$ +9.1 (c 0.75, $CHCl_3$); FTIR ($CHCl_3$ cast) 3294, 2214, 1758, 1671 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (s, 9 H), 1.83 (quintet, J = 7.0 Hz, 2 H), 2.56 (t, J = 7.0 Hz, 2 H), 2.75−2.90 (m, 2 H), 3.75 (t, J = 6.0 Hz, 2 H), 3.98 (dd, J = 9.0, 6.0 Hz, 1 H), 4.18−4.26 (m, 1 H), 4.54 (t, J = 9.0 Hz, 1 H), 5.42 (br s, 1 H), 7.35−7.48 (m, 6 H), 7.63−7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7 (t), 19.2 (s), 26.8 (q), 30.4 (t), 48.0 (d), 50.3 (t), 62.0 (t), 69.2 (t), 80.4 (s), 96.6 (s), 127.7 (d), 129.7 (d), 133.5 (s), 135.5 (d), 158.6 (s), 184.2 (s); exact mass (electrospray) m/z calcd for $C_{26}H_{31}NNaO_4Si$ (M + Na) 472.1915, found 472.1913.

(2*R*)-6-[3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]propyl]-2,3-dihydro-2-(hydroxymethyl)-4(1*H*)-pyridinone (21c). Cs_2CO_3 (0.432 g, 1.33 mmol) was added in two portions (at start and after 20 min) to a stirred solution of **21b** (0.205 g, 0.456 mmol) in MeOH (9 mL). Stirring was continued for 1 h after the second addition and then at 80 °C for 3 h. The solution was cooled and evaporated. The residue was diluted with water (10 mL) and EtOAc (10 mL), and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the yellow residue over silica gel (2 × 10 cm), using 1:10 MeOH−EtOAc, gave **21c** (0.135 g, 70% yield) as a greasy solid: $[\alpha]^{25}_D$ −81.3 (c 0.57, $CHCl_3$); FTIR ($CHCl_3$ cast) 3263, 1602, 1570, 1524 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.07 (s, 9 H), 1.80 (quintet, J = 6.0 Hz, 2 H), 2.20−2.42 (m, 5 H), 3.61 (t, J = 11.0 Hz, 1 H), 3.66−3.78 (m, 4 H), 4.99 (s, 1 H), 5.57 (br s, 1 H), 7.35−7.48 (m, 6 H), 7.63−7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2 (s), 26.9 (q), 30.4 (t), 31.5 (t), 37.2 (t), 54.4 (d), 62.6 (t), 64.2 (t), 98.4 (d), 127.7 (d), 129.8 (d), 133.5 (s), 135.5 (d), 165.9 (s), 191.6 (s); exact mass (electrospray) m/z calcd for $C_{25}H_{33}NNaO_3Si$ (M + Na) 446.2122, found 446.2125.

(2*R*)-2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-6-[3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]propyl]-2,3-dihydro-4(1*H*)-pyridinone (21d). DMAP (8.3 mg, 0.067 mmol), Et_3N (0.15 mL, 1.1 mmol), and *t*-$BuMe_2SiCl$ (38.3 mg, 0.255 mmol) were added to a stirred solution of **21c** (90.1 mg, 0.212 mmol) in CH_2Cl_2 (4 mL), and stirring was continued overnight. The mixture was quenched with saturated aqueous $NaHCO_3$, and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 1:4 EtOAc−hexane, gave **21d** (86.5 mg, 78% yield) as a colorless oil: $[\alpha]^{25}_D$ −90.5 (c 1.40, $CHCl_3$); FTIR ($CHCl_3$ cast) 3244, 1612, 1578, 1531 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.08 (s, 3 H), 0.09 (s, 3 H), 0.91 (s, 9 H), 1.06 (s, 9 H), 1.75−1.82 (m, 2 H), 2.19 (dd, J = 16.5, 12.5 Hz, 1 H), 2.27−2.39 (m, 3 H), 3.60 (t, J = 10.5 Hz, 1 H), 3.64−3.75 (m, 4 H), 4.98 (s, 1 H), 5.18 (br s, 1 H), 7.36−7.47 (m, 6 H), 7.62−7.69 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.4 (q), −5.3 (q), 18.3 (s), 19.3 (s), 25.92 (q), 26.9 (q), 30.5 (t), 31.7 (t), 37.6 (t), 54.5 (d), 62.7 (t), 64.9 (t), 98.7 (d), 127.8 (d), 129.8 (d), 133.6 (s), 135.57 (d), 135.58 (d), 165.2 (s), 191.7 (s); exact mass (electrospray) m/z calcd for $C_{31}H_{47}NNaO_3Si_2$ (M + Na) 560.2987, found 560.2985.

(2*R*)-2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-6-[3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]propyl]-3,4-dihydro-4-oxo-1(2*H*)-pyridinecarboxylic Acid Phenylmethyl Ester (21e). *n*-BuLi (2.5 M in hexane, 60 μL, 0.15 mmol) was added dropwise to

(19) Baldwin, J. E.; Romeril, S. P.; Lee, V.; Claridge, T. D. W. *Org. Lett.* **2001**, *3*, 1145–1148.

a stirred and cooled (−78 °C) solution of **21d** (75.3 mg, 0.139 mmol) in THF (2 mL). Stirring at −78 °C was continued for 5 min, and CbzCl (25 μL, 0.177 mmol) was added in one lot. Stirring at −78 °C was continued for 15 min, and then MeOH (1 mL) and saturated aqueous NH_4Cl (5 mL) were added. The cooling bath was removed, and the mixture was allowed to warm to room temperature (ca. 15 min). The aqueous phase was extracted with EtOAc (2 × 10 mL), and the combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 1:8 EtOAc−hexane, gave **21e** (79.2 mg, 84%) as an oil: $[\alpha]^{25}_D$ +92.0 (*c* 1.08, $CHCl_3$); FTIR ($CHCl_3$ cast) 1725, 1669, 1596 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ −0.02 (s, 3 H), −0.01 (s, 3 H), 0.84 (s, 9 H), 1.06 (s, 9 H), 1.71 (quintet, J = 7.0 Hz, 2 H), 2.50−2.62 (m, 2 H), 1.74 (dd, J = 17.5, 6.5 Hz, 1 H), 3.01−3.10 (m, 1 H), 3.54−3.65 (m, 3 H), 3.72 (dd, J = 10.0, 7.0 Hz, 1 H), 4.80−4.85 (m, 1 H), 5.20 (AB q, J = 12.0, $\Delta\nu_{AB}$ = 27.5 Hz, 2 H), 5.42 (s, 1 H), 7.32−7.47 (m, 11 H), 7.62−7.69 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.6 (q), 18.1 (s), 19.2 (s), 25.7 (q), 26.9 (q), 31.3 (t), 32.4 (t), 37.3 (t), 56.8 (d), 60.1 (t), 62.9 (t), 68.7 (t), 112.5 (d), 127.7 (d), 128.5 (d), 128.65 (d), 128.70 (d), 129.6 (d), 133.7 (s), 135.1 (s), 135.5 (d), 153.1 (s), 158.7 (s), 192.9 (s); exact mass (electrospray) m/z calcd for $C_{39}H_{53}NNaO_5Si_2$ (M + Na) 694.3355, found 694.3353.

(2*R*,4*S*)-2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-6-[3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]propyl]-3,4-dihydro-4-hydroxy-1(2*H*)-pyridinecarboxylic Acid Phenylmethyl Ester (21f). $NaBH_4$ (8.3 mg, 0.216 mmol) was added to a stirred and cooled (−40 °C) slurry of **21e** (65.0 mg, 0.097 mmol) and $CeCl_3 \cdot 7H_2O$ (79.4 mg, 0.213 mmol) in MeOH (5 mL). Stirring at −40 °C was continued for 30 min, and the mixture was quenched with acetone (0.1 mL) and saturated aqueous NH_4Cl. The cold bath was removed and replaced by an ice bath, and stirring was continued for 30 min. The aqueous phase was extracted with Et_2O (2 × 10 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 4:1 hexane−EtOAc, gave **21f** (44.0 mg, 68% yield) as an oil, which was used directly in the next step.

(2*S*,6*R*)-6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2-[3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]propyl]-5,6-dihydro-2-(2-oxoethyl)-1(2*H*)-pyridinecarboxylic Acid Phenylmethyl Ester (21g). A mixture of **21f** (39.0 mg, 0.058 mmol), $Hg(OAc)_2$ (1.5 mg, 0.005 mmol), and Et_3N (1 drop) in *n*-butyl vinyl ether (2 mL) was heated at 110 °C (oil bath temperature) in a sealed glass tube (Teflon seal) for 36 h. Volatile material was evaporated, and flash chromatography of the residue over silica gel (1 × 10 cm), using 1:5 EtOAc−hexane, gave **21g** (28.6 mg, 69%) as a pale yellow oil: $[\alpha]^{25}_D$ −11.3 (*c* 0.35, $CHCl_3$); FTIR ($CHCl_3$ cast) 1722, 1700, cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ −0.04 (s, 3 H), −0.02 (s, 3 H), 0.85 (s, 9 H), 1.05 (s, 9 H), 1.35−1.46 (m, 2 H), 1.71−1.86 (m, 1 H), 2.10−2.24 (m, 2 H), 2.40−2.51 (m, 2 H), 3.41 (t, J = 10 Hz, 1 H), 3.42−3.51 (m, 1 H), 3.51−3.70 (m, 3 H), 4.30−4.40 (m, 1 H), 5.13 (AB q, J = 12.5, $\Delta\nu_{AB}$ = 19.0 Hz, 2 H), 5.59 (dd, J = 10.0, 2.5 Hz, 1 H), 5.88 (t, J = 10.5 Hz, 1 H), 7.26−7.46 (m, 11 H), 7.62−7.69 (m, 4 H), 9.59 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.5 (q), −5.4 (q), 18.2 (s), 19.2 (s), 23.8 (t), 25.8 (q), 26.9 (q), 27.6 (t), 35.1 (s), 51.3 (t), 52.3 (t), 58.6 (d), 63.4 (t), 63.5 (t), 67.1 (t), 123.8 (d), 127.7 (d), 127.9 (d), 128.1 (d), 128.5 (d), 128.6 (d), 129.6 (d), 131.8 (d), 133.9 (d), 135.5 (d), 136.4 (s), 149.4 (s), 154.9 (s), 201.4 (d); exact mass (electrospray) m/z calcd for $C_{41}H_{57}NNaO_5Si_2$ (M + Na) 722.3668, found 722.3669.

(4*R*)-4-[2-Hydroxy-4-(trimethylsilyl)-3-butyn-1-yl]-2-oxazolidinone (23a). *n*-BuLi (2.5 M in THF, 0.700 μL, 1.75 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of trimethylsilylacetylene (0.245 mL, 1.74 mmol) in THF (8 mL). Stirring at −78 °C was continued for 30 min, and a solution of **16** (0.150 g, 1.16 mmol) in THF (2 mL plus 1 mL as a rinse) was added dropwise. Stirring at −78 °C was continued for 1.5 h, and then saturated aqueous NH_4Cl (8 mL) and EtOAc (10 mL) were added. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 10 cm), using 1:2 EtOAc−hexane, gave **23a** (0.217 g, 82%) as a colorless oil which was a mixture of two isomers: FTIR ($CHCl_3$ cast) 3381, 3270, 2180, 1728 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.18 (s, 9 H), 1.82−2.30 (m, 2 H), 2.49 (br s, 0.5 H), 2.67 (br s, 0.5 H), 4.00−4.35 (m, 2 H), 4.50−4.65 (m, 2 H), 5.90 (br s, 0.5 H), 6.08 (br s, 0.5 H); exact mass (electrospray) m/z calcd for $C_{10}H_{17}NNaO_3Si$ (M + Na) 250.0870, found 250.0869.

(4*R*)-4-[2-Oxo-4-(trimethylsilyl)-3-butyn-1-yl]-2-oxazolidinone (23b). Activated MnO_2 (0.803 g, 9.24 mmol) was added to a stirred solution of **23a** (0.211 g, 0.928 mmol) in CH_2Cl_2 (20 mL). Stirring was continued for 2 h, and the slurry was filtered through a short pad of Celite (1.5 × 2 cm), using EtOAc (3 × 10 mL) as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm), using 1:4 EtOAc/hexane, gave **23b** (0.185 g, 89% yield) as an oil: $[\alpha]^{25}_D$ +20.0 (*c* 0.63, $CHCl_3$); FTIR ($CHCl_3$ cast) 3260, 3161, 2146, 1739, 1677 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.26 (s, 9 H), 2.93 (dd, J = 15.0, 6.0 Hz, 1 H), 2.99 (dd, J = 18.5, 8.0 Hz, 1 H), 4.02 (dd, J = 9.0, 6.0 Hz, 1 H), 4.26 (quintet, J = 6.0 Hz, 1 H), 4.57 (t, J = 9.0 Hz, 1 H), 5.67 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −0.9 (q), 48.0 (d), 50.3 (t), 69.3 (t), 100.8 (s), 101.1 (s), 158.8 (s), 183.9 (s); exact mass (electrospray) m/z calcd for $C_{10}H_{15}NNaO_3Si$ (M + Na) 248.0713, found 248.0712.

(2*R*)-2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2,3-dihydro-4(1*H*)-pyridinone (23d). Cs_2CO_3 (0.266 g, 0.817 mmol) was added in two portions (at start and after ca. 10 min) to a stirred solution of **23b** (46.2 mg, 0.205 mmol) in MeOH (8 mL). Stirring was continued for 1 h after the second addition and then at 80 °C. When the reaction was complete (6 h, TLC control), the solution was cooled and evaporated, and the residue (**23c**) was kept under oilpump vacuum for 2 h to remove MeOH completely.

DMAP (7.7 mg, 0.063 mmol), Et_3N (0.14 mL, 1.0 mmol) and *t*-$BuMe_2SiCl$ (62.2 mg, 0.408 mmol) were added to a stirred solution of the above crude **23c** in CH_2Cl_2 (5 mL), and stirring was continued overnight. The mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 1:1 EtOAc−hexane, gave **23d** (32.3 mg, 65% yield over the two steps) as an oil: $[\alpha]^{25}_D$ −203.5 (*c* 0.39, $CHCl_3$); FTIR ($CHCl_3$ cast) 3254, 1627, 1578 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.08 (s, 3 H), 0.09 (s, 3 H), 0.91 (s, 9 H), 2.29 (dd, J = 16.0, 13.0 Hz, 1 H), 2.34 (dd, J = 16.0, 5.5 Hz, 1 H), 3.62 (t, J = 10 Hz, 1 H), 3.71 (dd, J = 10.0, 4.0 Hz, 1 H), 3.71−3.80 (m, 1 H), 5.02 (d, J = 7.5 Hz, 1 H), 5.32 (br s, 1 H), 7.20 (t, J = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.5 (q), 18.3 (s), 25.8 (q), 38.3 (t), 54.6 (d), 64.9 (t), 99.6 (d), 150.6 (d), 191.9 (s); exact mass (electrospray) m/z calcd for $C_{12}H_{24}NO_2Si$ (M + H) 242.1571, found 242.1573.

(2*R*)-2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-3,4-dihydro-4-oxo-1(2*H*)-pyridinecarboxylic Acid Phenylmethyl Ester (23e). *n*-BuLi (2.5 M in hexane, 0.112 mL, 0.282 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of **23d** (61.2 mg, 0.253 mmol) in THF (3 mL). Stirring −78 °C was continued for 5 min, and CbzCl (47 μL, 0.33 mmol) was added in one lot. Stirring at −78 °C was continued for 15 min, and then hexane (5 mL) and saturated aqueous NH_4Cl (5 mL) were added. The cooling bath was removed, and the mixture was allowed to warm to room temperature (ca. 15 min). The aqueous

phase was extracted with EtOAc (3 × 5 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 × 8 cm), using 1:4 EtOAc−hexane, gave **23e** (73.9 mg, 78%) as an oil: $[\alpha]^{25}_D$ +32.4 (*c* 0.51, $CHCl_3$); FTIR ($CHCl_3$ cast) 1728, 1676, 1607 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ −0.01 (s, 6 H), 0.85 (s, 9 H), 2.03 (d, J = 17.0, Hz, 1 H), 2.80 (dd, J = 17.0, 7.5 Hz, 1 H), 3.62−3.74 (m, 2 H), 4.60−4.70 (m, 1 H), 5.18−5.41 (m, 3 H), 7.34−7.44 (m, 5 H), 7.72−7.88 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (one signal is missing) δ −5.6 (q), 18.2 (s), 25.7 (q), 36.9 (t), 54.2 (d), 61.7 (t), 69.0 (t), 107.3 (d), 128.5 (d), 128.6 (d), 128.7 (d), 128.8 (d), 135.0 (s), 141.7 (d), 192.4 (s); exact mass (electrospray) m/z calcd for $C_{20}H_{29}NNaO_4Si$ (M + Na) 398.1758, found 398.1758.

(2*R*,4*S*)-2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-3,4-dihydro-4-hydroxy-1(2*H*)-pyridinecarboxylic Acid Phenylmethyl Ester (23f). $NaBH_4$ (12.5 mg, 0.330 mmol) was added to a stirred and cooled (−40 °C) slurry of **23e** (62.3 mg, 0.166 mmol) and $CeCl_3 \cdot 7H_2O$ (123 mg, 0.330 mmol) in MeOH (4 mL). Stirring at −40 °C was continued for 1 h, and the mixture was quenched with acetone (0.1 mL) and saturated aqueous NH_4Cl. The cold bath was removed and replaced by an ice bath, and stirring was continued for 30 min. The aqueous phase was extracted with Et_2O (3 × 5 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 3:1 hexane−EtOAc, gave **23f** (50.3 mg, 81%) as an oil: $[\alpha]^{25}_D$ +2.9 (*c* 1.58, $CHCl_3$); FTIR ($CHCl_3$ cast) 3414, 1712, 1655 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) (signals broad due to the presence of rotamers) δ 0.003 (s, 6 H), 0.87 (s, 9 H), 1.45 (br s, 1 H), 1.55−1.75 (m, 1 H), 2.50 (dd, J = 12.0, 6.5 Hz, 1 H), 3.45−3.79 (m, 2 H), 4.20−4.40 (m, 1 H), 4.41−4.55 (m, 1 H), 4.80−5.00 (m, 1 H), 5.19 (AB q, J = 12.0, $\Delta\nu_{AB}$ = 20.5 Hz, 2 H), 6.73−6.95 (m, 1 H), 7.29−7.48 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.6 (q), 18.2 (s), 25.8 (q), 31.7 (t), 52.7 (d), 61.5 (t), 61.7 (d), 67.8 (t), 109.9 (d), 125.0 (d), 128.2 (d), 128.3 (d), 128.6 (d), 135.9 (s), 153.2 (s); exact mass (electrospray) m/z calcd for $C_{20}H_{31}NNaO_4Si$ (M + Na) 400.1915, found 400.1916.

(2*S*,6*R*)-6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-5,6-dihydro-2-(2-oxoethyl)-1(2*H*)-pyridinecarboxylic Acid Phenylmethyl Ester (23g). A mixture of **23f** (30.2 mg, 0.080 mmol), $Hg(OAc)_2$ (2.5 mg, 0.008 mmol), and Et_3N (1 drop) in *n*-butyl vinyl ether (1.5 mL) was heated at 110 °C (oil bath temperature) in a sealed glass tube (Teflon seal) for 36 h. Volatile material was evaporated, and flash chromatography of the residue over silica gel (1 × 10 cm), using 1:4 EtOAc−hexane, gave **23g** (21.3 mg, 66%) as a colorless oil: $[\alpha]^{25}_D$ +70.3 (*c* 053, $CHCl_3$); FTIR ($CHCl_3$ cast) 1701, 1404 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ −0.02 (s, 6 H), 0.85 (s, 9 H), 2.20−2.30 (m, 1 H), 2.35−2.52 (m, 1 H), 2.71 (dd, J = 17.0, 7.0 Hz, 1 H), 2.88−3.02 (m, 1 H), 3.44 (t, J = 9.0 Hz, 1 H), 3.45−3.64 (m, 1 H), 4.14−4.23 (m, 1 H), 4.52−4.61 (m, 1 H), 5.15 (q, J = 12.5 Hz, 2 H), 5.81−5.94 (m, 2 H), 7.29−7.42 (m, 5 H), 9.74 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.5 (q), −5.4 (q), 18.2 (s), 23.9 (t), 25.8 (q), 48.1 (t), 49.4 (d), 52.5 (d), 62.2 (t), 67.3 (t), 124.0 (d), 128.09 (d), 128.14 (d), 128.3 (d), 128.5 (d), 136.3 (s), 156.0 (d), 200.3 (d); exact mass (electrospray) m/z calcd for $C_{22}H_{33}NNaO_4Si$ (M + Na) 426.2071, found 426.2074.

(2*S*,6*R*)-6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-5,6-dihydro-2-[[(4-methoxyphenyl)methoxy]methyl]-2-(2-propenyl)-1(2*H*)-pyridinecarboxylic Acid Phenylmethyl Ester (40). $(Me_3Si)_2NLi$ (1.0 M in PhMe, 0.30 mL, 0.30 mmol) was added dropwise to a stirred and cooled (0 °C) solution of Ph_3PCH_3Br (0.113 g, 0.317 mmol) in THF (4 mL). Stirring at 0 °C was continued for 15 min, and a solution of **20g** (60.4 mg, 0.106 mmol) in THF (1 mL plus 2 mL as a rinse) was added dropwise. Stirring at 0 °C was continued for 45 min, and then saturated aqueous NH_4Cl (5 mL) and Et_2O (5 mL) were added. The aqueous phase was extracted with Et_2O (2 × 5 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 10 cm), using 1:5 EtOAc−hexane, gave **40** (50.1 mg, 85%) as a colorless oil: $[\alpha]^{25}_D$ −18.3 (*c* 0.68, $CHCl_3$); FTIR ($CHCl_3$ cast) 1700, 1670, 1613 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ −0.08 (s, 6 H), 0.84 (s, 9 H), 2.11 (dd, J = 14.0, 6.0 Hz, 2 H), 2.32 (dd, J = 17.0, 7.0 Hz, 1 H), 3.10−3.48 (m, 3 H), 3.54 (t, J = 10.0 Hz, 1 H), 3.80 (s, 3 H), 3.82−4.10 (m, 1 H), 4.26−4.42 (m, 3 H), 4.96 (d, J = 12.0 Hz, 2 H), 5.13 (s, 2 H), 5.60 (dd, J = 10.0, 3.0 Hz, 1 H), 5.58−5.71 (m, 1 H), 5.79−5.87 (m, 1 H), 6.84 (d, J = 8.5 Hz, 2 H), 7.17 (d, J = 8.5 Hz, 2 H), 7.27−7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.5 (q), 18.2 (s), 23.7 (t), 25.9 (q), 38.7 (t), 52.0 (d), 55.2 (q), 61.2 (t), 63.4 (t), 66.4 (t), 73.0 (t), 73.4 (s), 113.7 (d), 117.8 (t), 122.9 (d), 127.8 (d), 128.4 (d), 129.2 (d), 130.6 (s), 131.7 (d), 133.2 (d), 137.1 (s), 154.5 (s), 159.0 (s); exact mass (electrospray) m/z calcd for $C_{32}H_{45}NNaO_5Si$ (M + Na) 574.2959, found 574.2958.

(2*S*,6*R*)-6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-5,6-dihydro-2-(hydroxy-methyl)-2-(2-propenyl)-1(2*H*)-pyridinecarboxylic Acid Phenylmethyl Ester (41). DDQ (33.8 mg, 0.148 mmol) was added to a stirred and cooled (0 °C) mixture of **40** (40.9 mg, 0.074 mmol), CH_2Cl_2 (6.5 mL), and water (0.5 mL), and vigorous stirring was continued for 1.5 h. The mixture was diluted with saturated aqueous $NaHCO_3$ and Et_2O (5 mL). The aqueous phase was extracted with Et_2O (2 × 5 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 1:4 EtOAc−hexane, gave **41** (28 mg, 88% yield) as an oil: $[\alpha]^{25}_D$ −7.9 (*c* 0.18, $CHCl_3$); FTIR ($CHCl_3$ cast) 3448, 1700, 1666 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.03 (s, 6 H), 0.88 (s, 9 H), 1.96−2.10 (m, 2 H), 2.18−2.32 (m, 1 H), 3.10−3.30 (m, 1 H), 3.38−3.50 (m, 1 H), 3.52−3.64 (m, 3 H), 4.20 (d, J = 10.8 Hz, 1 H), 4.56−4.68 (m, 1 H), 4.88−4.99 (m, 2 H), 5.02−5.10 (m, 1 H), 5.24 (d, J = 12.5 Hz, 1 H), 5.50 (dd, J = 10.5, 3.2 Hz, 1 H), 5.54−5.67 (m, 1 H), 5.90 (t, J = 8.0 Hz, 1 H), 7.27−7.40 (m, 5 H); exact mass (electrospray) m/z calcd for $C_{24}H_{37}NNaO_4Si$ (M + Na) 454.2384, found 454.2387.

(2*S*,6*R*)-6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2-formyl-5,6-dihydro-2-(2-propenyl)-1(2*H*)-pyridinecarboxylic Acid Phenylmethyl Ester (42). Dess-Martin periodinane (70.8 mg, 0.167 mmol) was added to a stirred and cooled (0 °C) slurry of **41** (24.0 mg, 0.056 mmol) and $NaHCO_3$ (14.1 mg, 0.167 mmol) in CH_2Cl_2 (3 mL). Stirring at 0 °C was continued for 1 h, the cold bath was removed, and stirring was continued for 1 h. Brine (5 mL) and Et_2O (5 mL) were added, and the aqueous phase was extracted with Et_2O (2 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated, and the residue was passed through a short column of flash chromatography silica gel (2 × 5 cm), using 1:1 EtOAc−hexane, to afford crude **42**, which was used without characterization.

(2*S*,6*R*)-6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-5,6-dihydro-2-[1-hydroxy-2-propenyl]-2-(2-propenyl)-1(2*H*)-pyridinecarboxylic Acid Phenylmethyl Ester (43). Vinylmagnesium bromide (1.0 M in THF, 75 μL, 0.075 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **42** (21.8 mg, 0.048 mmol) in THF (5 mL). Stirring at 0 °C was continued for 1 h, and then saturated aqueous NH_4Cl (5 mL) and Et_2O (5 mL) were added. The aqueous phase was extracted with Et_2O (2 × 5 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. The crude product (**43**) was used in the next step without characterization.

(5*S*,7*R*)-7-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-1-hydroxy-6-azaspiro-[4,5]deca-2,9-diene Carboxylic Acid Phenylmethyl Ester (44). A solution of the above crude **43** and Grubbs second generation catalyst[20] (4.2 mg, 0.005 mmol) in CH_2Cl_2

(20) [1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium.

(4 mL) was refluxed for 8 h, and then evaporated. Flash chromatography of the residue over silica gel (1 × 8 cm), using 1:4 EtOAc−hexane, gave **44** (12.0 mg, 51% over three steps) as an oil which was a single isomer: $[\alpha]^{25}_{D}$ +22.4 (*c* 0.36, $CHCl_3$); FTIR ($CHCl_3$ cast) 3505, 1683, 1665 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ −0.010 (s, 3 H), −0.002 (s, 3 H), 0.86 (s, 9 H), 2.13 (dt, J = 17.6, 2.5 Hz, 1 H), 2.22−2.42 (m, 2 H), 3.23 (d, J = 8.0 Hz, 1 H), 3.58 (t, J = 10.0 Hz, 1 H), 3.65 (dd, J = 10.0, 4.0 Hz, 1 H), 3.67−3.77 (m, 1 H), 4.10 (d, J = 11.0 Hz, 1 H), 4.50−4.61 (m, 1 H), 5.14 (AB q, J = 12.4, $\Delta\nu_{AB}$ = 26.6 Hz, 2 H), 5.41 (dd, J = 10.0, 3.0 Hz, 1 H), 5.54−5.62 (m, 1 H), 5.81−5.86 (m, 1 H), 5.92−5.98 (m, 1 H), 7.27−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.4 (q), 18.2 (s), 23.6 (t), 25.9 (q), 44.2 (t), 51.7 (d), 62.0 (d), 62.7 (t), 67.3 (t), 84.3 (s), 117.0 (d), 128.0 (d), 128.1 (d), 128.5 (d), 131.6 (s), 132.8 (d), 132.9 (d), 136.4 (d), 157.8 (s); exact mass (electrospray) m/z calcd for $C_{24}H_{35}NNaO_4Si$ (M + Na) 452.2228, found 452.2230.

Acknowledgment. We thank Dr. D. Liu for exploratory experiments and NSERC for financial support.

Supporting Information Available: Experimental procedures and copies of NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.