JOC Article

Model Studies and First Synthesis of the Antifungal and Antibacterial Agent Cladobotryal

Derrick L. J. Clive* and Xiaojun Huang

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

derrick.clive@ualberta.ca

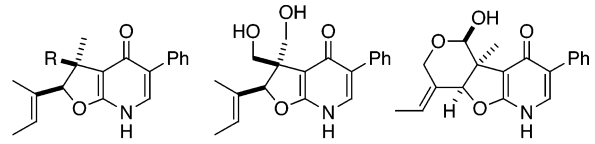
Received September 5, 2003

The antifungal and antibacterial agent cladobotryal (**1**) was synthesized by a convergent route from lactone **31** and aldehyde **13**, a key step in the elaboration of the pyridinone ring being conversion of a Boc group on nitrogen into a $CO_2SiPr\text{-}i_3$ group. The simple model compounds **9** and **10**, representing the core of cladobotryal and of **5**, respectively, were prepared as support studies for making the natural product.

Introduction

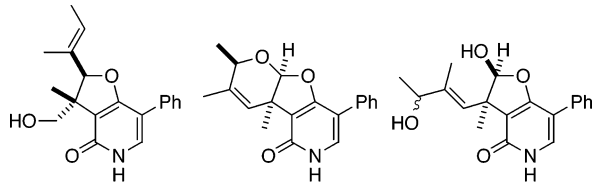
Cladobotryal (**1**), which is a metabolite of the fungus *Caldobotrium varium* Nees:Fries (CBS 331.95), was first described[1] in 1998 and reported to inhibit the growth of plant pathogens belonging to Oomyceta. Consequently, **1** may be useful as an agricultural fungicide.[2] A more recent publication[3] disclosed another potentially important biological property, as the compound was reported to show moderate activity against some drug-resistant bacteria such as methicillin-resistant *Staphylococcus aureus*. The related dihydrofuro[2,3-*b*]pyridinones **2**−**4** were isolated[3] from the same organism (*C. varium*, CL 12284), but the parent heterocyclic system is a rare structural type and examination of the Beilstein database shows no other dihydrofuro[2,3-*b*]pyridinones besides those that are benzo-fused.[4] The compounds **5**−**8** with the isomeric and better-known[5] dihydrofuro[3,2-*c*]pyridinone structure were also isolated[3] from *C. varium* (CL 12284). The absolute configuration of these furopyridines has not been established.

We give here full details of the first total synthesis of racemic **1**[6] as well as its naturally occurring congener **2**. Synthetic routes to the heterocyclic system represented by **1** had not been reported before our own work,[6] and



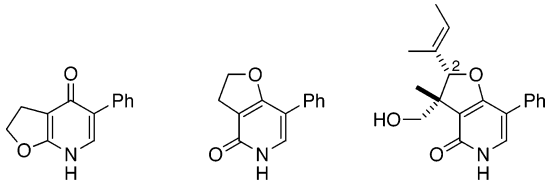
1 R = CHO
2 R = CH_2OH

3 **4**



5 **6** **7**, **8**

we also describe routes to the model compounds **9** and **10**, which represent the core structures of **1** and **5**, respectively; we have previously published[7] the synthesis of **11**, a C(2) epimer of (natural) **5**.



9 **10** **11**

Synthesis of model compounds 9 and 10. The route to **9**, the core of cladobotryal, is based on the two subunits γ-butyrolactone (**12**) and the known[8] β-amino aldehyde **13**, which we made (Scheme 1) by the sequence **19** → **18** → **13**, along lines reported[8] in the literature, but with minor modifications. We found it convenient to prepare the intermediate **19** by a route different from those

(1) Breinholt, J.; Jensen, H. C.; Kjær, A.; Olsen, C. E.; Rassing, B. R.; Rosendahl, C. N.; Søtofte, I. *Acta Chem. Scand.* **1998**, *52*, 631−634.

(2) Demuth, H.; Breinholt, J.; Rassing, B. R.; Roemer, B. WO 97/11076; *Chem. Abstr.* **1997**, *126*, 276432.

(3) Sakemi, S.; Bordner, J.; DeCosta, D. L.; Dekker: K. A.; Hirai, H.; Inagaki, T.; Kim, Y.-J.; Kojima, N.; Sims, J. C.; Sugie, Y.; Sugiura, A.; Sutcliffe, J. A.; Tachikawa, K.; Truesdell, S. J.; Wong, J. W.; Yoshikawa, N.; Kojima, Y. *J. Antibiot.* **2002**, *55*, 6−18. This publication assigns hydroxypyridine structures to **1** and **3**−**8**, but for simplicity, the pyridinone tautomers are used in this manuscript.

(4) E.g.: (a) Kappe, T.; Fritz, P. F.; Ziegler, E. *Ber.* **1973**, *106*, 1927−1942. See also (b) Goodwin, S.; Shoolery, J. N.; Johnson, L. F. *J. Am. Chem. Soc.* **1959**, *81*, 3065−3069. (c) Goodwin, S.; Smith, A. F.; Velasquez, A. A.; Horning, E. C. *J. Am. Chem. Soc.* **1959**, *81*, 6209−6213.

(5) E.g., 3,5-Dihydro-2*H*-furo[3, 2-*c*]pyridin-4-one (the parent system): Clark, B. A. J.; El-Bakoush, M. S.; Parrick, J. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1531−1536.

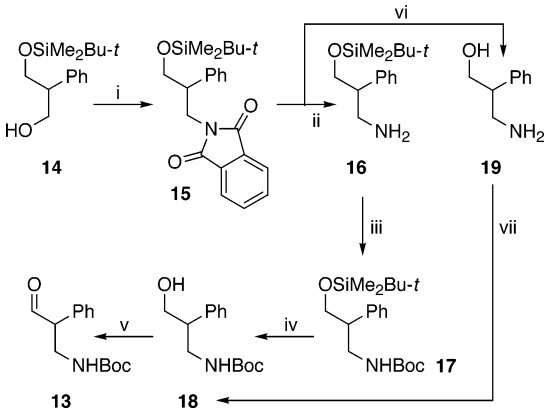
(6) Preliminary communication: Clive, D. L. J.; Huang, X. *Chem. Commun.* **2003**, 2062−2063.

(7) Clive, D. L. J.; Huang, X. *Tetrahedron* **2002**, *58*, 10243−10250.

(8) Campestrini, S.; Di Furia, F.; Modena, G. *J. Org. Chem.* **1990**, *55*, 3658−3660.

10.1021/jo030284g CCC: $27.50
Published on Web 02/12/2004

SCHEME 1[a]

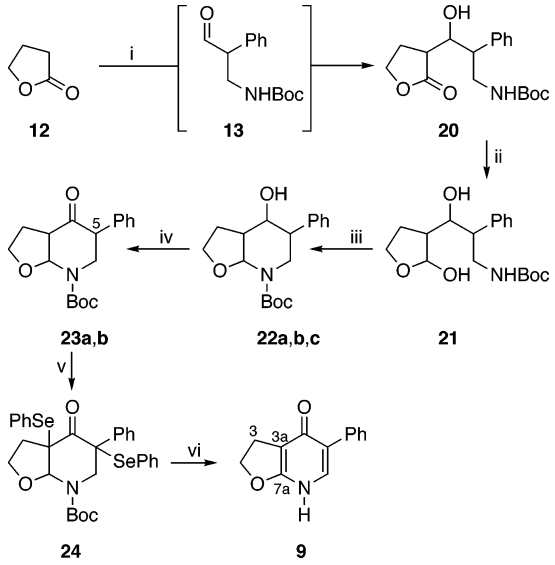


[a] Key: (i) phthalimide, DEAD, Ph_3P, THF, 91%; (ii) $N_2H_4 \cdot H_2O$, EtOH, 97%; (iii) Boc_2O, $NaHCO_3$, 4:1 acetone−water, 100%; (iv) Bu_4NF, THF, 74%; (v) Dess−Martin periodinane, CH_2Cl_2, 93%; (vi) $N_2H_4 \cdot H_2O$, EtOH, then HCl, 93%; (vii) Boc_2O, $NaHCO_3$, 4:1 acetone−water, 96%.

previously reported.[8,9] The readily available alcohol **14**[10] was converted (91%) into the phthalimide **15** under Mitsunobu conditions. Treatment with $N_2H_4 \cdot H_2O$ in EtOH liberated amine **16** (97%), which was protected (100%) as its *N*-Boc derivative (Boc_2O, aqueous acetone, $NaHCO_3$, **16** → **17**). Desilylation (Bu_4NF, 74%) and Dess−Martin oxidation (93%) afforded the required aldehyde **13**. The same compound was also made by a slightly shorter route in which phthalimide **15** was treated successively with $N_2H_4 \cdot H_2O$ and 5% hydrochloric acid to produce amino alcohol **19**[8,9] (93%), which was easily converted into **18**[8] (96%) by reaction with Boc_2O.

Deprotonation of γ-butyrolactone (**12**) and condensation (70%) with aldehyde **13** (Scheme 2) served to link the two subunits, the product (**20**) being obtained as a mixture of stereoisomers. Reduction of the lactone carbonyl (DIBALH, 99%, **20** → **21**) then set the stage for the key ring closure (**21** → **22a**−**c**). This was accomplished efficiently (83%) by exposure to pyridinium *p*-toluenesulfonate at room temperature. The cyclization product was separated into two fractions; one was a single isomer (**22a**) and the other a mixture of two isomers (**22b**,**c**). The stereochemistry of these materials was not established, and the fractions were individually subjected to Dess−Martin oxidation so as to produce a single ketone from each fraction. These ketones (**23a**,**b**) must differ in stereochemistry at C(5). To introduce the two double bonds (cf. **9**), a mixture of the ketones was deprotonated with $(Me_3Si)_2NK$ at 0 °C, treated with PhSeCl at −78 °C, deprotonated again in situ (0 °C), and quenched once more at −78 °C with PhSeCl. This sequence of operations gave bis-selenides **24** (62%), which were not fully characterized. On oxidation with $NaIO_4$ in aqueous methanolic $NaHCO_3$, double selenoxide fragmentation occurred as well as loss of the Boc group,

SCHEME 2[a]



[a] Key: (i) LDA, THF, HMPA, 70%; (ii) DIBALH, CH_2Cl_2, 99%; (iii) TsOH·pyridine, THF, 83% (36% for **22a**, 47% for **22b**,**c**); (iv) Dess−Martin periodinane, CH_2Cl_2, 79% for **23a**, 82% for **23b**; (v) $(Me_3Si)_2NK$, PhSeCl, $(Me_3Si)_2NK$, PhSeCl, THF, 62%; (vi) $NaIO_4$, $NaHCO_3$, MeOH, water, 42%.

affording (42%) the desired core structure of cladobotryal (**24** → **9**). We did not establish if the C(3a)−C(7a) double bond of **9** was formed directly or resulted by isomerization of an initially formed 3,3a-double bond.[11]

While the ^1H and ^{13}C NMR spectra of **9**[12] were compatible with the assigned structure, they were not, by themselves, sufficient to exclude structure **10**. The latter was unlikely, of course, when the synthetic route to **9** is taken into account; nonetheless, we confirmed our assignment by synthesizing **10**; fortunately, its structure could be proved by X-ray analysis. We used this indirect approach, as we were unable to obtain suitable crystals of **9** to analyze directly.

Compound **10** was prepared by the route shown in Scheme 3. This route is similar to one we had used previously[7] in work that led to **11**. Deprotonation of γ-butyrolactone (**12**) and condensation with the known aldehyde **25**[13] gave **26** as a mixture of two stereoisomers (77%), and Dess−Martin oxidation then afforded (72%) the derived ketone **27**, which exists largely in the keto form shown (keto/enol = ca. 9:1). Treatment with aqueous ammonia brought about a number of changes that resulted in isolation of the chromatographically inseparable lactams **28** (44%). These were dehydrated by heating in the presence of TsOH (**28** → **29**, 80%). Finally, dehydrogenation with DDQ in refluxing PhH gave **10** (36%)—the core of structure **5**—and the product (**30**) of further dehydrogenation (53%). The two compounds were

(9) (a) Testa, E.; Fontanella, L.; Cristiani, G. F.; Mariani, L. *Liebigs Ann.* **1961**, *639*, 166−180. (b) Secor, H. V.; Sanders, E. B. *J. Org. Chem.* **1978**, *43*, 2539−2541. (c) Gensler, W. J.; Dheer, S. K. *J. Org. Chem.* **1981**, *46*, 4051−4057.

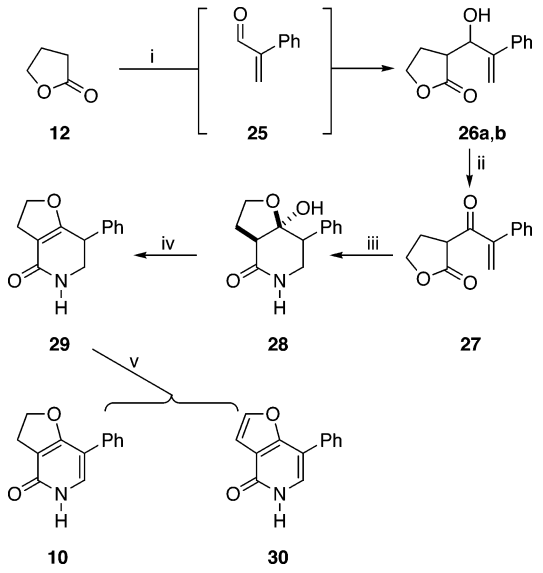
(10) (a) Yuasa, Y.; Fujimaki, N.; Yokomatsu, T.; Ando, J.; Shibuya, S. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3577−3584. (b) Guanti, G.; Narisano, E.; Podgorski, T.; Thea, S.; Williams, A. *Tetrahedron* **1990**, *46*, 7081−7090.

(11) Selenoxide elimination generally occurs away from oxygen, but for nitrogen (the present case) that tendency appears to be weaker: Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049−1132 (see, especially p 1104).

(12) Since some of the expected ^{13}C NMR signals of **9** could not be detected, we prepared the corresponding *O*-(*tert*-butyldimethylsilyl) derivative, for which all the expected ^{13}C NMR signals could be seen (see the Supporting Information).

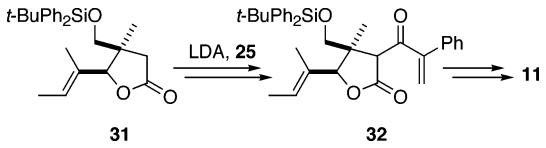
(13) Newman-Evans, R. H.; Simon, R. J.; Carpenter, B. K. *J. Org. Chem.* **1990**, *55*, 695−711. We used the Dess−Martin reagent for the final oxidation to the aldehyde.

SCHEME 3[a]



[a] Key: (i) LDA, THF, HMPA, 77%; (ii) Dess−Martin periodinane, CH_2Cl_2, 72%; (iii) NH_4OH, NH_4Cl, MeOH, 44%; (iv) TsOH, PhMe, heat, 80%; (v) DDQ, PhH, heat, 36% of **10**, 53% of **30**, 10% of **29**.

SCHEME 4



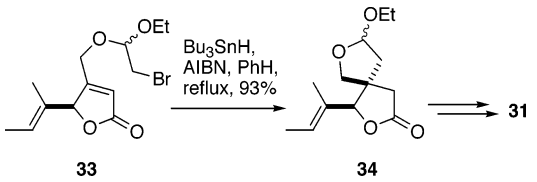
separated by flash chromatography, and the structure of **10** was established by single-crystal X-ray analysis, which showed that the crystalline material exists in the pyridinone form.

The methods used to make pyridinones **9** and **10** should be applicable to a number of derivatives, especially those in which the phenyl substituent has been modified, but we have not tested this possibility.

Synthesis of Racemic Cladobotryal (1). In exploratory work[7] leading to **11**, we had condensed the substituted lactone **31** with the simple aldehyde **25** (see Scheme 4). Our route to cladobotryal is also convergent and is based on the same γ-lactone, which was destined to provide the dihydrofuran segment of the natural product. We made many efforts to divert intermediates obtained from **31** and **25** (and also from **12** and **25**) into the cladobotryal system, but well before we had exhausted our plans to this end, it had became clear that an acceptable route would be most easily found by using, instead of **25**, an aldehyde carrying both the phenyl substituent and a suitably protected nitrogen β to the carbonyl group. In the event, several such aldehydes had to be tried before we established through the model studies described above (see Scheme 2) that **13** is a satisfactory one.

As described earlier,[7] lactone **31** was made by radical cyclization of **33**, and the product **34** was elaborated into **31** (Scheme 5). The radical cyclization **33** → **34** is stereoselective; the radical approaches the double bond from the face opposite to the adjacent substituent, thereby generating the required relative stereochemistry.

SCHEME 5



Deprotonation of lactone **31** (3 equiv LDA, THF) and addition of a mixture of aldehyde **13** (1.5 equiv) and HMPA (1.5 equiv) in THF gave the expected condensation product **35** as a mixture of isomers in 71% yield [100% after correction for recovered starting lactone (29%)]. DIBALH reduction generated the corresponding lactols (**35** → **36**, ca. 100%), and these could be cyclized in the required manner (**36** → **37**) under mildly acidic conditions (pyridinium *p*-toluenesulfonate). The product was isolated as two fractions, the chromatographically faster-moving fraction (**37a**) being obtained in 54% yield, and the slower-moving fraction (**37b**) in 27% yield. NMR measurements showed that each fraction was a single isomer, but the stereochemistry was not determined. Oxidation to the corresponding ketones was achieved with the Dess−Martin reagent (96% for **38a**; 85% for **38b**). Each ketone was a single isomer differing in stereochemistry at C(5).

Double phenylselenation of **38a** (**38b** was not examined), as in the model series (cf. Scheme 2, **23a**,**b** → **24**), was not successful, but introduction of the first of the required double bonds (**38a** and **38b** → **39**) could be achieved by phenylselenation [$(Me_3Si)_2NK$, THF, PhSeCl] and selenoxide elimination (H_2O_2, pyridine, CH_2Cl_2). However, the product **39** had the unexpected and unwelcome property of resisting further desaturation to **40**. Phenylselenation of **39** at C(3a) now proved impossible [LDA or $(Me_3Si)_2NK$, followed by PhSeCl], probably because severe steric crowding blocks access to C(3a). Phenylselenation of **39** after desilylation also failed, and introduction of a PhSe group at the eventual C(3a) position by selenation of lactone **31** *before* condensation with **13** was also unsuitable, because lactone reduction (cf. **35** → **36**, Scheme 6) after the condensation was accompanied by loss of the selenium group. Dehydrogenation of **39** using DDQ, Pd/C, MnO_2, $(NH_4)_2Ce(NO_3)_6$,[14] Ph_3CPF_6,[15] or $[PhSe(O)]_2O$, in some cases,[16] under a variety of conditions, was equally unsuccessful.

At this stage, we considered that removal of the *N*-Boc group would provide an alternative method (see below) for introducing the C(3a)−C(7a) double bond; however, attempted deprotection of the nitrogen of **39**, using CF_3CO_2H or bromocatecholborane, caused decomposition, and so we were forced to explore several modified versions of our route.

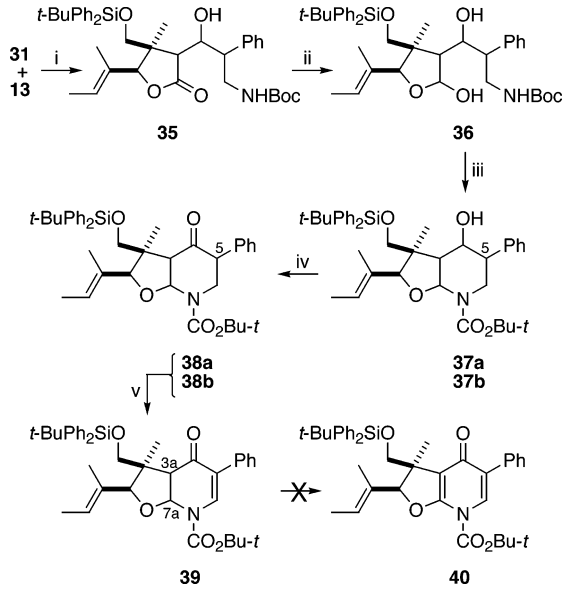
During these studies, we tried to protect the hydroxy of **35** as its triisopropylsilyl ether (*i*-$Pr_3SiOSO_2CF_3$, 2,6-lutidine), but found instead that the Boc group was

(14) Cf. Pfister, J. R. *Synthesis* **1990**, 689−690.

(15) Cf. Shu, C.; Alcudia, A.; Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2001**, *123*, 12477−12487.

(16) DDQ, PhH, reflux; Pd/C, xylene, reflux or PhOPh at 220 °C.; MnO_2, xylene, reflux; DDQ, CF_3CO_2H, PhMe, 80 °C.; $(NH_4)_2Ce(NO_3)_6$, water-acetone or MeCN.; $(NH_4)_2Ce(NO_3)_6$, 2,6-pyridinedicarboxylic acid *N*-oxide, water-MeCN.; Ph_3CPF_6, CH_2Cl_2; DDQ, $Me_3SiOSO_2CF_3$, PhH.; $[PhSe(O)]_2O$, PhMe, reflux.

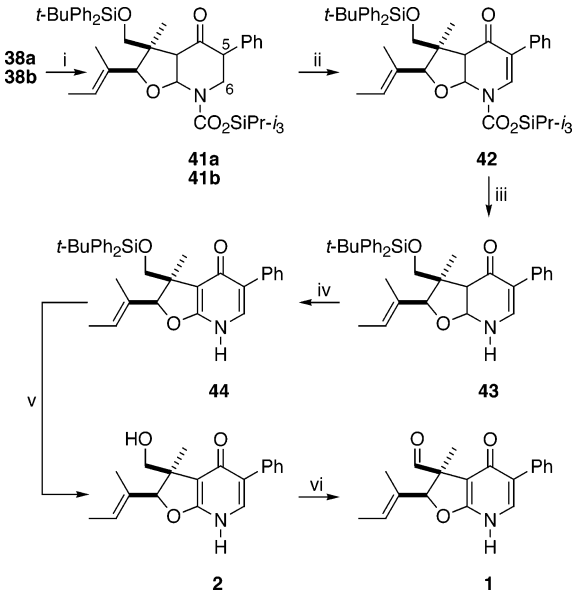
SCHEME 6[a]



[a] Key: (i) 3 equiv of LDA, THF, −78 °C, then room temperature; then add **13** in THF−HMPA at −78 °C, 71%, recovery of **31** = 29%; (ii) DIBALH, CH_2Cl_2, −78 °C, ca. 100%; (iii) TsOH·pyridine, THF, 45 °C, 54% of **37a**, 27% of **37b**; (iv) Dess−Martin periodinane, CH_2Cl_2, 96% for **37a**, 85% for **37b**; (v) (a) $(Me_3Si)_2NK$, THF, 0 °C, then PhSeCl, −78 C, (b) H_2O_2, pyridine, CH_2Cl_2, 74% overall for **38a**, 24% (not optimized) for **38b**.

converted into a $CO_2SiPr\text{-}i_3$ group before the hydroxy itself was silylated. The analogous conversion of *N*-Boc into *N*-$COOSiMe_2Bu\text{-}t$ has in fact been observed before, with $t\text{-}BuMe_2SiOSO_2CF_3$,[17] and our own experimental observation prompted us to treat **38a** and **38b** with $i\text{-}Pr_3SiOSO_2CF_3$. In the event, this was the key reaction that allowed us to bypass the barriers that had earlier thwarted introduction of the C(3a)−C(7a) double bond. Both **38a** and **38b** were converted quantitatively into the silyl carbamates **41a** and **41b**, respectively (Scheme 7). Each carbamate could be desaturated at C(5)−C(6) by phenylselenation and selenoxide elimination, under the conditions we had used to make **39**. The crude products (**42**) from **41a** and **41b** were identical, of course, although not very stable to chromatography over silica or alumina. The nitrogen protecting group could now be removed under nonacidic conditions (Bu_4NF, THF) to afford **43** (53% overall from **41a**, 49% overall from **41b**). Compound **43**, which was stable to flash chromatography over silica gel, provided an opportunity to generate an imine that would be expected to tautomerize spontaneously to **44**. Several methods are available for converting a CH−NH unit into an imine,[18] but the classical procedure[18b] of *N*-chlorination (*t*-BuOCl)[19] and base treatment (DBU), with which we had had direct experience several years ago,[20] again proved satisfactory (71%), and served to generate pyridinone **44**. Cladobotryal (**1**) was then easily reached via the natural product **2** by desilylation (Bu_4NF, THF, 97%) and Dess−Martin oxidation (**2** → **1**, 97%).

SCHEME 7[a]



[a] Key: (i) $i\text{-}Pr_3SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, reflux, 100% for both **38a** and **38b**; (ii) (a) $(Me_3Si)_2NK$, THF, −78 °C, PhSeCl, −78 C, (b) H_2O_2, pyridine, CH_2Cl_2; (iii) Bu_4NF, THF, 0 °C, 53% overall for **41a**, 49% for **41b**; (iv) (a) *t*-BuOCl, CH_2Cl_2, −78 °C, (b) DBU, PhMe, 71%; (v) Bu_4NF, THF, 97%; (vi) Dess−Martin, CH_2Cl_2, 97%.

The ^1H and ^{13}C NMR spectra of our racemic materials matched those reported for the natural products.

Conclusion

Our route to **1** provides the first method for making this natural product. The approach should also work to generate simple analogues in which the phenyl group is substituted, but we have not tried to do this. Replacement of an *N*-Boc group by *N*-$CO_2SiPr\text{-}i_3$, and related interconversions, may be generally useful where standard methods for Boc removal do not work—as found in the present synthesis. We expect that the method we have used to generate the second double bond of the pyridinone has general promise in cases where more traditional methods of dehydrogenation fail.

Experimental Section

Hexahydro-4-oxo-5-phenyl-3a,5-bis(phenylselanyl)furo-[2,3-*b*]pyridine-7-carboxylic Acid *tert*-Butyl Ester (24). $(Me_3Si)_2NK$ (0.5 M in PhMe, 0.430 mL, 0.215 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of ketones **23a**,**b** (65.0 mg, 0.205 mmol) in THF (4 mL). After 10 min,

(17) (a) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870−876. (b) Grieco, P. A.; Perez-Medrano, A. *Tetrahedron Lett.* **1988**, *29*, 4225−4228. (c) Busqué, F.; de March, P.; Figueredo, M.; Font, J.; Gallagher, T.; Milán, S. *Tetrahedron: Asymmetry* **2002**, *13*, 437−445. (d) Cf. Brosius, A. D.; Overman, L. E.; Schwink, L. *J. Am. Chem. Soc.* **1999**, *121*, 700−709.

(18) (a) Cf. Dayagi, S.; Degani, Y. In *The Chemistry of the Carbon−Nitrogen Double Bond*; Patai, S., Ed.; Interscience: New York, 1970; pp 117−120. (b) Bachmann, W. E.; Cava, M. P.; Dreiding, A. S. *J. Am. Chem. Soc.* **1954**, *76*, 5554−5555. (c) Cava, M. P.; Vogt, B. R. *Tetrahedron Lett.* **1964**, 2813−2816. (d) Cornejo, J. J.; Larson, K. D.; Mendenhall, G. D. *J. Org. Chem.* **1985**, *50*, 5382−5383 and references therein. (e) Reviews: Hoffman, R. V.; Bartsch, R. A.; Cho, B. R. *Acc. Chem. Res.* **1989**, *22*, 211−217. (f) Pawlenko, S. In *Methoden der Organischen Chemie (Houben-Weyl)*; Georg Thieme Verlag: Stuttgart, 1990; Vol. E14b, pp 226−233.

(19) (a) Mintz, M. J.; Walling, C. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 184−187. (b) **Hazard warning**: *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 183−184.

(20) Clive, D. L. J.; Bo, Y.; Tao, Y.; Daigneault, S.; Wu, Y.-J.; Meignan, G. *J. Am. Chem. Soc.* **1998**, *120*, 10332−10349.

the cold bath was replaced by an ice bath, and stirring was continued for 15 min. The mixture was recooled to −78 °C, and a solution of PhSeCl (41.0 mg, 0.214 mmol) in THF (2 mL) was injected dropwise. After 15 min at −78 °C, the mixture was again transferred to an ice bath, and stirring was continued for 15 min. The mixture was recooled to −78 °C, and $(Me_3Si)_2NK$ (0.5 M in PhMe, 0.615 mL, 0.308 mmol) was then added dropwise. Stirring at −78 °C was continued for 10 min and, as before, at 0 °C for 15 min. Finally, the mixture was cooled to −78 °C, and a solution of PhSeCl (62.0 mg, 0.324 mmol) in THF (2 mL) was injected dropwise. After 1 h at −78 °C, the mixture was quenched with saturated aqueous NH_4Cl (1 mL), diluted with Et_2O (50 mL), and washed with saturated aqueous NH_4Cl (twice) and brine. The organic phase was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 25 cm), using 1:5 EtOAc−hexane, gave **24** (80 mg, 62%) as a yellow oil, which was used the same day: exact mass (electrospray) *m*/*z* calcd for $C_{30}H_{31}NNaO_4{}^{80}Se_2$ 652.04757, found 652.04718.

3,7-Dihydro-5-phenyl-2*H*-furo[2,3-*b*]pyridin-4-one (9). $NaHCO_3$ (24.0 mg, 0.286 mmol) and $NaIO_4$ (140 mg, 0.655 mmol) were added to a vigorously stirred solution of **24** (90.5 mg, 0.144 mmol) in 6:1 MeOH−water (7 mL). After 5.5 h, the mixture was diluted with EtOAc (50 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL), and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (0.7 × 20 cm), using 1:40 MeOH−CH_2Cl_2, gave **9** (12.8 mg, 42%) as a white solid: mp 195−198 °C; FTIR (MeOH-acetone, cast) 2918, 2463, 1646, 1605, 1577, 1550, 1501 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 3.19 (t, J = 8.7 Hz, 2 H), 4.69 (t, J = 8.7 Hz, 2 H), 7.27−7.32 (m, 1 H), 7.34−7.41 (m, 2 H), 7.44−7.48 (m, 2 H), 7.54 (s, 1 H), ^{13}C NMR (CD_3OD, 100.6 MHz) (four signals are not observed in this spectrum) δ 26.9 (t), 72.5 (t), 106.3 (s), 128.2 (d), 129.2 (d), 130.4 (d), 136.6 (s); exact mass *m*/*z* calcd for $C_{13}H_{11}NO_2$ 213.07898, found 213.07862.

To obtain a ^{13}C NMR spectrum showing all the expected signals, compound **9** was silylated on oxygen, as described in the next experiment.

Dihydro-3-(1-hydroxy-2-phenyl-2-propenyl)furan-2-one (26a,b). BuLi (2.5 M in hexanes, 4.0 mL, 10 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2-NH (1.4 mL, 10 mmol) in THF (20 mL). Stirring at 0 °C was continued for 15 min, and the solution was then cooled to −78 °C. A solution of **12** (0.75 mL, 0.98 mmol) in THF (12 mL) was then added dropwise. The mixture was stirred at −78 °C for 90 min, and freshly made aldehyde **25**[13] (435 mg, 3.28 mmol) in THF (12 mL) was added dropwise. Stirring at −78 °C was continued for 1 h, and saturated aqueous NH_4Cl (10 mL) was added, followed by EtOAc (100 mL). The cooling bath was removed, and stirring was continued for 30 min. The mixture was washed with saturated aqueous NH_4Cl and brine, and the organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 30 cm), using 2:5 EtOAc−hexane, gave **26** as two isomers: isomer **26a** (less polar, 35 mg, 5%) was obtained as a liquid and isomer **26b** (more polar, 515 mg, 72%) as a solid.

Isomer **26a**: FTIR (CH_2Cl_2, cast) 3455, 3055, 2989, 2915, 1758, 1634, 1598, 1574; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.90 (dddd, J = 12.8, 9.6, 7.5, 3.3 Hz, 1 H), 2.34 (dq, J = 12.8, 9.6 Hz, 1 H), 2.39 (d, J = 4.0 Hz, 1 H), 2.64 (dt, J = 2.4, 9.6 Hz, 1 H), 4.11 (dt, J = 7.5, 8.9 Hz, 1 H), 4.33 (dt, J = 3.3, 8.9 Hz, 1 H); 5.34 (br s, 1 H), 5.39 (t, J = 1.3 Hz, 1 H), 5.51 (t, J = 1.5 Hz, 1 H), 7.27−7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.0 (t), 43.8 (d), 67.2 (t), 70.0 (d), 113.3 (t), 126.6 (d), 128.2 (d), 128.7 (d), 138.9 (s), 148.7 (s), 178.6 (s); exact mass *m*/*z* calcd for $C_{13}H_{14}O_3$ 218.09430, found 218.09472.

Isomer **26b**: mp 77−79 °C; FTIR (CH_2Cl_2, cast) 3477, 2988, 2914, 1749 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.77−2.04 (m, 2 H), 2.67 (dt, J = 11.2, 9.0 Hz, 1 H), 4.06 (ddd, J = 10.2, 9.0, 6.7 Hz, 1 H), 4.27 (dt, J = 2.2, 8.9 Hz, 1 H), 4.39 (s, 1 H), 4.65 (d, J = 8.9 Hz, 1 H), 5.41 (d, J = 1.1 Hz, 1 H), 5.44 (s, 1 H), 7.25−7.37 (m, 3 H), 7.46−7.53 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.1 (t), 43.6 (d), 67.0 (t), 75.8 (d), 117.3 (t), 127.7 (d), 128.0 (d), 128.4 (d), 139.1 (s), 147.8 (s), 179.8 (s); exact mass *m*/*z* calcd for $C_{13}H_{14}O_3$ 218.09430, found 218.09471.

Dihydro-3-(1-oxo-2-phenyl-2-propenyl)furan-2-one (27). Dess−Martin reagent (444 mg, 1.05 mmol) was added in one portion to a stirred solution of **26a**,**b** (mixture of isomers) (0.176 g, 0.806 mmol) in CH_2Cl_2 (18 mL). The mixture was stirred for 1 h, diluted with Et_2O (50 mL), washed with 1:1 saturated aqueous $NaHCO_3$−10% aqueous $Na_2S_2O_3$, and brine, dried (Na_2SO_4), and evaporated. Flash chromatography the residue over silica gel (1.5 × 20 cm), using CH_2Cl_2, gave **27** (125 mg, 72%) as an oil: FTIR (CH_2Cl_2, cast) 3057, 2991, 2917, 1767, 1682, 1575 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.41 (dddd, J = 12.8, 9.2, 8.0, 6.3 Hz, 1 H), 2.72 (ddt, J = 12.8, 8.0, 6.3 Hz, 1 H), 4.27−4.36 (m, 2 H), 4.43 (ddd, J = 8.8, 8.0, 6.3 Hz, 1 H), 6.16 (s, 1 H), 6.35 (s, 1 H), 7.28−7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.2 (t), 48.3 (d), 67.5 (t), 128.2 (d), 128.36 (d), 128.4 (d), 128.8 (s), 136.3 (s), 147.9 (t), 172.7 (s), 194.8 (s); exact mass *m*/*z* calcd for $C_{13}H_{12}O_3$ 216.07864, found 216.07823.

In earlier separate experiments, the individual isomers of **26** each gave **27**, under the above conditions, but in lower yield (ca 65%).

Hexahydro-7a-hydroxy-7-phenylfuro[3,2-*c*]pyridin-4-one (28). NH_4Cl (890 mg, 16.6 mmol) and concentrated (28−30% w/w) ammonia solution (13 mL) were added successively to a stirred solution of **27** (420 mg, 1.94 mmol) in MeOH (50 mL), and stirring was continued for 1 h. The mixture was then placed in a preheated oil bath set at 50 °C, and stirring was continued for 1 h. The mixture was cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (2 × 25 cm), using 1:25 MeOH−CH_2Cl_2, gave **28** (200 mg, 44%) as an oil, which was a mixture of two isomers: FTIR (CH_2Cl_2, cast) 3304, 2891, 1660 cm^{-1}; the ^1H NMR spectrum was too complex to be of diagnostic value; ^{13}C NMR ($CDCl_3$, 50.3 MHz) (signals for both isomers) δ 28.8 (t), 29.2 (t), 42.4 (t), 43.7 (t), 48.5 (d), 50.3 (d), 51.2 (d), 51.5 (d), 66.7 (t), 67.3 (t), 103.5 (s), 104.4 (s), 128.0 (d), 128.2 (d), 128.7 (d), 128.8 (d), 129.0 (d), 129.9 (d), 135.2 (s), 135.7 (s), 173.2 (s), 173.5 (s); exact mass *m*/*z* calcd for $C_{13}H_{15}NO_3$ 233.10519, found 233.10471.

3,5,6,7-Tetrahydro-7-phenyl-2*H*-furo[3,2-*c*]pyridin-4-one (29). $TsOH\cdot H_2O$ (24.0 mg, 0.139 mmol) was added to a stirred solution of **28** (mixture of isomers) (65.0 mg, 0.279 mmol) in PhMe (30 mL), and the mixture was stirred at 115 °C (oil bath) for 5 h, cooled and evaporated. Flash chromatography the residue over silica gel (1.5 × 15 cm), using 1:30 MeOH−CH_2Cl_2, gave **29** (48 mg, 80%) as a white solid: mp 165−166 °C; FTIR ($CDCl_3$, cast) 3216, 3062, 2870, 1671, 1637 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.88−3.06 (m, 2 H), 3.45 (dd, J = 14.0, 8.8 Hz, 1 H), 3.73−3.81 (m, 2 H), 4.51−4.63 (m, 2 H), 5.62 (br s, 1 H), 7.21−7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.8 (t), 40.4 (d), 47.3 (t), 73.1 (t), 106.0 (s), 127.8 (d), 127.9 (d), 128.9 (d), 137.2 (s), 168.0 (s), 170.0 (s); exact mass *m*/*z* calcd for $C_{13}H_{13}NO_2$ 215.09464, found 215.09507.

3,5-Dihydro-7-phenyl-2*H*-furo[3,2-*c*]pyridin-4-one (10) and 7-Phenyl-5*H*-furo[3,2-*c*]pyridin-4-one (30). DDQ (75.0 mg, 0.330 mmol) was added to a stirred solution of **29** (48.0 mg, 0.223 mmol) in PhH (40 mL). The mixture was lowered into a preheated oil bath set at 85 °C, stirred for 3 days, cooled to room temperature, and evaporated. The residue was dissolved in EtOAc (100 mL), and the solution was washed with 5% NaOH (20 mL) and brine (20 mL). The aqueous phase was extracted with EtOAc (3 × 40 mL). All the organic extracts were combined, dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (1.5 × 35 cm), using 1:30 to 1:10 MeOH−CH_2Cl_2, gave **10** (17 mg, 36%), **30** (25 mg, 53%) and starting material (**29**) (5 mg, 10%).

Compound **10**: mp 242−244 °C; FTIR (CH_2Cl_2 cast) 2927, 2850, 1655, 1597, 1576, 1566, 1502 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 3.15 (t, J = 9.2 Hz, 2 H), 4.74 (t, J = 9.2 Hz, 2 H),

7.28−7.34 (m, 1 H), 7.36−7.43 (m, 2 H), 7.45 (s, 1 H), 7.49−7.54 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 27.0 (t), 73.6 (t), 109.8 (s), 111.1 (s), 127.7 (d), 127.9 (d), 128.9 (d), 133.7 (s), 134.3 (d), 163.1 (s), 167.8 (s); exact mass *m*/*z* calcd for $C_{13}H_{11}NO_2$ 213.07898, found 213.07930. The structure was confirmed by single-crystal X-ray analysis.

Compound **30**: mp 195−197 °C; FTIR ($CDCl_3$, cast) 3106, 3050, 1665, 1598, 1556, 1523 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.09 (d, J = 2.1 Hz, 1 H), 7.33−7.50 (m, 3 H), 7.52 (s, 1 H), 7.62 (d, J = 2.1 Hz, 1 H), 7.64−7.71 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 106.9 (d), 112.2 (s), 116.1 (s), 127.5 (d), 127.9 (d), 128.3 (d), 128.9 (d), 132.5 (s), 143.8 (d), 158.9 (s), 161.6 (s); exact mass *m*/*z* calcd for $C_{13}H_9NO_2$ 211.06332, found 211.06346.

[3-[(4*R,5*S**)-4-[(*tert*-Butyldiphenylsilanyl)oxymethyl]-tetrahydro-4-methyl-5-[(1*E*)-1-methyl-1-propenyl]-2-oxofuran-3-yl]-3-hydroxy-2-phenylpropyl]carbamic Acid *tert*-Butyl Ester (35).** BuLi (2.5 M in hexanes, 1.6 mL, 4.0 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (0.55 mL, 3.9 mmol) in THF (16 mL). Stirring at 0 °C was continued for 15 min, and the solution was then cooled to −78 °C. A solution of **31** (0.5520 g, 1.306 mmol) in THF (16 mL) was added dropwise to the LDA solution. The mixture was stirred at −78 °C for 30 min, the dry ice-acetone bath was changed to an ice bath, and stirring was continued for 40 min. The mixture was recooled to −78 °C and a solution of **13** (0.490 g, 1.97 mmol) and HMPA (0.34 mL, 2.0 mmol) in THF (10 mL) was added dropwise. Stirring at −78 °C was continued for 90 min, and saturated aqueous NH_4Cl (5 mL) was added, followed by Et_2O (100 mL). The cooling bath was removed, and stirring was continued for 30 min. The mixture was washed with saturated aqueous NH_4Cl (twice) and brine, dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (1.8 × 40 cm), using 1:8 to 1:5 EtOAc−hexane, gave starting lactone **31** (0.160 g, 29%) and **35** (0627 g, 71%) as a mixture of isomers: FTIR ($CDCl_3$, cast) 3355, 2965, 2931, 2859, 1763, 1711, 1689, 1589, 1511 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.82−1.58 (m, 27 H), 2.53 (s, 0.7 H), 2.96−4.30 (m, 3.5 H), 3.09 (AB q, J = 10.1 Hz, $\Delta\nu_{AB}$ = 84.4 Hz, 1.4 H), 3.58 (dt, J = 10.7, 3.2 Hz, 0.7 H), 4.16 (d, J = 10.7 Hz, 0.7 H), 4.70−4.83 (m, 1.1 H), 4.91 (s, 0.7 H), 4.98−5.06 (m, 0.2 H), 5.31−5.42 (m, 0.1 H), 5.47 (q, J = 6.7 Hz, 0.7 H), 5.52−5.61 (m, 0.2 H), 7.14−7.65 (m, 16 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, major isomer only) δ 12.7 (q), 13.7 (q), 16.1 (q), 19.0 (s), 26.7 (q), 28.3 (q), 42.6 (t), 47.0 (s), 48.7 (d), 48.8 (d), 67.9 (t), 67.7 (d), 80.4 (s), 89.7 (d), 122.1 (d), 127.0 (d), 127.5 (d), 127.8 (d), 128.4 (d), 129.0 (d), 129.2 (s), 129.5 (d), 132.8 (s), 133.0 (s), 135.5 (d), 135.6 (d), 140.8 (s), 158.0 (s), 176.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{40}H_{53}NNaO_6Si$ 694.353987, found 694.353635.

[3-[(4*R,5*S**)-4-[(*tert*-Butyldiphenylsilanyl)oxymethyl]-tetrahydro-2-hydroxy-4-methyl-5-[(1*E*)-1-methyl-1-propenyl]furan-3-yl]-3-hydroxy-2-phenylpropyl]carbamic Acid *tert*-Butyl Ester (36).** DIBALH (1.0 M in hexane, 2.4 mL, 2.4 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of **35** (284 mg, 0.423 mmol) in CH_2Cl_2 (19 mL). Stirring at −78 °C was continued for 2.5 h, and 3:1 MeOH-water (4 mL) was added dropwise. The cooling bath was removed and stirring was continued for 1 h. The mixture was filtered through a pad of Celite (3 × 3 cm), using EtOAc (80 mL) as a rinse, and the filtrate was dried (Na_2SO_4) and evaporated. The residue was kept under oil pump vacuum for 4 h to afford crude **36** (286 mg, 100%), which was a mixture of isomers and was used without further purification: exact mass (electrospray) *m*/*z* calcd for $C_{40}H_{55}NNaO_6Si$ 696.369637, found 696.369017.

(2*R,3*S**)-3-[(*tert*-Butyldiphenylsilanyl)oxymethyl]-hexahydro-4-hydroxy-3-methyl-2-[(1*E*)-1-methyl-1-propenyl]-5-phenylfuro[2,3-*b*]pyridine-7-carboxylic Acid *tert*-Butyl Ester (37a,b).** TsOH·pyridine (148 mg, 0.589 mmol) was added in one portion to a stirred solution of **36** (286 mg, 0.423 mmol) in THF (30 mL). The mixture was lowered into an oil bath set at 45 °C, and stirring was continued for 15 h. The mixture was cooled to room temperature, diluted with Et_2O (100 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.5 × 40 cm), using 1:6 to 1:4 EtOAc−hexane, gave **37** as two fractions: fraction A (less polar, 150 mg, 54%) and fraction B (more polar, 76 mg, 27%).

Fraction A (**37a**): mp 77−80 °C; FTIR (CH_2Cl_2, cast) 3517, 3070, 2962, 2930, 2889, 2858, 1703, 1589 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.10 (s, 9 H), 1.45 (s, 3 H), 1.47 (s, 12 H), 1.50 (d, J = 6.8 Hz, 3 H), 2.26 (d, J = 7.9 Hz, 1 H), 2.34 (s, 1 H), 2.78 (dd, J = 12.2, 3.2 Hz, 1 H), 3.22 [d (formally part of AB q), J = 10.3 Hz, 1 H], 3.42−3.74 (m containing part of AB q, 2 H), 3.84−4.14 (m, 2 H), 4.34 (s, 1 H), 5.49 (q, J = 6.8 Hz, 1 H), 5.61−5.87 (m, 1 H), 7.25−7.50 (m, 11 H), 7.62−7.69 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 12.8 (q), 14.3 (q), 18.1 (q), 19.6 (s), 27.2 (q), 28.4 (q), 37.7 (t), 45.9 (d), 47.0 (d), 49.7 (s), 68.0 (t), 69.3 (d), 80.7 (s), 82.5 (d), 88.2 (d), 119.8 (d), 127.3 (d), 128.08 (d), 128.12 (d), 128.4 (d), 128.9 (d), 130.1 (d), 130.2 (d), 133.4 (s), 133.9 (s), 134.0 (s), 135.98 (d), 136.02 (d), 141.4 (s), 155.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{40}H_{53}NNaO_5Si$ 678.359072, found 678.358975.

Fraction B (**37b**): mp 54−56 °C; FTIR (CH_2Cl_2, cast) 3465, 3070, 2963, 2930, 2858, 1703, 1602, 1589 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.01 (s, 9 H), 1.29 (s, 3 H), 1.39 (s, 9 H), 1.46 (s, 3 H), 1.54 (d, J = 6.8 Hz, 3 H), 2.48−2.58 (m, 1 H), 3.22 (d, J = 4.8 Hz, 1 H), 3.39 (dd, J = 13.2, 4.0 Hz, 1 H), 3.42 (AB q, J = 10.1 Hz, $\Delta\nu_{AB}$ = 156.3 Hz, 2 H), 4.02−4.16 (m, 2 H), 4.25 (s, 1 H), 5.49 (q, J = 6.8 Hz, 1 H), 6.03 (br s, 1 H), 7.24−7.49 (m, 12 H), 7.57−7.65 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 13.1 (q), 14.0 (q), 19.1 (q), 19.6 (s), 27.1 (q), 28.3 (q), 42.6 (t), 45.1 (d), 46.7 (d), 51.1 (s), 67.6 (t), 68.5 (d), 80.5 (s), 83.5 (d), 88.1 (d), 121.5 (d), 127.5 (d), 128.0 (d), 128.1 (d), 128.9 (d), 129.9 (d), 130.0 (d), 130.2 (d), 132.5 (s), 133.8 (s), 134.0 (s), 136.0 (d), 139.5 (s), 155.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{40}H_{53}NNaO_5Si$ 678.359072, found 678.358885.

(2*R,3*S**)-3-[(*tert*-Butyldiphenylsilanyl)oxymethyl]-hexahydro-3-methyl-2-[(1*E*)-1-methyl-1-propenyl]-4-oxo-5-phenylfuro[2,3-*b*]pyridine-7-carboxylic Acid *tert*-Butyl Ester (38a).** Dess−Martin reagent (128 mg, 0.302 mmol) was added in one portion to a stirred solution of **37a** (less polar isomer) (132 mg, 0.201 mmol) in CH_2Cl_2 (18 mL). After 30 min, another portion of Dess−Martin reagent (128 mg, 0.302 mmol) was added. Stirring was continued for 2 h, and the mixture was diluted with Et_2O (100 mL), washed with 1:1 saturated aqueous $NaHCO_3$-10% aqueous $Na_2S_2O_3$, and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 × 40 cm), using 1:9 EtOAc−hexane, gave **38a** (126 mg, 96%) as a solid: mp 57−59 °C; FTIR (CH_2Cl_2, cast) 3070, 2964, 2931, 2858, 1704, 1589 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.39 (s, 9 H), 1.41 (s, 3 H), 1.79 (s, 12 H), 1.84 (d, J = 6.8 Hz, 3 H), 3.66 (d, J = 7.3 Hz, 1 H), 3.71 (AB q, J = 10.0 Hz, $\Delta\nu_{AB}$ = 120.6 Hz, 2 H), 3.81−4.09 (m, 2 H), 4.63 (s, 1 H), 4.60−4.77 (m, 1 H), 5.84 (q, J = 6.8 Hz, 1 H), 6.60 (br s, 1 H), 7.44−7.52 (m, 2 H), 7.56−7.78 (m, 9 H), 7.91−7.98 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 13.2 (q), 14.0 (q), 19.7 (s), 20.0 (q), 27.2 (q), 28.5 (q), 43.2 (t), 53.9 (s), 54.8 (d), 56.1 (d), 68.3 (t), 81.3 (s), 84.4 (d), 91.5 (d), 122.8 (d), 127.8 (d), 128.10 (d), 128.13 (d), 129.0 (d), 129.2 (d), 130.2 (d), 131.6 (s), 133.8 (s), 133.9 (s), 136.08 (d), 136.10 (d), 136.8 (s), 154.4 (s), 207.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{40}H_{51}NNaO_5Si$ 676.343422, found 676.343928.

(2*R,3*S**)-3-[(*tert*-Butyldiphenylsilanyl)oxymethyl]-hexahydro-3-methyl-2-[(1*E*)-1-methyl-1-propenyl]-4-oxo-5-phenylfuro[2,3-*b*]pyridine-7-carboxylic Acid *tert*-Butyl Ester (38b).** Dess−Martin reagent (146 mg, 0.344 mmol) was added in one portion to a stirred solution of **37b** (more polar isomer) (105 mg, 0.160 mmol) in CH_2Cl_2 (15 mL). Stirring was continued for 3 h, and the mixture was diluted with Et_2O (40 mL), washed with 1:1 saturated aqueous $NaHCO_3$−10% aqueous $Na_2S_2O_3$ and brine, dried (Na_2SO_4),and evaporated. Flash chromatography of the residue over silica gel (1.5 × 30 cm),

using 1:9 EtOAc−hexane, gave **38b** (89 mg, 85%) as an oil: FTIR (CH_2Cl_2, cast) 3361, 2974, 2931, 2859, 1746, 1708, 1589 cm^{-1}; ^1H NMR (CD_2Cl_2, 500 MHz) δ 1.08 (s, 3 H), 1.09 (s, 9 H), 1.43 (s, 9 H), 1.50 (s, 3 H), 1.55 (d, J = 6.8 Hz, 3 H), 3.33 (d, J = 6.4 Hz, 1 H), 3.39 (AB q, J = 10.2 Hz, $\Delta\nu_{AB}$ = 152.1 Hz, 2 H), 3.92−4.02 (m, 2 H), 4.07 (dd, J = 9.0, 7.0 Hz, 1 H), 4.44 (s, 1 H), 5.57 (q, J = 6.8 Hz, 1 H), 6.23 (d, J = 5.1 Hz, 1 H), 7.16−7.22 (m, 2 H), 7.29−7.49 (m, 9 H), 7.61−7.68 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 13.1 (q), 14.1 (q), 19.6 (s), 20.0 (q), 27.1 (q), 28.3 (q), 47.7 (t), 52.8 (s), 53.9 (d), 56.6 (d), 66.7 (t), 81.1 (s), 85.5 (d), 89.8 (d), 122.2 (d), 127.8 (d), 128.07 (d), 128.13 (d), 128.8 (d), 129.3 (d), 130.1 (d), 130.2 (d), 131.6 (s), 133.6 (s), 133.7 (s), 136.0 (d), 136.1 (d), 137.1 (s), 154.8 (s), 207.3 (s); exact mass (electrospray) m/z calcd for $C_{40}H_{51}NNaO_5Si$ 676.343422, found 676.343733.

(2*R,3*S**)-3-[(*tert*-Butyldiphenylsilanyl)oxymethyl]-hexahydro-3-methyl-2-[(1*E*)-1-methyl-1-propenyl]-4-oxo-5-phenylfuro[2,3-*b*]pyridine-7-carboxylic Acid Triisopropylsilyl Ester (41a).** 2,6-Lutidine (0.34 mL, 2.9 mmol) and *i*-$Pr_3SiOSO_2CF_3$ (0.63 mL, 2.3 mmol) were added successively to a stirred solution of **38a** (less polar isomer) (189 mg, 0.289 mmol) in CH_2Cl_2 (25 mL). After 15 min, the mixture was lowered into a preheated oil bath set at 45 °C, and stirring was continued for 60 h. The mixture was cooled, diluted with Et_2O (100 mL), washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.5 × 35 cm), using 1:25 EtOAc−hexane, gave **41a** (218 mg, 100%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3070, 2944, 2866, 1692, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.99−1.12 (m, 30 H), 1.32 (septet, J = 7.5 Hz, 3 H), 1.43 (s, 3 H), 1.50 (d, J = 6.4 Hz, 3 H), 3.31−3.92 (m, 3 H), 3.35 (AB q, J = 10.0 Hz, $\Delta\nu_{AB}$ = 161.8 Hz, 2 H), 4.20−4.60 (m, 2 H), 5.40−5.60 (m, 1 H), 6.20−6.50 (m, 1 H), 7.10−7.44 (m, 11 H), 7.56−7.62 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz, major rotamer only) δ 12.1 (d), 12.3 (q), 12.9 (q), 17.8 (q), 19.4 (s), 19.6 (q), 27.0 (q), 43.2 (s), 53.5 (t), 54.2 (d), 55.6 (d), 67.7 (t), 84.9 (d), 90.7 (d), 122.2 (d), 127.6 (d), 127.7 (d), 128.6 (d), 129.7 (d), 129.8 (d), 131.0 (s), 133.3 (s), 133.4 (s), 135.6 (d), 135.7 (d), 153.8 (s), 207.2 (s); exact mass (electrospray) m/z calcd for $C_{45}H_{63}NNaO_5Si_2$ 776.41370, found 776.41333.

When the ^1H NMR spectrum was run at 45 °C many signals coalesced: ^1H NMR ($CDCl_3$, 400 MHz) δ 0.99−1.12 (m, 30 H), 1.30 (septet, J = 7.5 Hz, 3 H), 1.41 (s, 3 H), 1.48 (d, J = 6.6 Hz, 3 H), 3.34 (d, J = 7.0 Hz, 1 H), 3.35 (AB q, J = 10.0 Hz, $\Delta\nu_{AB}$ = 130.1 Hz, 2 H), 3.54 (br s, 1 H), 3.71 (br s, 1 H), 4.26 (s, 1 H), 4.42 (br s, 1 H), 5.39−5.53 (m, 1 H), 6.31 (br s, 1 H), 7.11 (d, J = 7.3 Hz, 2 H), 7.21−7.41 (m, 9 H), 7.57 (d, J = 7.0 Hz, 4 H). At −60 °C (and at −20 °C) well-separated sets of signals appeared (values for −60 °C): ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89−1.12 (m, 30 H), 1.24 (septet, J = 7.3 Hz, 3 H), 1.35 (s, 1.5 H), 1.36 (s, 1.5 H), 1.45 (d, J = 6.7 Hz, 3 H), 3.02−3.13 (m, 1 H), 3.30−3.82 (m, 4 H), 4.22−4.34 (m, 1.5 H), 4.40−4.50 (m, 0.5 H), 5.43 (q, J = 6.7 Hz, 0.5 H), 5.53 (q, J = 6.7 Hz, 0.5 H), 6.26 (d, J = 7.0 Hz, 0.5 H), 6.40 (d, J = 7.7 Hz, 0.5 H), 7.02−7.09 (m, 2 H), 7.20−7.42 (m, 9 H), 7.48−7.55 (m, 4 H).

(2*R,3*S**)-3-[(*tert*-Butyldiphenylsilanyl)oxymethyl]-hexahydro-3-methyl-2-[(1*E*)-1-methyl-1-propenyl]-4-oxo-5-phenylfuro[2,3-*b*]pyridine-7-carboxylic Acid Triisopropylsilyl Ester (41b).** 2,6-Lutidine (0.045 mL, 0.39 mmol) and *i*-$Pr_3SiOSO_2CF_3$ (0.075 mL, 0.28 mmol) were added successively to a stirred solution of **38b** (28.0 mg, 0.0428 mmol) in CH_2Cl_2 (3 mL). After 15 min, the mixture was lowered into a preheated oil bath set at 45 °C, and stirring was continued for 2 days. The mixture was cooled, diluted with Et_2O (20 mL), washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 1:20 EtOAc−hexane, gave **41b** (32.3 mg, 100%) as a colorless oil: FTIR ($CDCl_3$, cast) 3070, 2944, 2892, 2866, 1723, 1692, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.98−1.13 (m, 30 H), 1.29 (septet, J = 7.4 Hz, 3 H), 1.44 (s, 3 H), 1.50 (d, J = 6.7 Hz, 3 H), 3.18 [d (formally part of AB q), J = 10.2 Hz, 1 H], 3.37 (d, J = 4.9 Hz, 1 H), 3.51 [d (broad signal, formally part of AB q), J = 8.4 Hz, 1 H], 3.99−4.16 (m, 3 H), 4.42 (s, 1 H), 5.56 (br s, 1 H), 6.14−6.45 (m, 1 H), 7.11−7.44 (m, 11 H), 7.55−7.61 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) (major rotamer only) δ 12.0 (d), 12.3 (q), 12.9 (q), 17.8 (q), 19.4 (s), 19.8 (q), 26.9 (q), 47.5 (t), 52.4 (s), 53.5 (d), 67.0 (t), 86.0 (d), 121.9 (d), 127.7 (d), 128.7 (d), 129.8 (d), 131.0 (s), 133.2 (s), 135.6 (d), 135.7 (d), 154.1 (s), 206.7 (s); exact mass (electrospray) m/z calcd for $C_{45}H_{63}NNaO_5Si_2$ 776.414251, found 776.414651.

When the ^1H NMR spectrum was run at 45 °C many signals coalesced: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.00−1.14 (m, 30 H), 1.30 (septet J = 7.4 Hz, 3 H), 1.44 (s, 3 H), 1.51 (d, J = 6.6 Hz, 3 H), 3.36 (AB q, J = 10.3 Hz, $\Delta\nu_{AB}$ = 130.3 Hz, 2 H), 3.37 (d, J = 6.1 Hz, 1 H), 3.99−4.15 (m, 3 H), 4.41 (s, 1 H), 5.50−5.62 (m, 1 H), 6.29 (br s, 1 H), 7.17 (d, J = 7.1 Hz, 2 H), 7.23−7.44 (m, 9 H), 7.55−7.62 (m, 4 H). At −60 °C (and at −20 °C) well-separated sets of signals appeared (values for −60 °C): ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84−1.04 (m, 30 H), 1.21 (septet, J = 7.5 Hz, 3 H), 1.34 (s, 3 H), 1.41−1.48 (m, 3 H), 3.02−3.11 (m, 1 H), 3.28−3.44 (m, 2 H), 3.77−3.92 (m, 1 H), 3.95−4.06 (m, 1 H), 4.12−4.23 (m, 1 H), 4.36 (s, 0.5 H), 4.38 (s, 0.5 H), 5.49 (q, J = 7.0 Hz, 0.5 H), 5.61 (q, J = 7.0 Hz, 0.5 H), 6.17 (d, J = 5.7 Hz, 0.5 H), 6.30 (d, J = 6.0 Hz, 0.5 H), 7.08−7.14 (m, 2 H), 7.23−7.43 (m, 9 H), 7.47−7.55 (m, 4 H).

(2*R,3*S**)-3-[(*tert*-Butyldiphenylsilanyl)oxymethyl]-2,3,3a,7a-tetrahydro-3-methyl-2-(1-methyl-1-propenyl)-4-oxo-5-phenyl-4*H*-furo[2,3-*b*]pyridine-7-carboxylic Acid Triisopropylsilyl Ester (42).** $(Me_3Si)_2NK$ (0.5 M in PhMe, 0.60 mL, 0.30 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of ketone **41a** (208 mg, 0.275 mmol) in THF (10 mL), and stirring at −78 °C was continued for 90 min. A solution of PhSeCl (58.5 mg, 0.305 mmol) in THF (5 mL) was added dropwise. After 45 min at −78 °C, the mixture was quenched with saturated aqueous NH_4Cl (5 mL), diluted with Et_2O (100 mL), and washed with saturated aqueous NH_4Cl and brine. The organic phase was dried (Na_2SO_4) and evaporated to give the crude selenide (266 mg), which was used directly for the next step.

Pyridine (0.15 mL, 1.9 mmol) and H_2O_2 (30%, 0.24 mL, 2.1 mmol) were added to a vigorously stirred and cooled (0 °C) solution of the crude selenide (266 mg, ca. 0.175 mmol) in CH_2Cl_2 (30 mL). The cooling bath was removed and stirring was continued for 35 min. The mixture was diluted with EtOAc (80 mL), washed successively with water, saturated aqueous $CuSO_4$, water, and brine, dried (Na_2SO_4), and evaporated. The residue was kept under oil pump vacuum for 30 min to afford the crude material (200 mg), which was used directly for next step without purification.

(2*R,3*S**)-3-[(*tert*-Butyldiphenylsilanyl)oxymethyl]-3,-3a,7,7a-tetrahydro-3-methyl-2-[(1*E*)-1-methyl-1-propenyl]-5-phenyl-2*H*-furo[2,3-*b*]pyridine-4-one (43).** Bu_4NF (1.0 M in THF, 0.20 mL, 0.20 mmol) was added dropwise to a stirred and cooled (0 °C) solution of crude **42** (200 mg) in THF (20 mL). After 5 min, the mixture was quenched with saturated aqueous NH_4Cl (5 mL), diluted with EtOAc (60 mL), washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 25 cm), using 1:3 EtOAc−hexane, gave **43** (79.8 mg, 53% from **41a**) as a colorless oil: FTIR (CH_2Cl_2 cast) 3247, 3049, 2960, 2930, 2858, 1826, 1602, 1584 cm^{-1}; ^1H NMR (CD_2Cl_2, 500 MHz) δ 1.08 (s, 9 H), 1.17 (s, 3 H), 1.62 (d, J = 6.7 Hz, 3 H), 1.66 (s, 3 H), 2.99 (d, J = 7.9 Hz, 1 H), 3.55 (AB q, J = 10.2 Hz, $\Delta\nu_{AB}$ = 18.1 Hz, 2 H), 4.36 (s, 1 H), 5.42 (d, J = 6.3 Hz, 1 H), 5.60 (q, J = 6.7 Hz, 1 H), 5.66 (d, J = 7.9 Hz, 1 H), 7.16−7.48 (m, 12 H), 7.61−7.72 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 125.7 MHz) δ 13.3 (q), 14.5 (q), 19.6 (s), 19.7 (q), 27.2 (q), 52.4 (s), 55.2 (d), 68.4 (t), 86.6 (d), 90.9 (d), 111.4 (s), 122.4 (d), 126.2 (d), 127.96 (d), 127.97 (d), 128.3 (d), 128.4 (d), 129.9 (d), 130.0 (d), 132.6 (s), 133.89 (s), 133.94 (s), 136.2 (d), 136.4 (s), 148.4 (d), 189.7 (s); exact mass (electrospray) m/z calcd for $C_{35}H_{41}NNaO_3Si$ 574.275343, found 574.275410.

(2*R,3*S**)-3-[(*tert*-Butyldiphenylsilanyl)oxymethyl]-3,3a,7,7a-tetrahydro-3-methyl-2-(1-methyl-1-propenyl)-5-phenyl-2*H*-furo[2,3-*b*]pyridin-4-one (43).** $(Me_3Si)_2NK$ (0.5 M in PhMe, 0.10 mL, 0.050 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of **41b** (32.0 mg, 0.0428 mmol) in THF (2 mL), and stirring at −78 °C was continued for 90 min. A solution of PhSeCl (10 mg, 0.052 mmol) in THF (1 mL) was added dropwise. After 45 min at −78 °C, the mixture was quenched with saturated aqueous NH_4Cl (1 mL), diluted with Et_2O (20 mL), washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4), and evaporated to give the crude selenide (44.4 mg), which was used directly for the next step.

Pyridine (0.030 mL, 0.37 mmol) and H_2O_2 (30%, 0.050 mL, 0.44 mmol) were added to a vigorously stirred and cooled (0 °C) solution of the crude selenide (44.4 mg) in CH_2Cl_2 (6 mL). The cooling bath was removed, and stirring was continued for 45 min. The mixture was diluted with EtOAc (20 mL), washed successively with water, saturated aqueous $CuSO_4$, water, and brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over Al_2O_3 (Grade III), using 1:20 to 1:5 EtOAc−hexane, gave **43** (11.5 mg, 49% from **41b**), which had the same spectral characteristics as material from the less polar series.

(2*R,3*S**)-3-[(*tert*-Butyldiphenylsilanyl)oxymethyl]-3,7-dihydro-3-methyl-2-[(1*E*)-1-methyl-1-propenyl]-5-phenyl-2*H*-furo[2,3-*b*]pyridin-4-one (44).** All steps in this experiment were done with protection from light.

Freshly prepared *t*-BuOCl[19] (0.1 M in CH_2Cl_2, 1.4 mL, 0.14 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of **43** (31.0 mg, 0.0562 mmol) in CH_2Cl_2, the mixture being protected from light by alumina foil. After 15 min at −78 °C, the solvent was evaporated and the residue was kept under oil pump vacuum for 15 min.

PhMe (5 mL) was injected into the reaction flask (protection from light), followed by DBU (0.080 mL, 0.53 mmol). Stirring was continued for 1 h at room temperature, and the solvent was evaporated. Flash chromatography of the residue over silica gel (0.7 × 20 cm), using 1:3 EtOAc−hexane, gave **44** (22 mg, 71%) as a white solid: mp 99−101 °C; FTIR (CH_2Cl_2, cast) 3050, 2960, 2930, 2858, 1827, 1647, 1595, 1556 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.10 (s, 9 H), 1.35 (s, 3 H), 1.41 (d, J = 6.7 Hz, 3 H), 1.48 (s, 3 H), 3.57 (AB q, J = 10.0 Hz, $\Delta\nu_{AB}$ = 144.3 Hz, 2 H), 4.64 (s, 1 H), 5.34 (q, J = 6.7 Hz, 1 H), 7.28−7.67 (m, 15 H), 7.95 (s, 1 H), 9.34 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 12.8 (q), 12.9 (q), 19.2 (s), 24.7 (q), 26.9 (q), 49.0 (s), 69.4 (t), 94.1 (d), 110.0 (s), 120.9 (s), 124.2 (d), 126.9 (d), 127.98 (d), 128.01 (d), 128.2 (d), 129.3 (d), 130.3 (d), 130.5 (d), 131.2 (s), 131.3 (s), 131.5 (s), 135.3 (s), 135.5 (d), 135.9 (d), 149.1 (d), 158.5 (s), 167.9 (s); exact mass (electrospray) m/z calcd for $C_{35}H_{40}NO_3Si$ 550.27720, found 550.27768.

(2*R,3*S**)-3,7-Dihydro-3-hydroxymethyl-3-methyl-2-[(1*E*)-1-methyl-1-propenyl]-5-phenyl-2*H*-furo[2,3-*b*]pyridin-4-one (2).** Bu_4NF (1.0 M in THF, 0.12 mL, 0.12 mmol) was added dropwise to a stirred solution of **44** (21.5 mg, 0.0391 mmol) in THF (7 mL). Stirring was continued for 15 min, and then saturated aqueous NH_4Cl (10 mL) was added. The mixture was extracted with EtOAc (2 × 10 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography the residue over silica gel (0.9 × 20 cm), using 1:1 EtOAc−hexane, gave **2** (11.8 mg, 97%) as a colorless solid: mp 213-214 °C; FTIR (CH_2Cl_2, cast) 3057, 2926, 2860, 2742, 1695, 1598, 1502 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 1.51 (s, 3 H), 1.54 (s, 3 H), 1.63 (d, J = 6.8 Hz, 3 H), 3.76 (AB q, J = 10.1 Hz, $\Delta\nu_{AB}$ = 13.6 Hz, 2 H), 4.84 (s, 1 H), 5.63 (q, J = 6.8 Hz, 1 H), 7.25−7.31 (m, 1 H), 7.34−7.41 (m, 2 H), 7.50−7.56 (m, 2 H), 7.82 (s, 1 H); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 13.4 (q), 13.5 (q), 25.7 (q), 50.5 (s), 67.3 (t), 95.3 (d), 111.8 (s), 125.3 (d), 128.0 (d), 129.3 (d), 130.6 (d), 133.7 (s), 137.3 (s); exact mass m/z calcd for $C_{19}H_{21}NO_3$ 311.15213, found 311.15171.

(2*R,3*R**)-2,3,4,7-Tetrahydro-3-methyl-2-[(1*E*)-1-methyl-1-propenyl]-4-oxo-5-phenylfuro[2,3-*b*]pyridine-3-carbaldehyde (Cladobotryal) (1).** Dess−Martin reagent (30.0 mg, 0.0708 mmol) was added in one portion to a stirred solution of **2** (11.0 mg, 0.0353 mmol) in CH_2Cl_2 (6 mL). After 15 min, saturated aqueous $NaHCO_3$ (10 mL) and 10% aqueous $Na_2S_2O_3$ (5 mL) were added. The mixture was extracted with EtOAc (2 × 10 mL), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (0.9 × 25 cm), using 2:3 EtOAc−hexane, gave aldehyde **1** (10.6 mg, 97%) as a solid: mp 95−97 °C; FTIR ($CDCl_3$, cast) 2923, 2859, 2721, 1727, 1648, 1595, 1555, 1501 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 1.57 (s, 3 H), 1.63 (s, 3 H), 1.65 (d, J = 6.8 Hz, 3 H), 5.01 (s, 1 H), 5.82 (q, J = 6.8 Hz, 1 H), 5.30−5.49 (m, 5 H), 7.78 (s, 1 H), 9.61 (s, 1 H); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 13.5 (q), 20.7 (q), 59.2 (s), 107.8 (s), 125.5 (d), 128.8 (d), 129.9 (d), 130.8 (d), 131.8 (s), 136.1 (s), 201.2 (d); exact mass m/z calcd for $C_{19}H_{19}NO_3$ 309.13651, found 309.13632.

Acknowledgment. We thank NSERC and Crompton Co. (Elmira, Ontario) for financial support and Dr. R. McDonald (X-ray Crystallography Laboratory) for the crystal structure determination. X.H. holds a Graduate Research Assistantship.

Supporting Information Available: NMR spectra of new compounds, except **21**, **24**, **36**, and **42**, X-ray data for **10**, and experimental procedures for **9** → silylated derivative, **13**, **15**, **16**, **17**, **17** → **18**, **19**, **19** → **18**, **20**, **21**, **22a**, **22b**,**c**, **23a**, **23b**, **38a** → **39**, and **38b** → **39**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO030284G