Articles

Total Synthesis of (±)-Atpenin B. An Original "Clockwise" Functionalization of 2-Chloropyridine

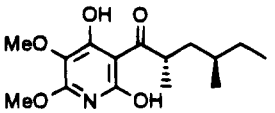
François Trécourt, Marc Mallet, Olivier Mongin, and Guy Quéguiner*

Laboratoire de Chimie Organique Hétérocyclique de l'Institut de Recherche en Chimie Organique Fine, URA CNRS 1429, Institut National des Sciences Appliquées de Rouen, BP 08, 76131 Mont-Saint-Aignan Cedex, France

Received June 22, 1994®

(−)-Atpenin B (**1**) is an antibiotic produced by *Penicillium* sp. FO-125. The first synthesis of 2,4-dihydroxy-5,6-dimethoxy-3-((2*RS*,4*RS*)-2,4-dimethyl-1-oxohexyl)pyridine (atpenin B) (**16**) is reported. This molecule, which exhibits a pentasubstituted pyridine structure, was prepared from 2-chloropyridine in 13 steps, by metalating and then functionalizing, one after another, all the remaining positions of the pyridine ring. The methodology involves four metalation steps (including metalation of 2,3-dimethoxypyridine and pyridyl *N*,*N*-diisopropylcarbamates), one halogen-scrambling step, and one bromine−lithium exchange step.

Many natural molecules endowed with biological and pharmacological properties exhibit a pyridine nucleus substituted with methoxyl and hydroxyl groups such as the alkaloid orelline,[1,2] or the antibiotics caerulomycins,[3] for which syntheses have already been proposed. However, in this class of natural products are several compounds whose structure features a pentasubstituted pyridine with three or four groups containing oxygen atoms and a common 2,3-dimethoxy-4-pyridinol (or 4-pyridone) pattern: piericidins[4] (isolated from *Streptomyces mobaraensis* and *pactum*), atpenins[5] (three antibiotics produced by *Penicillium* sp. FO-125, such as (−)-atpenin B (**1**)), harzianopyridone[6] (an antifungal metabolite of

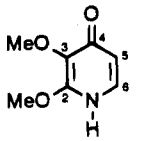


1

Trichoderma harzianum), and the recently isolated angiogenesis inhibitors WF-16775 A1 and A2[7] (from *Chaetasbolisia erysiophoides*).

Although isolated in 1988, there is to our knowledge no chemical synthesis of any atpenin. Because of our interest in the synthesis of pyridine-containing natural products,[8] and our expertise in the metalation field,[9] we chose them as target molecules. We now report the first synthesis of one of these atpenins, 2,4-dihydroxy-5,6-dimethoxy-3-((2*RS*,4*RS*)-2,4-dimethyl-1-oxohexyl)pyridine (atpenin B), from commercially available 2-chloropyridine, by using mainly metalation, halogen migration, and halogen−metal exchange reactions.

The original aspect of our synthetic strategy consists of metalating and then functionalizing, one after another, all the remaining positions on a 2-monosubstituted pyridine: namely a "clockwise" functionalization of the pyridine ring. We chose to introduce first the groups present in all the cited natural molecules: the two methoxyl groups at C-2 and C-3 and the hydroxyl group at C-4; so 2,3-dimethoxypyrid-4(1*H*)-one (**2**) is our key intermediate.



2

Results and Discussion

Metalation of 2-chloropyridine (**3**) is currently well known; two metalating agents can be used: LDA[10] or phenyllithium (PhLi).[11] We prepared 2-chloro-3-hydroxy-

® Abstract published in *Advance ACS Abstracts*, September 1, 1994.

(1) (a) Dehmlow, E. V.; Schulz, H. J. *Tetrahedron Lett.* **1985**, *26*, 4903; *Liebigs Ann. Chem.* **1987**, 857. (b) Tiecco, M.; Tingoli, M.; Testaferri, L.; Chianelli, D.; Wenkert, E. *Tetrahedron* **1986**, *42*, 1475. (c) Hasseberg, H.-A.; Gerlach, H. *Helv. Chim. Acta* **1988**, *71*, 957.

(2) Trécourt, F.; Mallet, M.; Mongin, O.; Gervais, B.; Quéguiner, G. *Tetrahedron* **1993**, *49*, 8373.

(3) (a) Ranganathan, S.; Singh, B. B., Divekar, P. V. *Can. J. Chem.* **1969**, *47*, 165. (b) Alreja, B. D.; Kattige, S. L.; Lal, B.; De Souza, N. J. *Heterocycles* **1986**, *24*, 1637.

(4) (a) Jansen, R.; Höfle, G. *Tetrahedron Lett.* **1983**, 5485 and references cited therein. (b) Schmidtchen, F. P.; Rapoport, H. *J. Am. Chem. Soc.* **1977**, 7014. (c) Chung, K. H.; Cho, K. Y.; Asami, Y.; Takahashi, N.; Yoshida, S. *Z. Naturforsch.* **1989**, *44c*, 609.

(5) (a) Omura, S.; Tomoda, H.; Kimura, K., Zhen, D.-Z.; Kumagai, H.; Igarashi, K.; Imamura, N.; Takahashi, Y.; Tanaka, Y.; Iwai, Y. *J. Antibiot.* **1988**, *41*(12), 1769. (b) Omura, S.; Koda, H.; Imamura, N.; Tanaka, Y.; Iwai, Y. *Jpn Kokai Tokkyo Koho* JP 01, 199, 582 [89, 199, 582]. (c) Oshino, K.; Kumagai, H.; Tomoda, H.; Omura, S. *J. Antibiot.* **1990**, *43* (9), 1064. (d) Kumagai, H.; Nishida, H.; Imamura, N.; Tomoda, H.; Omura, S.; Bordner, J. *J. Antibiot.* **1990**, *43*(9), 1553.

(6) (a) Dickinson, J. M.; Hanson, J. R.; Hitchcock, P. B. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1885. (b) Rodgers, P. B. *Pestic. Sci.* **1989**, *27*, 155. (c) Cutler, H. G.; Jacyno, J. M. *Agric. Biol. Chem.* **1991**, *55*(10), 2629.

(7) Otsuka, T.; Takase, S.; Terano, H.; Okuhara, M. *J. Antibiot.* **1992**, *45*(12), 1970.

(8) Godard, A.; Marsais, F.; Plé, N.; Trécourt, F.; Turck, A.; Quéguiner, G. *Heterocycles*, in press.

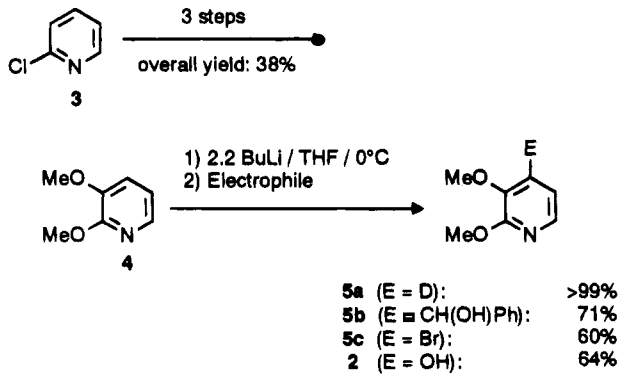
(9) For a review on directed ortho metalation of pyridines and some other π-deficient azaaromatics, see: Quéguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187.

(10) Trécourt, F.; Marsais, F.; Güngör, T.; Quéguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2409.

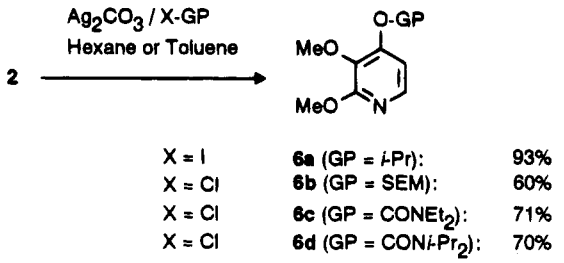
(11) Mallet, M. *J. Organomet. Chem.* **1991**, *406*, 49.

0022-3263/94/1959-6173$04.50/0

Scheme 1



Scheme 2



pyridine[12] by reaction of trimethylborate on 2-chloro-3-lithiopyridine at low temperature, followed by an *in situ* oxidation of the boronic intermediate with peracetic acid.[2,13] (overall yield: 65%). 2,3-Dimethoxypyridine[14] (**4**) was then prepared in a two-step sequence with an overall yield of 58% by a selective O-methylation,[12,15] followed by a previously described[14a] nucleophilic substitution of the chlorine atom by sodium methoxide.

No lithiation was observed when 2,3-dimethoxypyridine (**4**) was treated with 2.2 equiv of *n*-butyllithium (BuLi) in THF at −70 °C, unlike 3,4-dimethoxypyridine.[2] Using 1.2 equiv of BuLi at 0 °C gave only a very poor metalation yield (15%). It seems that, in this case, 1 equiv of base was entirely chelated by the two methoxyl groups and the nitrogen ring atom. Metalation of **4** occurred at the C-4 position, requiring 2.2 equiv of BuLi in THF at 0 °C, without side reactions (nucleophilic addition, ring opening, ...). Various electrophiles were tested with rather good yields (Scheme 1).

Pyridone **2** was prepared (64% yield), by again using the metalation/boronation/oxidation technique ($B(OMe)_3$/CH_3CO_3H). 2- and 4-Pyridylboronic acids are known to be unstable,[16] so an *in situ* oxidation was performed.

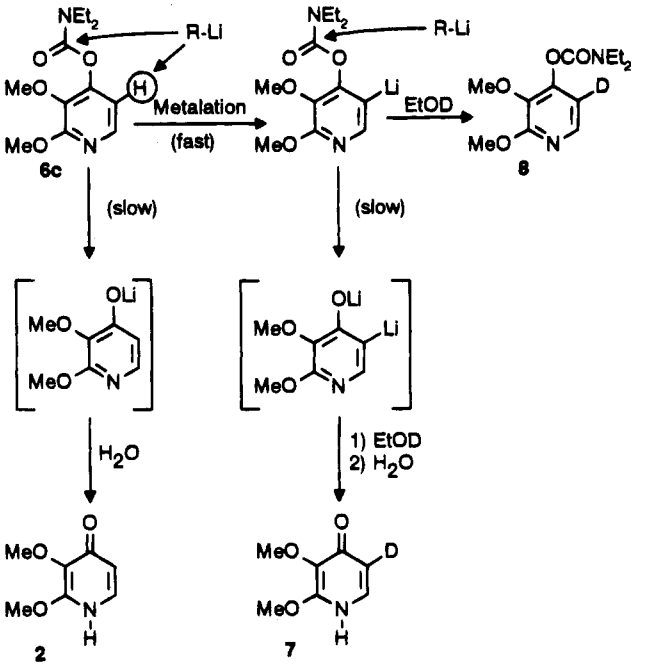
The protective group of the 4-pyridone (**2**) had to fulfill two conditions: it should be selectively cleaved at the end of the synthesis and it had to be a directed metalation group. Several protective groups were tested. Compound **2** was allowed to react via its silver salt[17] in the nonpolar solvents *n*-hexane or toluene. Protection of **2** by isopropyl ether synthesis as well as protection by the (2-(trimethylsilyl)ethoxy)methyl group (SEM) were first chosen. However, **6a** and **6b** could not be lithiated. Since carbamates are renowned for being very powerful directed metalation groups,[18] **6c** and **6d** were synthesized (Scheme 2).

Table 1 Metalation of 6c[a]

metalation time (min)	**8**[b] (%)	**7**[b] (%)
90	0	100 (>98% d)
10	67 (>98% d)	33 (>98% d)
2	92 (90% d)	8 (>98% d)

[a] Metalation of **6c** was carried out with 4 equiv of *s*-BuLi/TMEDA at −70 °C, and then the lithio species were quenched with EtOD. [b] The **8**:**7** ratio and the deuterium incorporation were determined from the ^1H NMR integration values.

Scheme 3



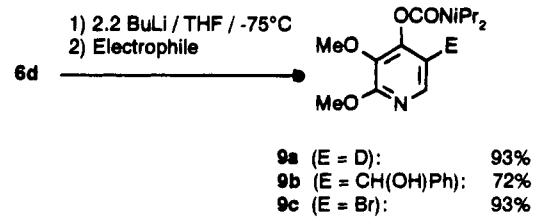
Treatment of *N,N*-diethylcarbamate **6c** with an excess of LDA at −70 °C only led to 25% lithiation, as shown by quenching with EtOD. If metalation was carried out at a higher temperature (−40 °C), only the anionic ortho-Fries type rearrangement product could be isolated.[18a] When stronger bases (PhLi, BuLi, or *s*-BuLi) were used at −70 °C for 1.5 h, deuterated carbamate **8** was obtained together with partially deuterated pyridone (**2** and **7**) (Scheme 3).

We can assume a competition between two different reactions: metalation leading to **8** and nucleophilic addition of the alkyl- or aryllithium to the carbonyl group of the carbamate leading to **2** and **7**. Note that only **7** (and not **2**) was obtained besides **8** with *s*-BuLi/TMEDA. We can consider that the two reactions are simultaneous, but the rate of the metalation seems to be greater than that of the nucleophilic addition (Table 1). In order to obtain a good metalation yield, the reaction time was drastically reduced from 1.5 h to 2 min.

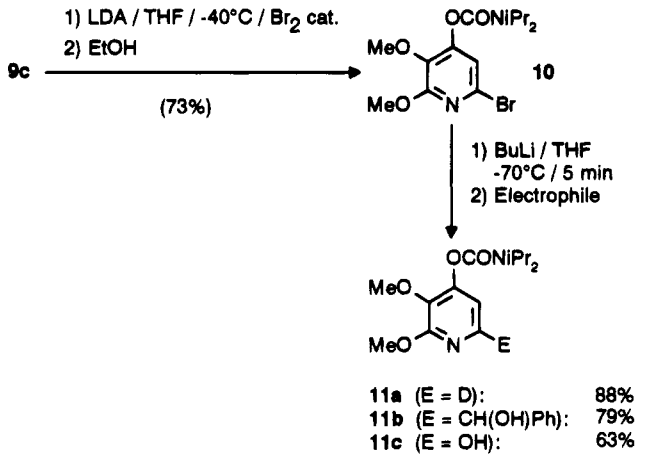
While *N,N*-diethylcarbamate is a widely used directed metalation group,[18] the great sensitivity of **6c** toward

(12) Heinert, D.; Martell, A. E. *Tetrahedron* **1958**, *3*, 49.
(13) (a) Green, K. *J. Org. Chem.* **1991**, *56*, 4325. (b) Marsais, F.; Godard, A.; Quéguiner, G. *J. Heterocycl. Chem.* **1989**, *26*, 1589.
(14) (a) Strogryn, E. L. *J. Heterocycl. Chem.* **1974**, 251. (b) Testaferri, L.; Tiecco, M.; Tingoli, M.; Bartoli, D.; Massoli, A. *Tetrahedron* **1985**, *41*, 1373.
(15) We prepared 2-chloro-3-methoxypyridine starting from 2-chloro-3-hydroxypyridine using 1.05 equiv of MeONa, followed by the reaction of 1.05 equiv of CH_3I in DMF at rt for 1.5 h (yield 77%).
(16) (a) Fisher, F. C.; Havinga, E. *Recueil* **1965**, *84*, 839. (b) Rocca, P. Thesis 1992, 30.
(17) (a) Hopkins, G. C.; Jonak, J. P.; Minnemeyer, H. J.; Tieckelmann, H. *J. Org. Chem.* **1967**, *32*, 4040. (b) Chung, N. M., Tieckelmann, H. *J. Org. Chem.* **1970**, *35*, 2517.
(18) (a) Miah, M. A. J.; Snieckus, V. *J. Org. Chem.* **1985**, *50*, 5436. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (c) Godard, A.; Robin, Y.; Quéguiner, G. *J. Organomet. Chem.* **1987**, *336*, 1. (d) Jacquelin, J. M.; Robin, Y.; Godard, A.; Quéguiner, G. *Can. J. Chem.* **1988**, *66*, 1135.

Scheme 4



Scheme 5



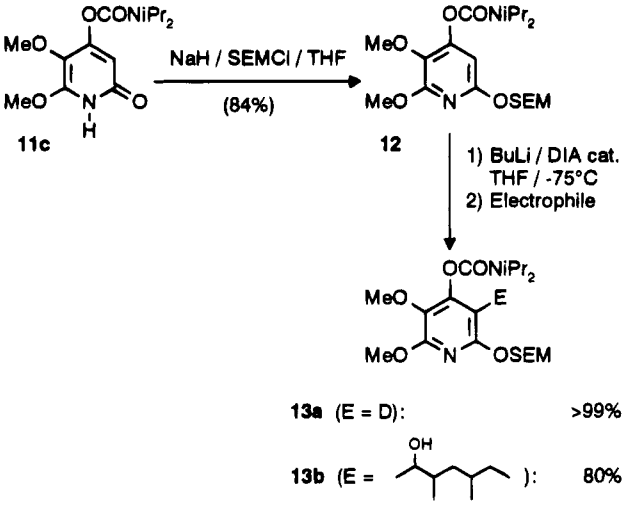
nucleophilic addition led us to prefer the protection of **2** as a *N,N*-diisopropylcarbamate **6d**. The increased steric hindrance between the two groups was sufficient to avoid nucleophilic addition at the carbonyl group. Only metalation occurred, even with a reaction time of 1 h. Carbamate **6d** was selectively lithiated at C-5 by BuLi in THF at −75 °C, and the resulting 5-lithiopyridine derivative could be quenched with electrophiles (Scheme 4). By using BrCN as an electrophile, **9c** could be prepared in a 93% yield.

This 5-bromo derivative was lithiated and isomerized by LDA at −40 °C in the presence of small amounts of bromine, as previously described by us for other cases.[19] After ethanolysis, the 6-bromo derivative **10** was obtained in 73% yield. It was essential to operate in a very concentrated solution to obtain a good yield for this halogen scrambling reaction (also called "halogen-dance"). It can be assumed that an equilibrium exists between the 5-bromo-6-lithiopyridine and the 6-bromo-5-lithiopyridine derivatives, which is shifted to the more stable 5-lithio species.[19]

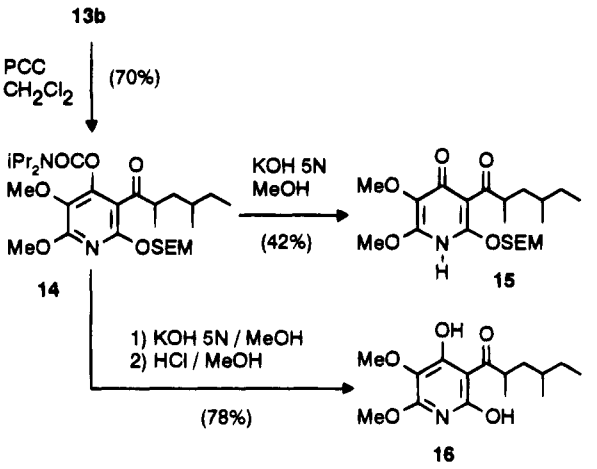
Bromine−lithium exchange on **10**, using BuLi in THF at −70 °C for 5 min, followed by trapping the lithio derivative by electrophiles, gave the expected 6-substituted compounds. The $B(OMe)_3/CH_3CO_3H$ procedure was used for the third time to prepare the 6-pyridone **11c** (Scheme 5).

Pyridone **11c** had to be protected in order to allow a second metalation at C-5. Several groups were tested at C-6, including *N,N*-diisopropylcarbamate (the same group as at C-4), but the best results were obtained with SEM protection. Compound **12** was prepared by reaction of SEMCl with the sodium salt of **11c** in THF in 84% yield; exclusive O-alkylation was surprisingly observed, whereas in these conditions pyridones give generally only N-alkylated products.[20]

Scheme 6



Scheme 7



Pyridine **12** was metalated at C-5 by BuLi catalyzed by some diisopropylamine (DIA) in THF at −75 °C. Reaction of EtOD and 2,4-dimethylhexanal[21] with this lithio derivative gave **13a** and **13b**, respectively, in quite good yields (Scheme 6). Alcohol **13b** was oxidized with pyridinium chlorochromate (PCC)[22] to ketone **14**.

KOH in methanol allowed the cleavage of the carbamate in **14** and 4-pyridone **15** was obtained. An acidic treatment led to atpenin B (**16**), obtained as a mixture of four stereoisomers (two chiral centers). The first deprotection step (**14** → **15**) gave only a 42% yield if **15** was isolated and purified; otherwise the overall yield of the two deprotection steps (**14** → **16**) was 78% (Scheme 7).

Atpenin B (**16**) was therefore synthesized from a "clockwise" functionalization of 2-chloropyridine, in 13 steps (including four metalation steps, one halogen scrambling step, and one halogen−metal exchange step), with a 2.6% overall yield.

(19) (a) Bunnett, J. F. *Acc. Chem. Res.* **1972**, *5*, 139. (b) Mallet, M.; Marsais, F.; Quéguiner, G.; Pastour, P. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1972**, *275*, 1439. (c) Mallet, M.; Quéguiner, G. *Tetrahedron* **1982**, *38*, 3035. (d) Mallet, M.; Quéguiner, G. *Tetrahedron* **1985**, *41*, 3433. (e) Marsais, F.; Pineau, Ph.; Nivolliers, F.; Mallet, M.; Turck, A.; Godard, A.; Quéguiner, G. *J. Org. Chem.* **1992**, *57*, 565.

(20) Meghani, P.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1.

(21) The 2,4-dimethylhexanal used was a mixture of four stereoisomers (two chiral centers). It was prepared according to the following published procedure: Brown, H. C.; Kabalka, G. W.; Rathke, M. W.; Rogic, M. M. *J. Am. Chem. Soc.* **1968**, 4165.

(22) (a) Corey E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647. (b) Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis* **1982**, 245.

Experimental Section

General. Spectroscopic measurements were made as reported recently.[2] Tetrahydrofuran (THF) was distilled from benzophenone/sodium. The water content of the solvent was estimated to be lower than 45 ppm by the modified Karl-Fischer method.[23]

All solutions were dried over $MgSO_4$, the solvents were evaporated under reduced pressure, and the crude product was chromatographed on a silica gel column (eluent is given in the product description).

Starting Materials. Commercial 2-chloropyridine (**3**), diisopropylamine, and *N,N,N,N*-tetramethyl-1,2-ethylenediamine (TMEDA) were distilled from CaH_2 and stored over CaH_2 under a dry argon atmosphere. 2,3-Dimethoxypyridine (**4**)[14] was prepared in a three-step sequence from **3** by metalation[11] and oxidation [(1) 1,3 equiv of PhLi/THF/−40 °C/1 h; (2) $B(OMe_3)$/−70 °C/2 h; (3) CH_3CO_3H: 65%] to give 2-chloro-3-hydroxypyridine. This compound[12] was methylated (MeONa/CH_3I/DMF/rt/1.5 h: 77%) and 2-chloro was substituted by MeONa to afford, after distillation, bp 98 °C/15 Torr (lit.[14a] bp 100 °C/17 Torr), **4** in 75% yield.[14a] 2,4-Dimethylhexanal was synthesized from tri-*sec*-butylborane and methacrolein.[21] Commercial solutions of *n*-butyllithium (BuLi, 2.5 M), *sec*-butyllithium (*s*-BuLi), and phenyllithium (PhLi) were employed as received. Metalations were carried out under dry argon.

General Procedure A: Synthesis of 4-Substituted 2,3-Dimethoxypyridines. BuLi (4.4 mmol) was slowly added to a cold (−70 °C) solution of 2,3-dimethoxypyridine (**4**) (0.278 g, 2.0 mmol) in THF (15 mL), and the mixture was stirred for 1 h at 0 °C and cooled to −70 °C before addition of the required electrophile as mentioned in the product description. After the electrophile had reacted, the solution was hydrolyzed at −70 °C, warmed to room temperature, treated with 10 mL of water and with K_2CO_3, and then extracted several times with CH_2Cl_2.

4-Deuterio-2,3-dimethoxypyridine (5a). The general procedure A, using DCl in THF, gave quantitatively **5a** (^1H NMR integration >99%). Eluent: CH_2Cl_2. The physical characteristics of this product were found to be identical to those described for **4**[14] excepted for the ^1H and ^{13}C NMR spectra; ^1H NMR ($CDCl_3$) δ 3.85 (s, 3H), 4.00 (s, 3H), 6.82 (d, 1H, J = 5.0 Hz), 7.71 (d, 1H, J = 5.0 Hz); ^{13}C NMR ($CDCl_3$) δ 53.4, 55.4, 116.5, 116−117 (t), 136.9, 143.9, 154.2.

1-(2,3-Dimethoxy-4-pyridyl)phenylmethanol (5b). The general procedure A, using benzaldehyde in THF at −70 °C, with stirring for 2 h, gave 71% of **5b** (eluent: CH_2Cl_2/Et_2O (95/5)): oil; ^1H NMR ($CDCl_3$) δ 3.57 (s, 3H), 3.64 (d, 1H, J = 4 Hz), 3.95 (s, 3H), 6.01 (d, 1H, J = 4 Hz), 7.03 (d, 1H, J = 5.2 Hz), 7.22−7.37 (m, 5H), 7.82 (d, 1H, J = 5.2 Hz); ^{13}C NMR ($CDCl_3$) δ 53.4, 59.8, 70.5, 114.9, 126.4, 127.6, 128.3, 140.2, 140.6, 142.6, 145.3, 157.3; IR (KBr) 3400, 2946, 1598, 1463, 1397, 1237, 1096, 1035. Anal. Calcd for $C_{14}H_{15}NO_3$ (245.28): C, 68.56; H, 6.16; N, 5.71. Found: C, 68.23; H, 6.10; N, 5.84.

4-Bromo-2,3-dimethoxypyridine (5c). The general procedure A, using BrCN in THF at −70 °C, with stirring for 1 h, gave 60% of **5c** (eluent: CH_2Cl_2/hexane (1/1)): mp <40 °C; ^1H NMR ($CDCl_3$) δ 3.88 (s, 3H), 4.00 (s, 3H), 7.06 (d, 1H, J = 5.4 Hz), 7.70 (d, 1H, J = 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 53.9, 60.3, 121.3, 126.0, 141.0, 141.7, 158.3; IR (KBr) 2933, 1568, 1467, 1396, 1026. Anal. Calcd for $C_7H_8BrNO_2$ (218.05): C, 38.56; H, 3.70; N, 6.42. Found: C, 38.71; H, 3.75; N, 6.19.

2,3-Dimethoxypyrid-4(1*H*)-one (2). The general procedure A, using trimethylborate slowly added at −70 °C, with stirring for 2 h. A solution of peracetic acid (32 wt % in dilute acetic acid) was then added, and the mixture was slowly warmed to room temperature. After the mixture was cooled to −10 °C, an aqueous solution of sodium hydrogenosulfite was poured dropwise. A 64% yield of **2** was obtained (eluent: CH_2Cl_2/Et_2O (94/6)): mp 77 °C; ^1H NMR ($CDCl_3$) 3.81 (s, 3H), 3.97 (s, 3H), 6.54 (d, 1H, J = 5.7 Hz), 7.2 (s, 1H), 7.69 (d, 1H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 53.7, 60.4, 107.0, 130.4, 141.1, 156.2, 157.5; IR (KBr) 3200, 3000, 1605, 1468, 1410, 1150, 1106. Anal. Calcd for $C_7H_9NO_3$ (155.15): C, 54.19; H, 5.85; N, 9.03. Found: C, 54.19; H, 5.79; N, 8.82.

General Procedure B: Protection of 2,3-Dimethoxypyrid-4(1*H*)-one (2). To the pyridone **2** (3.9 g, 0.025 mol) in toluene or hexane (100 mL) were added silver carbonate (8.3 g) and halo derivative (0.030 mmol). The mixture was stirred in the dark; reaction conditions (solvent, time and temperature) are given in the product description. Silver salts were filtered on Celite and washed with CH_2Cl_2.

2,3-Dimethoxy-4-isopropoxypyridine (6a). The general procedure B, using isopropyl iodide in hexane at room temperature for 7 d, gave 93% of **6a** (eluent: CH_2Cl_2/Et_2O (97/3)): oil; ^1H NMR ($CDCl_3$) δ 1.31 (d, 6H, J = 6.1 Hz), 3.75 (s, 3H), 3.91 (s, 3H), 4.55 (sept, 1H, J = 6.1 Hz), 6.47 (d, 1H, J = 5.8 Hz), 7.70 (d, 1H, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$) δ 21.8, 53.5, 60.2, 71.0, 104.8, 132.5, 141.1, 157.2, 158.9; IR (film) 2978, 1590, 1489, 1465, 1401, 1287, 1228, 1114. Anal. Calcd for $C_{10}H_{15}NO_3$ (197.24): C, 60.90; H, 7.67; N, 7.10. Found: C, 60.80; H, 7.86; N, 7.22.

2,3-Dimethoxy-4-((2-(trimethylsilyl)ethoxy)methoxy)-pyridine (6b). The general procedure B, using (2-(trimethylsilyl)ethoxy)methyl chloride (SEMCl) in toluene at 50 °C for 4 d, gave 60% of **6b** (eluent: CH_2Cl_2/Et_2O (96/4)): oil; ^1H NMR ($CDCl_3$) δ −0.02 (s, 9H), 0.94 (t, 2H, J = 8.3 Hz), 3.77 (t, 2H, J = 8.3 Hz), 3.84 (s, 3H), 3.98 (s, 3H), 5.30 (s, 2H), 6.77 (d, 1H, J = 5.8 Hz), 7.77 (d, 1H, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$) δ −1.5, 18.0, 53.7, 60.6, 66.8, 92.9, 105.9, 132.5, 141.3, 156.7, 158.8; IR (film) 2952, 1593, 1467, 1401, 1119, 1076. Anal. Calcd for $C_{13}H_{23}NO_4Si$ (285.42): C, 54.71; H, 8.12; N, 4.91. Found: C, 54.86; H, 8.16; N, 4.91.

2,3-Dimethoxy-4-pyridyl *N,N*-Diethylcarbamate (6c). The general procedure B, using diethylcarbamyl chloride in toluene at 80 °C for 48 h, gave 71% of **6c** (eluent: CH_2Cl_2/Et_2O (97/3)): oil; ^1H NMR ($CDCl_3$) δ 1.19 and 1.24 (2t, 2 × 3H, J = 7.1 Hz), 3.37 and 3.42 (2q, 2 × 2H, J = 7.1 Hz), 3.83 (s, 3H), 3.98 (s, 3H), 6.72 (d, 1H, J = 5.6 Hz), 7.81 (d, 1H, J = 5.6 Hz); IR (film) 2977, 2944, 1728, 1593, 1469, 1401, 1268, 1255, 1152, 1097, 1076. Anal. Calcd for $C_{12}H_{18}N_2O_4$ (254.29): C, 56.68; H, 7.13; N, 11.02. Found: C, 56.78; H, 7.16; N, 11.14.

2,3-Dimethoxy-4-pyridyl *N,N*-Diisopropylcarbamate (6d). The general procedure B, using diisopropylcarbamyl chloride in toluene at 80 °C for 48 h, gave 70% of **6d** (eluent: CH_2Cl_2/Et_2O (96/4)): mp 74−75 °C; ^1H NMR ($CDCl_3$) δ 1.28 (d, 12H, J = 6.8 Hz), 3.81 (s, 3H), 3.96 (s, 3H), 3.99 (sept., 2H, J = 6.8 Hz), 6.70 (d, 1H, J = 5.6 Hz), 7.79 (d, 1H, J = 5.6 Hz); ^{13}C NMR ($CDCl_3$) δ 20.2−21.0, 46.6, 53.5, 59.9, 112.6, 135.7, 140.4, 150.8, 152.1, 158.8; IR (KBr) 2970, 1718, 1593, 1460, 1396, 1093, 1074. Anal. Calcd for $C_{14}H_{22}NO_4$ (282.34): C, 59.56; H, 7.85; N, 9.92. Found: C, 59.64; H, 7.85; N, 9.72.

5-Deuterio-2,3-dimethoxy-4-pyridyl *N,N*-Diethylcarbamate (8). *s*-BuLi (2.9 mmol) and TMEDA (0.44 mL, 2.9 mmol) in THF (6 mL) were stirred for 10 min at −75 °C. Carbamate **6c** (0.147 g, 0.58 mmol) in THF (2 mL) was quickly added, and the mixture was stirred for 2 min before addition at this temperature of EtOD in THF. The mixture was warmed to room temperature, treated with 5 mL of a saturated aqueous solution of NH_4Cl, and extracted with CH_2Cl_2. Eluent: CH_2Cl_2/Et_2O (97/3). The yield was 92% of **8** with a deuterium incorporation of 90% (determined from the ^1H NMR integration values). The physical characteristics of this product were found to be identical to those described for **6c** except for the ^1H NMR spectrum: ^1H NMR ($CDCl_3$) δ 1.20 and 1.25 (2t, 2 × 3H, J = 7.1 Hz), 3.38 and 3.42 (2q, 2 × 2H, J = 7.1 Hz), 3.84 (s, 3H), 3.98 (s, 3H), 7.82 (s, 1H).

General Procedure C: Synthesis of 5-Substituted 2,3-Dimethoxy-4-pyridyl *N,N*-Diisopropylcarbamates. BuLi (1.65 mmol) was slowly added to a cold (−75 °C) solution of 2,3-dimethoxy-4-pyridyl *N,N*-diisopropylcarbamate (**6d**) (0.212 g, 0.75 mmol) in THF (12 mL), and the mixture was stirred for 1 h at −75 °C before addition at this temperature of the required electrophile as mentioned in the product description. After the electrophile had reacted, the solution was hydrolyzed at −75 °C by an excess of H_2O/EtOH/THF, warmed to room temperature, treated with 5 mL of a saturated aqueous solution of NH_4Cl, and extracted with CH_2Cl_2.

(23) Bizot, J. *Bull. Soc. Chim. Fr.* **1967**, *1*, 151.

5-Deuterio-2,3-dimethoxy-4-pyridyl *N,N*-Diisopropylcarbamate (9a). The general procedure C, using EtOD in THF, gave 93% of **9a**. Eluent: CH_2Cl_2/Et_2O (98/2). The physical characteristics of this product were found to be identical to those described for **6d** except for the ^1H NMR spectrum: ^1H NMR ($CDCl_3$) δ 1.29 (d, 12H, J = 6.8 Hz), 3.82 (s, 3H), 3.98 (s, 3H), 4.00 (sept., 2H, J = 6.8 Hz), 7.81 (s, 1H).

2,3-Dimethoxy-5-(1-hydroxy-1-phenylmethyl)-4-pyridyl *N,N*-Diisopropylcarbamate (9b). The general procedure C, using benzaldehyde in THF, with stirring for 2 h, gave 72% of **9b** (eluent: CH_2Cl_2/Et_2O (90/10)): oil; ^1H NMR ($CDCl_3$) δ 1.21 and 1.27 (2d, 2 × 6H, J = 6.7 Hz), 3.62 (s, 1H), 3.81 (s, 3H), 3.84 and 3.95 (2 sept, 2 × 1H, J = 6.7 Hz), 3.99 (s, 3H), 5.85 (s, 1H), 7.18–7.40 (m, 5H), 7.84 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.2–20.9, 46.6–47.2, 53.7, 60.0, 69.8, 126.2, 127.2, 127.7, 128.1, 135.8, 140.6, 142.2, 149.1, 152.4, 158.1; IR (KBr) 3432, 2971, 1719, 1601, 1471, 1405, 1314, 1107. Anal. Calcd for $C_{21}H_{28}N_2O_5$ (388.47): C, 64.93; H, 7.27; N, 7.21. Found: C, 64.66; H, 7.41; N, 7.24.

5-Bromo-2,3-dimethoxy-4-pyridyl *N,N*-Diisopropylcarbamate (9c). The general procedure C, using BrCN in THF, with stirring for 2 h, gave 93% of **9c** (eluent: CH_2Cl_2/Et_2O (98/2)): oil; ^1H NMR ($CDCl_3$) δ 1.29 and 1.34 (2d, 2 × 6H, J = 6.7 Hz), 3.84 (s, 3H), 3.96 (s, 3H), 4.01 and 4.04 (2 sept, 2 × 1H, J = 6.7 Hz), 7.97 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.2–21.3, 46.9–47.0, 53.9, 60.2, 107.8, 137.5, 141.4, 148.7, 151.0, 157.9; IR (KBr) 2970, 1729, 1574, 1470, 1402, 1315, 1093. Anal. Calcd for $C_{14}H_{21}N_2O_4Br$ (361.24): C, 46.55; H, 5.86; N, 7.75. Found: C, 46.67; H, 5.91; N, 7.88.

6-Bromo-2,3-dimethoxy-4-pyridyl *N,N*-Diisopropylcarbamate (10). Lithium diisopropylamide (LDA) was prepared by reaction of BuLi (0.030 mol) and diisopropylamine (0.030 mol) in THF (25 mL) at −70 °C for 15 min. 5-Bromo-2,3-dimethoxy-4-pyridyl *N,N*-diisopropylcarbamate (**9c**) (0.010 mol) in THF (10 mL) was added at −70 °C. The solution was warmed to −40 °C and 2 μL of bromine was added to catalyze the isomerization. It was kept under stirring for 1 h at −40 °C and then cooled to −70 °C, whereupon an excess of EtOH in THF was added. The mixture was warmed to room temperature, treated with a saturated aqueous solution of NH_4Cl, and then extracted with CH_2Cl_2. Eluent: CH_2Cl_2/Et_2O (99.5/0.5). The yield was 2.64 g (73%): oil; ^1H NMR ($CDCl_3$) δ 1.29 (d, 12H, J = 6.8 Hz), 3.81 (s, 3H), 3.98 (s, 3H), 3.99 (sept, 2H, J = 6.8 Hz), 6.93 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.2–21.1, 46.8, 54.3, 60.0, 116.0, 130.0, 135.2, 151.6, 152.0, 157.7; IR (KBr) 2970, 1726, 1584, 1475, 1423, 1374, 1299, 1095. Anal. Calcd for $C_{14}H_{21}N_2O_4Br$ (361.24): C, 46.55; H, 5.86; N, 7.75. Found: C, 46.31; H, 6.06; N, 7.88.

General Procedure D: Synthesis of 6-Substituted 2,3-Dimethoxy-4-pyridyl *N,N*-Diisopropylcarbamates. 6-Bromo-2,3-dimethoxy-4-pyridyl *N,N*-diisopropyl)carbamate (**10**) (0.252 g, 0.70 mmol) in THF (5 mL) was quickly added to a cold (−75 °C) solution of BuLi (1.54 mmol) in THF (20 mL), and the mixture was stirred for 5 min, before addition at −75 °C of the required electrophile as mentioned in the product description. After the electrophile had reacted, the solution was treated by an excess of EtOH in THF. The mixture was warmed to room temperature, a saturated aqueous solution of NH_4Cl was added, and then the mixture was extracted with CH_2Cl_2.

6-Deuterio-2,3-dimethoxy-4-pyridyl *N,N*-Diisopropylcarbamate (11a). The general procedure D, using EtOD in THF, gave 88% of **11a** (eluent: CH_2Cl_2/Et_2O (98/2)). The physical characteristics of this product were found to be identical to those described for **6d** and **9a** except for the ^1H NMR spectrum: ^1H NMR ($CDCl_3$) δ 1.29 (d, 12H, J = 6.8 Hz), 3.82 (s, 3H), 3.98 (s, 3H), 4.00 (sept, 2H, J = 6.8 Hz), 6.70 (s, 1H).

2,3-Dimethoxy-6-(1-hydroxy-1-phenylmethyl)-4-pyridyl *N,N*-Diisopropylcarbamate (11b). The general procedure D, using benzaldehyde in THF, with stirring for 2 h gave 79% of **11b** (eluent: CH_2Cl_2/Et_2O (95/5)): oil; ^1H NMR ($CDCl_3$) δ 1.29 (d, 12H, J = 6.8 Hz), 3.84 (s, 3H), 3.99 (sept, 2H, J = 6.8 Hz), 4.04 (s, 3H), 4.68 (d, 1H, J = 4.1 Hz), 5.62 (d, 1H, J = 4.1 Hz), 6.63 (s, 1H), 7.22–7.44 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.2–21.1, 46.7, 53.7, 59.9, 74.6, 109.4, 126.8, 127.5, 128.2, 134.3, 142.8, 151.5, 152.0, 152.6, 157.4; IR (KBr) 3439, 2971, 1720, 1591, 1479, 1380, 1308, 1095. Anal. Calcd for $C_{21}H_{28}N_2O_5$ (388.47): C, 64.93; H, 7.27; N, 7.21. Found: C, 64.79; H, 7.28; N, 6.98.

4-((*N,N*-Diisopropylcarbamoyl)oxy)-2,3-dimethoxypyrid-6(1*H*)-one (11c). The general procedure D, using trimethylborate, with stirring for 2 h. A solution of peracetic acid (32 wt % in dilute acetic acid) was then added, and the mixture was warmed to 0 °C under stirring for 2 h and then cooled to −10 °C, whereupon an aqueous solution of sodium hydrogenosulfite was poured dropwise. A 63% yield of **11c** was obtained (eluent: CH_2Cl_2/Et_2O (gradient from 96/4 to 90/10)): mp 113–114 °C; ^1H NMR ($CDCl_3$) δ 1.29 (d, 12H, J = 6.8 Hz), 3.74 (s, 3H), 3.89 (s, 3H), 4.00 (sept, 2H, J = 6.8 Hz), 6.08 (s, 1H), 8.4 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.2–21.0, 46.7, 54.1, 60.2, 95.4, 129.6, 152.1, 154.2, 156.3, 156.6; IR (KBr) 3340, 2974, 1708, 1616, 1597, 1482, 1426, 1315, 1147, 1100. Anal. Calcd for $C_{14}H_{22}N_2O_5$ (298.34): C, 56.36; H, 7.43; N, 9.39. Found: C, 56.06; H, 7.74; N, 9.46.

6-((2-(Trimethylsilyl)ethoxy)methoxy)-2,3-dimethoxy-4-pyridyl *N,N*-Diisopropylcarbamate (12). To a stirred solution of NaH (80% in mineral oil, 0.5 g) in THF (20 mL) was added pyridone **11c** (0.84 g, 2.8 mmol) in 15 mL of THF. After the mixture was stirred for 15 min, SEMCl (4.2 mmol) was added at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 45 min. Another portion of SEMCl (4.2 mmol) was then added, and the mixture was stirred at room temperature for 30 min. The hydride excess was treated by AcOH/EtOH/THF at 0 °C and then by an aqueous solution of K_2CO_3. Extraction by CH_2Cl_2, drying over $MgSO_4$, and solvent removal afforded a crude product which was purified by column chromatography on silica gel (eluent: CH_2Cl_2/Et_2O (98/2)). The yield was 1.02 g (84%): oil; ^1H NMR ($CDCl_3$) δ 0.00 (s, 9H), 0.97 (t, 2H, J = 8.4 Hz), 1.31(d, 12H, J = 6.8 Hz), 3.77 (s, 3H), 3.79 (t, 2H, J = 8.4 Hz), 3.95 (s, 3H), 4.01 (sept, 2H, J = 6.8 Hz), 5.44 (s, 2H, OCH_2O, NOE effect (3.2%) between this signal and the H_5 signal), 6.23 (s, 1H, H_5); ^{13}C NMR ($CDCl_3$) δ −1.5, 18.0, 20.3–21.3, 46.7, 53.6, 60.2, 66.8, 90.8, 96.6, 130.3, 152.2, 153.7, 156.1, 156.2; IR (KBr) 2952, 1725, 1591, 1482, 1383, 1309, 1099. Anal. Calcd for $C_{20}H_{36}N_2O_6Si$ (428.61): C, 56.05; H, 8.47; N, 6.54. Found: C, 56.45; H, 8.49; N, 6.47.

General Procedure E: Synthesis of 5-Substituted 2,3-Dimethoxy-6-((2-(trimethylsilyl)ethoxy)methoxy)-4-pyridyl *N,N*-Diisopropylcarbamates. BuLi (2.4 mmol) was slowly added to a cold (−75 °C) solution of **12** (0.345g, 0.8 mmol) in THF (10 mL), and the mixture was stirred for 1 h at −75 °C, before addition of the required electrophile as mentioned in the product description. After the electrophile had reacted, the solution was hydrolyzed at −75 °C by an excess of $AcOH/H_2O/EtOH/THF$, warmed to room temperature, treated with an aqueous solution of K_2CO_3, and extracted by CH_2Cl_2.

5-Deuterio-2,3-dimethoxy-6-((2-(trimethylsilyl)ethoxy)methoxy)-4-pyridyl *N,N*-Diisopropylcarbamate (13a). The general procedure E, using EtOD in THF, gave **13a** quantitatively (^1H NMR integration >99%). The physical characteristics of this product were found to be identical to those described for **12** except for the ^1H NMR spectrum where the H_5 signal at 6.23 ppm disappeared.

2,3-Dimethoxy-5-(2,4-dimethyl-1-hydroxyhexyl)-6-((2-(trimethylsilyl)ethoxy)methoxy)-4-pyridyl *N,N*-Diisopropylcarbamate (13b). The general procedure E, using 2,4-dimethylhexanal (added pure and quickly), with stirring for 45 min, gave 80% of **13b** (eluent: CH_2Cl_2/Et_2O (97/3)): oil; ^1H NMR ($CDCl_3$) δ −0.01 (s, 9H), 0.65–2.2 (m, 15H), 1.29 (d, 12H, J = 6.7 Hz), 3.75 (s, 3H), 3.77 (m, 2H), 3.92 (s, 3H), 4.08 (m, 2H), 4.42 (m, 1H), 5.57 (m, 2H); ^{13}C NMR ($CDCl_3$) δ −1.6, 10.7–10.9–11.0–11.4, 15.9–16.5–16.7–17.7, 17.9, 18.3–18.5–18.6–18.8, 20.3–21.2, 27.7–28.0–29.3–30.6, 31.3–31.6–31.8–32.0, 36.1–36.4–36.8–37.0, 40.2–40.4–40.7–41.1, 46.5–46.9, 53.3, 59.7–59.8, 67.3–67.4, 72.4–72.5, 90.3–90.4, 110.8–111.0, 130.3, 151.4–151.6–151.8, 152.7–152.8, 153.9–154.0; IR (KBr) 3435, 2958, 1725, 1590, 1470, 1083, 1042. Anal. Calcd for $C_{28}H_{52}N_2O_7Si$ (556.82): C, 60.40; H, 9.41; N, 5.03. Found: C, 60.19; H, 9.57; N, 4.84.

2,3-Dimethoxy-5-(2,4-dimethyl-1-oxohexyl))-6-((2-(tri-

methylsilyl)ethoxy)methoxy)-4-pyridyl *N,N*-Diisopropylcarbamate (14). To a solution of alcohol **13b** (0.278 g, 0.5 mmol) in CH_2Cl_2 (7 mL) was added molecular sieves (0.32 g) and pyridinium chlorochromate (PCC, 1.5 mmol). The mixture was well stirred for 1.5 h at room temperature and then diluted in Et_2O and filtered on Celite. After the mixture was dried over Na_2SO_4, solvents were removed to afford a crude product, which was purified by column chromatography on silica gel (eluent: CH_2Cl_2/Et_2O (98/2)). The yield was 0.194 g (70%): oil; ^1H NMR ($CDCl_3$) δ −0.02 (s, 9H), 0.83−1.45 (m, 13H), 0.94 (t, 2H, J = 8.4 Hz), 1.25 and 1.29 (2d, 2 × 6H, J = 6.5 Hz), 1.71−1.82 (m, 1H), 3.18−3.31 (m, 1H), 3.73 (t, 2H, J = 8.4 Hz), 3.76 (s, 3H), 3.95 (s, 3H), 3.95 (sept, 2H, J = 6.5 Hz), 5.46−5.61 (m, 2H); ^{13}C NMR ($CDCl_3$) δ −1.5, 11.1, 15.5−16.8, 18.0, 19.2−19.6, 20.3−21.0, 28.9−30.2, 31.7−31.8, 39.0−39.9, 44.0, 46.5−47.0, 53.8, 60.0, 67.3, 90.4, 111.4, 130.7, 151.3, 151.5, 152.8, 156.2, 204.3−204.6; IR (KBr) 2959, 1726, 1589, 1469, 1310, 1086, 1041. Anal. Calcd for $C_{28}H_{50}N_2O_7Si$ (554.81): C, 60.62; H, 9.08; N, 5.05. Found: C, 60.79; H, 9.29; N, 5.36.

2,3-Dimethoxy-5-(2,4-dimethyl-1-oxohexyl)-6-((2-(trimethylsilyl)ethoxy)methoxy) pyrid-4(1H)-one (15). Carbamate **14** (0.166 g, 0.3 mmol) was refluxed for 20 h in a 5 N solution of KOH in methanol. Solvent was removed, and diluted AcOH was added. The mixture was treated by $NaHCO_3$, extracted with CH_2Cl_2, and dried over $MgSO_4$. Solvent removal afforded a crude product which was purified by chromatography (eluent: CH_2Cl_2). The yield was 0.054 g (42%): oil; ^1H NMR ($CDCl_3$) δ 0.02 (s, 9H), 0.83−2.0 (m, 14H), 1.00 (t, 2H, J = 8.3 Hz), 3.81 (t, 2H, J = 8.3 Hz), 3.82 (s, 3H), 3.88−4.04 (m, 1H), 3.99 (s, 3H), 5.61−5.75 (m, 2H), 14.33 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −1.45, 11.3, 17.3−18.6, 18.1, 18.9−19.5, 29.6−30.0, 32.2−32.3, 40.0−40.5, 41.8−42.0, 53.9, 60.6, 68.1, 91.2−91.4, 100.7−100.9, 125.4, 157.2−158.0, 165.8, 210.9−211.1; IR (KBr) 2957, 1628, 1574, 1448, 1289, 1249, 1103. Anal. Calcd for $C_{21}H_{37}NO_6Si$ (427.62): C, 58.99; H, 8.72; N, 3.28. Found: C, 58.71; H, 8.59; N, 3.17.

2,4-Dihydroxy-5,6-dimethoxy-3-((2*RS*,4*RS*)-2,4-dimethyl-1-oxohexyl)pyridine (Atpenin B) (16). **14** (0.101 g, 0.18 mmol) was dissolved in a 5 N solution of KOH in methanol and refluxed for 24 h. Diluted AcOH was added, and the mixture was treated by $NaHCO_3$ and extracted. Solvent removal afforded crude **15**, which was *not* purified, but dissolved in a solution of concd HCl in MeOH (1/10) and refluxed for 1 h. Methanol was evaporated, and the reaction mixture was treated by an aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, and dried over $MgSO_4$. Solvent removal afforded a product which was purified by chromatography on silica gel (eluent: CH_2Cl_2/Et_2O (98/2)) to give 42.5 mg of **16**. The yield was 78% from **14**: mp 77−78 °C (lit.[5a] mp 78 °C for natural (−)-atpenin B); ^1H NMR ($CDCl_3$) δ 0.83−0.90 (m, 3H + 3H), 1.13 and 1.15 (2d, 3H, J = 6.8 Hz), 1.0−2.0 (m, 5H), 3.80 (s, 3H), 4.00−4.15 (m, 1H), 4.17 (s, 3H); ^1H NMR (C_5D_5N) δ 0.71 and 0.75 (2t, 3H, J = 7.2 Hz), 0.83 and 0.86 (2d, 3H, J = 6.5 Hz), 1.19 and 1.22 (2d, 3H, J = 6.7 Hz), 0.9−2.1 (m, 5H), 3.71 (s, 3H), 3.78 (s, 3H), 4.26−4.45 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 11.1−11.2, 16.9−18.2, 18.7−19.3, 29.3−29.8, 32.0−32.2, 39.7−40.1, 40.2−40.4, 57.2, 61.3, 100.0, 121.4, 155.6, 161.6, 210.5; ^{13}C NMR (C_5D_5N) δ 11.6−11.8, 17.1−18.6, 19.1−20.0, 29.8−30.7, 32.7−32.9, 41.1−41.4, 41.7−41.9, 54.3, 60.6, 100.7−101.0, 124.9, 159.9, 162.6, 165.8, 211.6−211.7; IR (KBr) 2960, 1647, 1604, 1443, 1328, 1196, 1163, 995; HRMS (EI) calcd for $C_{15}H_{23}NO_5$ 297.1576, found 297.1572 ($M^{\bullet+}$, 20), 240.0839 ($M^{\bullet+} - C_4H_9$, 30), 198.0382 ($M^{\bullet+} - C_7H_{15}$, 100). Anal. Calcd for $C_{15}H_{23}NO_5$ (297.35): C, 60.59; H, 7.80; N, 4.71. Found: C, 60.53; H, 7.82; N, 4.36. These data are in agreement with those reported[5] for natural (−)-atpenin B.

Acknowledgment. Financial support of this research by the French Ministère de la Recherche et de la Technologie (MRT Grant No. 9126) is gratefully acknowledged.