First Synthesis of (±)-Harzianopyridone by Metalation of Polysubstituted *O*-Pyridylcarbamates

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The first synthesis of (±)-harzianopyridone, an antifungal metabolite of *Trichoderma harzianum*, has been achieved by metalation of 6-substituted-2,3-dimethoxy-4-pyridyl-*N,N*-diisopropylcarbamates. Moreover, the chosen strategy allowed the preparation of harzianopyridone analogs, by varying the groups at C-4, C-5 and C-6 on the pyridine ring.

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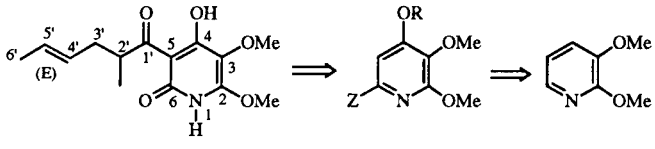
Introduction.

Harzianopyridone (**1**) is an antifungal metabolite of *Trichoderma harzianum* [1]. Its structure [2] features a penta-substituted pyridine with a 2,3-dimethoxy-4-pyridinol pattern, common with other natural molecules endowed with biological and pharmacological properties, such as piericidins [3] (isolated from *Streptomyces mobaraensis* and *pactum*), atpenins [4] (three antibiotics produced by *Penicillium* sp. FO-125) and the recently isolated angiogenesis inhibitors WF-16775 A1 and A2 [5] (from *Chaestasbolisia erysiophoides*).

Because of our interest in the synthesis of pyridine-containing natural products [6], and our expertise in the metalation field [7], we chose them as target molecules. We now report the first synthesis of (±)-harzianopyridone (**1**), in which the side chain at C-5 could be introduced by metalation of conveniently tetrasubstituted pyridines (Scheme I).

Scheme I



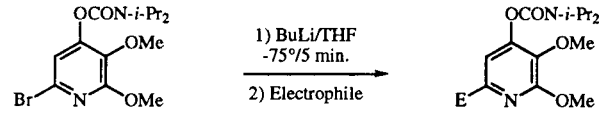
1

Harzianopyridone exhibits a moderate antifungal activity. Rodgers prepared hemisynthetic derivatives of the natural molecule, but this led to very limited structural modifications [1b]. Our strategy was chosen because it allows us to synthesize a large number of analogs, in order to obtain compounds enhancing the activity of harzianopyridone. The retrosynthetic Scheme I shows that it is possible to vary the side chain at C-5, as well as to introduce different groups at C-4 and C-6.

Results.

6-Bromo-2,3-dimethoxy-4-pyridyl *N,N*-diisopropylcarbamate (**2**) could be prepared in four steps from 2,3-dimethoxypyridine (overall yield, 30%) [8]. Bromine-lithium exchange at C-6 on **2**, using *n*-butyllithium at -70°, followed by reaction of the lithio derivative with the trimethylborate-peracetic acid tandem [8], or with hexachloroethane, gave respectively the expected 6-substituted derivatives **3** and **4** (Scheme II).

Scheme II

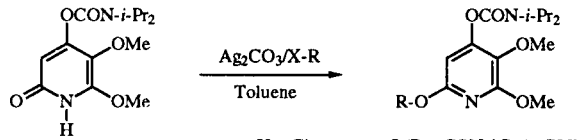


2

3 (E = OH): 63%
4 (E = Cl): 67%

The pyridone **3** was protected *via* its silver salt to give the *N,N*-diisopropylcarbamate **5** and the isopropoxyl derivative **6**. A protection *via* the sodium salt gave the [2-(trimethylsilyl)ethoxy]methoxy (OSEM) derivative **7** [8]. In all cases, an exclusive *O*-alkylation was observed (Scheme III).

Scheme III



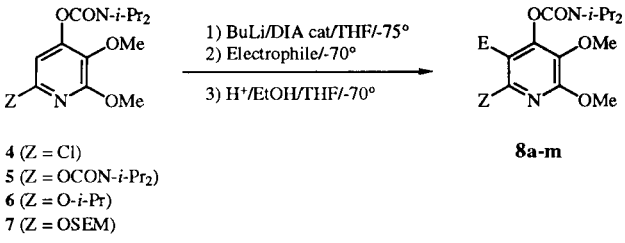
3

X = Cl
X = I

5 (R = CON-*i*-Pr$_2$): 72%
6 (R = *i*-Pr): 86%

The metalation conditions of the 6-chloropyridine **4** were first studied. Attempts with lithium diisopropylamide (LDA), even with 4 equivalents, gave no metalation, and the starting material was quantitatively recovered. A stronger metalating reagent, *n*-butyllithium, was then successfully used for the 6-chloropyridine **4** as well as for the protected pyridones **5**, **6** and **7**. Metalation

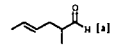
Scheme IV



4 (Z = Cl)
5 (Z = OCON-*i*-Pr$_2$)
6 (Z = O-*i*-Pr)
7 (Z = OSEM)

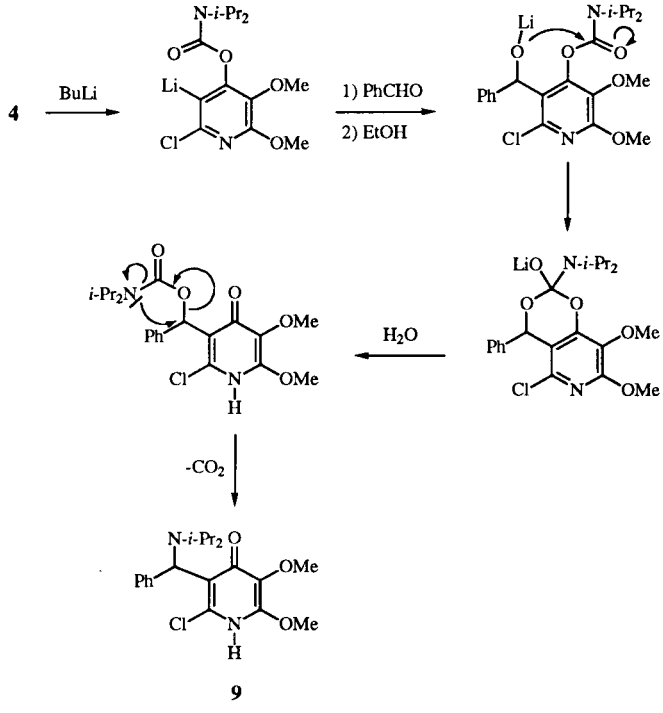
Table I

Metalation of 6-Substituted 2,3-Dimethoxy-4-pyridyl *N,N*-Diisopropylcarbamates

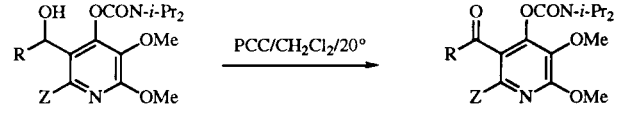
Entry	Z	Electrophile		Product	Yield (%)
1	Cl (**4**)	EtOD	**8a**	D-	>99
2	"	CH_3I	**8b**	CH_3-	94
3	"	CH_3CHO	**8c**	CH_3(OH)CH-	73
4	"	PhCHO	**8d**	Ph(OH)CH-	96
5	OCON-*i*-Pr$_2$ (**5**)	EtOD	**8e**	D-	90
6	"	CH_3I	**8f**	CH_3-	88
7	"	CH_3CHO	**8g**	CH_3(OH)CH-	60
8	"	PhCHO	**8h**	Ph(OH)CH-	87
9	O-*i*-Pr (**6**)	EtOD	**8i**	D-	75
10	"	PhCHO	**8j**	Ph(OH)CH-	82
11	"		**8k**		70
12	OSEM (**7**)	PhCHO	**8l**	Ph(OH)CH-	79
13	"		**8m**		75

[a] (2*RS*, 4*E*)-2-methyl-4-hexenal was prepared according to ref [9].

Scheme V



Scheme VI



8d,g-h,j-m **10a-g**

occurred with good yields at C-5 under the same following conditions: *n*-butyllithium catalyzed by 5% diisopropylamine (DIA) in tetrahydrofuran (THF) at -75° (Scheme IV and Table I).

When the electrophile used was an aldehyde, the treatment of the reaction mixture with ethanol did not lead to the expected alcohols, which could however be isolated in good yields with an acidic hydrolysis at -70°.

For example, metalation of **4** and reaction of benzaldehyde on the lithiated intermediate, followed by an acidic hydrolysis with hydrochloric acid at -70°, gave the alcohol **8d** in a 96% yield (entry 4), whereas in the same conditions, treatment of the reaction mixture with ethanol led to pyridone **9** in a 30% yield, and **8d** was not isolated. By analogy with the mechanism proposed by Jacquelin *et al.* for *O*-quinolyl carbamates [10], the following pathway could be assumed to explain the formation of **9** (Scheme V).

Alcohols thus prepared were then oxidized to ketones with pyridinium chlorochromate (PCC) [11] (Scheme VI and Table II).

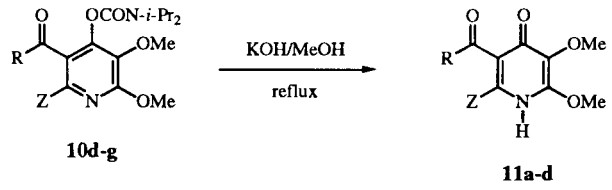
In order to obtain analogs with a structure closer to harzianopyridone, the carbamate at C-4 was then selectively cleaved by potassium hydroxide in methanol (Scheme VII and Table III).

The protective group Z at C-6 could be cleaved. Harzianopyridone analog **12** could be prepared either from pyridones **11a** or **11c**. Treatment of **11a** with boron trichloride [12,13] in dichloromethane, afforded a 30% yield. Acidic treatment of **11c** gave a better yield (42%) (Scheme VIII). But in the case of **11b**, the treatment with boron trichloride failed, due to a competition between deisopropylation and demethylation.

Table II

Z	R-	Alcohol	Ketone	Yield (%)
Cl	Ph-	**8d**	**10a**	89
OCON-*i*-Pr$_2$	Me-	**8g**	**10b**	80
OCON-*i*-Pr$_2$	Ph-	**8h**	**10c**	98
O-*i*-Pr	Ph-	**8j**	**10d**	55
O-*i*-Pr		**8k**	**10e**	40
OSEM	Ph-	**8l**	**10f**	88
OSEM		**8m**	**10g**	63

Scheme VII



10d-g **11a-d**

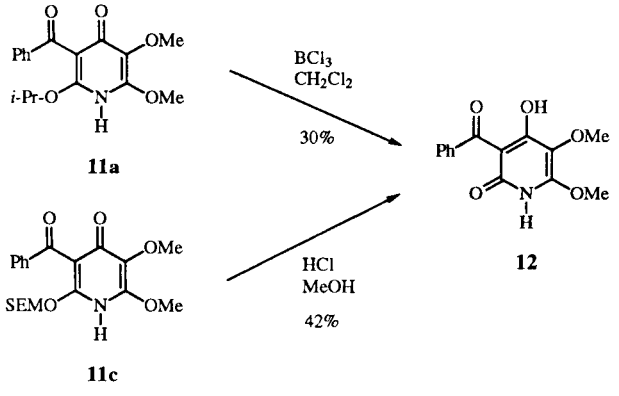
Table III

Z	R-	Carbamate	Pyridone	Yield (%)
O-*i*-Pr	Ph-	**10d**	**11a**	88
O-*i*-Pr		**10e**	**11b**	60
OSEM	Ph-	**10f**	**11c**	63
OSEM		**10g**	**11d**	51

The target (±)-harzianopyridone (**1**) was obtained by an acidic treatment of pyridone **11d** in a 70% yield (Scheme IX).

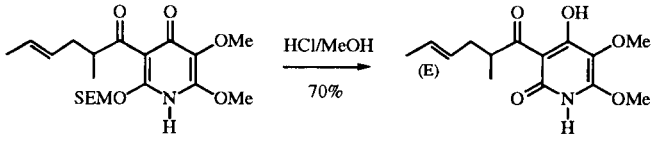
(±)-Harzianopyridone (**1**) was therefore synthesized from carbamate **4** in a 6-step sequence with a 9% overall yield.

Scheme VIII



11a **12** **11c**

Scheme IX



11d **1**

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. The ^1H and ^{13}C nmr spectra were recorded in deuteriochloroform with tetramethylsilane as the internal standard on a Bruker AC 200 instrument. Microanalyses were performed on a Carlo Erba CHNOS 1106 apparatus. The ir spectra were obtained as potassium bromide pellets with a Perkin Elmer 1600 spectrophotometer. Tetrahydrofuran (THF) was distilled from benzophenone/sodium. Water content of the solvent was estimated to be lower than 45 ppm by the modified Karl-Fischer method [14]. Metalations were performed under a dry argon atmosphere whose water content was regularly checked. Reagents were handled with syringes through septa.

Starting Materials.

6-Bromo-2,3-dimethoxy-4-pyridyl *N,N*-diisopropylcarbamate (**2**) was prepared in a four-step sequence from 2,3-dimethoxypyridine (30% overall yield) [8]. 4-(*N,N*-Diisopropylcarbamoyloxy)-2,3-dimethoxy-6(1*H*)-pyridone (**3**) and 2,3-dimethoxy-6-{[2-(trimethylsilyl)ethoxy]methoxy}-4-pyridyl *N,N*-diisopropylcarbamate (**7**) were prepared from **2** [8]. 2,4-Dimethylhexanal was synthesized from tri-*sec*-butylborane and methacrolein [15] and (2*RS*, 4*E*)-2-methyl-4-hexenal was synthesized in a four-step sequence from 3-buten-2-ol and triethyl orthopropionate [9].

6-Chloro-2,3-dimethoxy-4-pyridyl *N,N*-Diisopropylcarbamate (**4**).

6-Bromo-2,3-dimethoxy-4-pyridyl *N,N*-diisopropylcarbamate (3.25 g, 9 mmoles) in THF (20 ml) was quickly added to a cold (-75°) solution of *n*-butyllithium (2.5 *M* in hexane, 7.9 ml, 19.8 mmoles) in THF (230 ml), and the mixture was stirred for 5 minutes, before addition at -75° of hexachloroethane (5.35 g, 22.5 mmoles) in THF (10 ml). Stirring was continued for 1 hour at -70°, then the mixture was treated with an excess of ethanol in THF, warmed to room temperature, treated with a saturated aqueous solution of ammonium chloride, and extracted with dichloromethane. The organic layer was dried over magnesium sulphate. Solvents removal afforded a crude product which was purified by chromatography on a silica gel column. The eluent was dichloromethane/light petroleum (gradient from 80:20 to 100:0, v/v). A colorless oil was obtained, 1.91 g (67%); ^1H nmr (deuteriochloroform): δ 1.30 (d, 12H, J = 6.8 Hz, 2 $CH(CH_3)_2$), 3.81 (s, 3H, 3-OCH_3), 3.98 (s, 3H, 2-OCH_3), 4.00 (sept, 2H, J = 6.8 Hz, 2 $CH(CH_3)_2$), 6.78 (s, 1H, H_5); ^{13}C nmr (deuteriochloroform): δ 20.3-21.2 (2 $CH(CH_3)_2$), 47.0 (2 $CH(CH_3)_2$), 54.3 (2-OCH_3), 60.2 (3-OCH_3), 112.2 (C_5), 134.8 (C_3), 140.9 (C_6), 151.7, 152.3, 157.7 (C_2); ir: ν 2971, 1726, 1586, 1477 cm^{-1}.

Anal. Calcd. for $C_{14}H_{21}ClN_2O_4$: C, 53.08; H, 6.68; N, 8.84. Found: C, 53.3; H, 6.8; N, 8.9.

General Procedure for the Protection of 4-(*N,N*-Diisopropylcarbamoyloxy)-2,3-dimethoxy-6(1*H*)-pyridone (**3**).

To a solution of pyridone **3** (1.5 g, 5 mmoles) in toluene (50 ml) were added silver carbonate (1.0 g) and the halo derivative (6 mmoles). The mixture was stirred in the dark; reaction conditions are given in the product description. Silver salts were removed by filtration through Celite. The Celite was washed with dichloromethane. The solution was dried over magnesium sulphate. Solvent removal afforded a crude product which was purified by chromatography on a silica gel column. The eluent was a mixture of dichloromethane and ether (98:2).

6-(*N,N*-Diisopropylcarbamoyloxy)-2,3-dimethoxy-4-pyridyl *N,N*-Diisopropylcarbamate (**5**).

The general procedure, using diisopropylcarbamyl chloride (0.98 g, 6 mmoles) at 90° for 36 hours, gave 1.54 g (72%) of **5** as a colorless oil; ^1H nmr (deuteriochloroform): δ 1.27 (d, 24H,

J = 6.5 Hz, 4 CH(CH_3)$_2$), 3.77 (s, 3H, 3-OCH_3), 3.92 (s, 3H, 2-OCH_3), 3.96 (sept, 4H, J = 6.5 Hz, 4 C*H*(CH_3)$_2$), 6.53 (s, 1H, H_5); ir: ν 2971, 1722, 1599, 1464, 1425 cm^{-1}.

Anal. Calcd. for $C_{21}H_{35}N_3O_6$: C, 59.28; H, 8.29; N, 9.87. Found: C, 59.2; H, 8.1; N, 9.7.

2,3-Dimethoxy-6-isopropoxy-4-pyridyl *N,N*-Diisopropylcarbamate (**6**).

The general procedure, using isopropyl iodide (0.6 ml, 6 mmoles) at room temperature for 5 days, gave 1.48 g (86%) of **6** as a white powder, mp 69°; ^{1}H nmr (deuteriochloroform): δ 1.28 (d, 12H, J = 6.7 Hz, 2 N-CH(CH_3)$_2$), 1.29 (d, 6H, J = 6.2 Hz, O-CH(CH_3)$_2$), 3.74 (s, 3H, 3-OCH_3), 3.92 (s, 3H, 2-OCH_3), 3.99 (sept, 2H, J = 6.7 Hz, 2 N-C*H*(CH_3)$_2$), 5.09 (sept, 1H, J = 6.2 Hz, O-C*H*(CH_3)$_2$), 6.06 (s, 1H, H_5); ir: ν 2974, 1713, 1587, 1478, 1427 cm^{-1}.

Anal. Calcd. for $C_{17}H_{28}N_2O_5$: C, 59.98; H, 8.29; N, 8.23. Found: C, 60.1; H, 8.2; N, 8.2.

General Procedure for Metalation.

A solution of *n*-butyllithium (2.5 *M* in hexane, 0.96 ml, 2.4 mmoles) was slowly added to a cold (-75°) solution of the pyridine derivative **4**, **5**, **6**, or **7** (0.8 mmole) in THF (10 ml), and the mixture was stirred for 1 hour at -75°. The electrophile was added and stirring was continued for 1 hour at -75°. The solution was then hydrolyzed at -75° using a mixture of 35% aqueous hydrochloric acid (1 ml), ethanol (1 ml) and THF (2 ml) for derivatives of **4**, **5**, and **6**, or a mixture of acetic acid (1 ml), ethanol (1 ml) and THF (2 ml) for derivatives of **7**. The solution was then warmed to room temperature, made slightly basic with an aqueous solution of potassium carbonate (5 ml), and extracted with dichloromethane. The organic extract was dried over magnesium sulphate and evaporated. The crude product was purified by chromatography on a silica gel column.

6-Chloro-5-deuterio-2,3-dimethoxy-4-pyridyl *N,N*-Diisopropylcarbamate (**8a**).

Metalation of **4** (0.254 g, 0.8 mmole) according to the general procedure and reaction with deuterated ethanol (1 ml), gave, after purification by chromatography on silica gel (dichloromethane) **8a** quantitatively. The physical characteristics of this product were found to be identical to those described for **4** except for the ^{1}H nmr spectrum; ^{1}H nmr (deuteriochloroform): δ 1.29 (d, 12H, J = 6.8 Hz, 2 CH(CH_3)$_2$), 3.81 (s, 3H, 3-OCH_3), 3.98 (s, 3H, 2-OCH_3), 3.99 (sept, 2H, J = 6.8 Hz, 2 C*H*(CH_3)$_2$).

6-Chloro-2,3-dimethoxy-5-methyl-4-pyridyl *N,N*-Diisopropylcarbamate (**8b**).

Metalation of **4** (0.254 g, 0.8 mmole) according to the general procedure and reaction with methyl iodide (0.15 ml, 2.4 mmoles) gave after purification by column chromatography on silica gel (dichloromethane) 0.249 g (94%) of **8b** as a white powder, mp 57-58°; ^{1}H nmr (deuteriochloroform): δ 1.29 and 1.34 (2 d, 12H, J = 6.9 Hz, 2 CH(CH_3)$_2$), 2.15 (s, 3H, 5-CH_3), 3.81 (s, 3H, 3-OCH_3), 3.96 (s, 3H, 2-OCH_3), 4.00 and 4.02 (2 sept, 2H, J = 6.9 Hz, 2 C*H*(CH_3)$_2$); ir: ν 2969, 1713, 1598, 1471, 1399 cm^{-1}.

Anal. Calcd for $C_{15}H_{23}ClN_2O_4$: C, 54.46; H, 7.01; N, 8.47. Found: C, 54.6; H, 7.1; N, 8.25.

6-Chloro-2,3-dimethoxy-5-(1-hydroxyethyl)-4-pyridyl *N,N*-Diisopropylcarbamate (**8c**).

Metalation of **4** (0.254 g, 0.8 mmole) according to the general procedure and reaction with acetaldehyde (0.5 ml, 9 mmoles) gave after purification by column chromatography on silica gel with a mixture of dichloromethane and ether (97:3) as an eluent 0.211 g (73%) of **8c** as a white powder, mp 85°; ^{1}H nmr (deuteriochloroform): δ 1.30 and 1.32 (2d, 12H, J = 6.8 Hz, 2 CH(CH_3)$_2$), 1.52 (d, 3H, J = 6.7 Hz, CH(OH)C*H*$_3$), 2.73 (br s, 1H, OH), 3.81 (s, 3H, 3-OCH_3), 3.97 (s, 3H, 2-OCH_3), 3.88 and 4.15 (2 sept, 2H, J = 6.8 Hz, C*H*(CH_3)$_2$), 5.18 (q, 1H, J = 6.7 Hz, C*H*(OH)CH_3); ir: ν 3455, 2975, 2935, 1700, 1589, 1477 cm^{-1}; ms: (chemical ionization, ammonia) m/z 378/380 ($M+NH_4^+$, 14%), 361/363 ($M+H^+$, Cl pattern, 12%), 343/345 ($M+H^+ - H_2O$, 100%).

Anal. Calcd. for $C_{16}H_{25}ClN_2O_5$: C, 53.26; H, 6.98; N, 7.76. Found: C, 53.2; H, 6.8; N, 7.6.

6-Chloro-2,3-dimethoxy-5-(1-hydroxy-1-phenylmethyl)-4-pyridyl *N,N*-Diisopropylcarbamate (**8d**).

Metalation of **4** (0.254 g, 0.8 mmole) according to the general procedure and reaction with benzaldehyde (0.30 g, 2.8 mmoles) gave after purification by column chromatography on silica gel with a mixture of dichloromethane and ether (97:3) as an eluent 0.326 g (96%) of **8d** as a white powder, mp 138-139°; ^{1}H nmr (deuteriochloroform): δ 1.10 and 1.28 (2 d, 12H, J = 6.7 Hz, 2 CH(CH_3)$_2$), 3.66 (sept, 2H, J = 6.7 Hz, 2 C*H*(CH_3)$_2$), 3.79 (s, 3H, 3-OCH_3), 3.90 (br s, 1H, OH), 4.01 (s, 3H, 2-OCH_3), 6.26 (s, 1H, C*H*-OH), 7.19-7.38 (m, 5H, phenyl); ^{13}C nmr (deuteriochloroform): δ 20.1-20.6 (2 CH(CH_3)$_2$), 46.1-47.5 (2 *C*H(CH_3)$_2$), 54.2 (2-OCH_3), 60.0 (3-OCH_3), 70.1 (CH-OH), 124.8 (C_5), 125.0 ($C_{2'}$), 126.6 ($C_{4'}$), 127.9 ($C_{3'}$), 135.7 (C_3), 140.6, 142.2 ($C_{1'}$), 151.4 (O*C*ON-*i*-Pr_2), 156.4 (C_2); ir: ν 3434, 2969, 1698, 1594, 1474, 1420 cm^{-1}.

Anal. Calcd. for $C_{21}H_{27}ClN_2O_5$: C, 59.64; H, 6.44; N, 6.62. Found: C, 59.9; H, 6.4; N, 6.5.

6-Chloro-2,3-dimethoxy-5-[1-(*N,N*-diisopropylamino)-1-phenylmethyl]-4(1*H*)-pyridone (**9**).

The same procedure as for **8d**, except that the solution was not hydrolyzed, but treated by a mixture of ethanol (2 ml) and THF (2 ml) at -70° for 15 minutes, then gently warmed to room temperature. Hydrolysis was then carried out using a saturated ammonium chloride solution (5 ml). The mixture was extracted with dichloromethane. The organic extract was dried over magnesium sulphate and evaporated. The crude product was purified by chromatography on a silica gel column with a mixture of dichloromethane and methanol (95:5) as an eluent to afford 0.091 g (30%) of **9** as a white solid, mp 126-127°, obtained instead of the expected alcohol **8d**; ^{1}H nmr (deuteriochloroform): δ 1.16-1.21 (2 d, 12 H, J = 6.8 Hz, 2 CH(CH_3)$_2$), 3.39 (sept, 2H, J = 6.8 Hz, 2 C*H*(CH_3)$_2$), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.38 (s, 1H, C*H*-N-*i*-Pr_2), 7.27-7.33 (m, 5H, phenyl), 7.64 (br s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 18.6-21.0 (2 CH(CH_3)$_2$), 49.5 (2 *C*H(CH_3)$_2$), 53.6 (2-OCH_3), 60.1 (3-OCH_3), 65.5 (*C*H-N-*i*-Pr_2), 116.4 (C_5), 128.5, 128.7, 129.6, 131.4, 137.4, 138.5, 156.6, 164.0; ir: ν 2986, 2967, 1571, 1479 cm^{-1}; ms: (chemical ionization, ammonia) m/z 379/381 ($M+H^+$, Cl pattern, 53%), 102 (*i*-$Pr_2NH_2^+$, 100%).

Anal. Calcd. for $C_{20}H_{27}ClN_2O_3$: C, 63.40; H, 7.18; N, 7.39. Found: C, 63.5; H, 7.3; N, 7.2.

5-Deuterio-6-(*N,N*-diisopropylcarbamoyloxy)-2,3-dimethoxy-4-pyridyl *N,N*-Diisopropylcarbamate (**8e**).

Metalation of **5** (0.34 g, 0.8 mmole) according to the general procedure and reaction with deuterated ethanol (1 ml), gave, after purification by chromatography on silica gel with a mixture of dichloromethane and ether (98:2) as an eluent 0.306 g (90%) of **8e**. The physical characteristics of this product were found to be identical to those described for **5** except for the ^{1}H nmr spectrum; ^{1}H nmr (deuteriochloroform): δ 1.25 (d, 24H, J = 6.5 Hz, 4 CH(CH_3)$_2$), 3.75 (s, 3H, 3-OCH_3), 3.90 (s, 3H, 2-OCH_3), 3.95 (sept, 4H, J = 6.5 Hz, 4 CH(CH_3)$_2$).

6-(*N,N*-Diisopropylcarbamoyloxy)-2,3-dimethoxy-5-methyl-4-pyridyl *N,N*-Diisopropylcarbamate (**8f**).

Metalation of **5** (0.34 g, 0.8 mmole) according to the general procedure and reaction with methyl iodide (0.175 ml, 2.8 mmoles) gave after purification by column chromatography on silica gel with a mixture of dichloromethane and ether (96:4) as an eluent 0.309 g (88%) of **8f** as a white powder, mp 123-124°; ^{1}H nmr (deuteriochloroform): δ 1.26 and 1.31 (2 d, 24H, J = 6.8 Hz, 4 CH(CH_3)$_2$), 1.96 (s, 3H, CH_3), 3.77 (s, 3H, 3-OCH_3), 3.90 (s, 3H, 2-OCH_3), 4.00 (sept, 4H, J = 6.8 Hz, 4 CH(CH_3)$_2$); ir: ν 2970, 1718, 1613, 1478, 1408 cm^{-1}.

Anal. Calcd. for $C_{22}H_{37}N_3O_6$: C, 60.12; H, 8.48; N, 9.56. Found: C, 60.0; H, 8.6; N, 9.55.

6-(*N,N*-Diisopropylcarbamoyloxy)-2,3-dimethoxy-5-(1-hydroxyethyl)-4-pyridyl *N,N*-Diisopropylcarbamate (**8g**).

Metalation of **5** (0.34 g, 0.8 mmole) according to the general procedure and reaction with acetaldehyde (0.5 ml, 9 mmoles) gave after purification by column chromatography on silica gel with a mixture of dichloromethane and ether (92:8) as an eluent 0.225 g (60%) of **8g** as a yellow oil; ^{1}H nmr (deuteriochloroform): δ 1.31 and 1.35 (2 d, 24H, J = 6.8 Hz, 4 CH(CH_3)$_2$), 1.53 (d, 3H, J = 6.8 Hz, CH(OH)CH_3), 3.06 (br s, 1H, OH), 3.81 (s, 3H, 3-OCH_3), 3.94 (s, 3H, 2-OCH_3), 4.00 and 4.04 (2 sept, 4H, J = 6.8 Hz, 4 CH(CH_3)$_2$), 4.94 (q, 1H, J = 6.8 Hz, CH(OH)CH_3); ir: ν 3463, 2971, 1714, 1604, 1477, 1421 cm^{-1}.

Anal. Calcd. for $C_{23}H_{39}N_3O_7$: C, 58.83; H, 8.37; N, 8.95. Found: C, 58.9; H, 8.4; N, 8.8.

6-(*N,N*-Diisopropylcarbamoyloxy)-2,3-dimethoxy-5-(1-hydroxy-1-phenylmethyl)-4-pyridyl *N,N*-Diisopropylcarbamate (**8h**).

Metalation of **5** (0.34 g, 0.8 mmole) according to the general procedure and reaction with benzaldehyde (0.30 g, 2.8 mmoles) gave after purification by column chromatography on silica gel with a mixture of dichloromethane and ether (95:5) as an eluent 0.37 g (87%) of **8h** as a colorless oil; ^{1}H nmr (deuteriochloroform): δ 1.22, 1.23, 1.25 and 1.26 (4 d, 24H, J = 6.7 Hz, 4 CH(CH_3)$_2$), 3.80 (s, 3H, 3-OCH_3), 3.87 and 3.97 (2 sept, 4H, J = 6.7 Hz, 4 CH(CH_3)$_2$), 3.95 (s, 3H, 2-OCH_3), 4.4 (br s, 1H, OH), 5.95 (s, 1H, CH-OH), 7.15-7.43 (m, 5H, phenyl); ir: ν 3420, 2972, 1721, 1604, 1477, 1420 cm^{-1}.

Anal. Calcd. for $C_{28}H_{41}N_3O_7$: C, 63.26; H, 7.77; N, 7.90. Found: C, 63.4; H, 7.7; N, 7.7.

5-Deuterio-2,3-dimethoxy-6-isopropoxy-4-pyridyl *N,N*-Diisopropylcarbamate (**8i**).

Metalation of **6** (0.273 g, 0.8 mmole) according to the general procedure and reaction with deuterated ethanol (1 ml), gave, after purification by chromatography on silica gel with a mixture of dichloromethane and ether (99:1) as an eluent 0.205 g (90%) of **8i**. The physical characteristics of this product were found to be identical to those described for **6** except for the ^{1}H nmr spectrum; ^{1}H nmr (deuteriochloroform): δ 1.30 (2 d, 12H, J = 6.5 Hz, 2 N-CH(CH_3)$_2$), 1.30 (d, 6H, J = 6.0 Hz, O-CH(CH_3)$_2$), 3.75 (s, 3H, 3-OCH_3), 3.95 (s, 3H, 2-OCH_3), 4.00 (sept, 2H, J = 6.5 Hz, 2 N-CH(CH_3)$_2$), 5.10 (sept, 1H, J = 6.0 Hz, O-CH(CH_3)$_2$).

2,3-Dimethoxy-5-(1-hydroxy-1-phenylmethyl)-6-isopropoxy-4-pyridyl *N,N*-Diisopropylcarbamate (**8j**).

Metalation of **6** (0.273 g, 0.8 mmole) according to the general procedure and reaction with benzaldehyde (0.30 g, 2.8 mmoles) gave after purification by column chromatography on silica gel with a mixture of dichloromethane and ether (98:2) as an eluent 0.294 g (82%) of **8j** as a colorless oil; ^{1}H nmr (deuteriochloroform): δ 1.05 and 1.32 (2 d, 6 H, J = 6.2 Hz, O-CH(CH_3)$_2$), 1.23 and 1.25 (2 d, 12H, J = 6.8 Hz, 2 N-CH(CH_3)$_2$), 3.78 (s, 3H, 3-OCH_3), 3.93 (s, 3H, 2-OCH_3), 4.01 (sept, 2H, J = 6.8 Hz, 2 N-CH(CH_3)$_2$), 5.19 (sept, 1H, J = 6.2 Hz, O-CH(CH_3)$_2$), 5.98 (s, 1H, CH-OH), 7.14-7.42 (m, 5H, phenyl); ir: ν 3428, 2974, 1722, 1588, 1469, 1421 cm^{-1}.

Anal. Calcd. for $C_{24}H_{34}N_2O_6$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.5; H, 7.8; N, 6.5.

2,3-Dimethoxy-5-(2,4-dimethyl-1-hydroxyhexyl)-6-isopropoxy-4-pyridyl *N,N*-Diisopropylcarbamate (**8k**).

Metalation of **6** (0.273 g, 0.8 mmole) according to the general procedure and reaction with 2,4-dimethylhexanal (1 g, 7.8 mmoles) gave after purification by column chromatography on silica gel with a mixture of dichloromethane and ether (98:2) as an eluent 0.263 g (70%) of **8k** as a colorless oil; ^{1}H nmr (deuteriochloroform): δ 0.63-2.2 (m, 15H), 1.25 (d, 12H, J = 6.7 Hz, 2 N-CH(CH_3)$_2$), 1.31 (d, 6H, J = 6.2 Hz, O-CH(CH_3)$_2$), 3.71 (s, 3H, 3-OCH_3), 3.87 (s, 3H, 2-OCH_3), 3.93 and 4.03 (2 sept, 2H, J = 6.7 Hz, 2 N-CH(CH_3)$_2$), 4.31 (m, 1H, CH-OH), 5.25 (sept, 1H, J = 6.2 Hz, O-CH(CH_3)$_2$); ir: ν 3556, 2965, 1724, 1587, 1468, 1421 cm^{-1}.

Anal. Calcd. for $C_{25}H_{44}N_2O_6$: C, 64.07; H, 9.46; N, 5.98. Found: C, 63.8; H, 9.3; N, 5.8.

2,3-Dimethoxy-5-(1-hydroxy-1-phenylmethyl)-6-{[2-(trimethylsilyl)ethoxy]methoxy}-4-pyridyl *N,N*-Diisopropylcarbamate (**8l**).

Metalation of **7** (0.343 g, 0.8 mmole) according to the general procedure and reaction with benzaldehyde (0.30 g, 2.8 mmoles) gave after purification by column chromatography on silica gel with a mixture of dichloromethane and ether (97:3) as an eluent 0.338 g (79%) of **8l** as a colorless oil; ^{1}H nmr (deuteriochloroform): δ -0.03 (s, 9H, $SiMe_3$), 0.86 (t, 2H, J = 8.3 Hz, CH_2-Si), 1.27 and 1.28 (2 d, 12H, J = 6.7 Hz, 2 CH(CH_3)$_2$), 3.49 (t, 2H, J = 8.3 Hz, O-CH_2-CH_2), 3.77 (s, 3H, 3-OCH_3), 3.80 and 3.92 (2 sept, 2H, J = 6.7 Hz, CH(CH_3)$_2$), 3.95 (s, 3H, 2-OCH_3), 5.51 (s, 2H, O-CH_2-O), 6.05 (d, 1H, CH-OH), 7.17-7.42 (m, 5H, phenyl); ir: ν 3434, 2952, 1723, 1590, 1470 cm^{-1}.

Anal. Calcd. for $C_{27}H_{42}N_2O_7Si$: C, 60.65; H, 7.92; N, 5.24. Found: C, 60.5; H, 8.2; N, 5.5.

2,3-Dimethoxy-5-[(4*E*)-1-hydroxy-2-methyl-4-hexenyl]-6-{[2-(trimethylsilyl)ethoxy]methoxy}-4-pyridyl *N,N*-Diisopropylcarbamate (**8m**).

Metalation of **7** (0.343 g, 0.8 mmole) according to the general procedure and reaction with (4*E*)-2-methyl-4-hexenal (0.9 g, 8 mmoles) gave after purification by column chromatography on

silica gel with a mixture of dichloromethane and ether (98:2) as an eluent 0.325 g (75%) of **8m** as a colorless oil; ^{1}H nmr (deuteriochloroform): δ 0.00 (s, 9H, $SiMe_3$), 0.99 (m, 2H, CH_2-Si), 0.65-3.2 (m, 9H), 1.30 (d, 12H, J = 6.6 Hz, 2 CH(CH_3)$_2$), 4.06 (m, 1H, C*H*-OH), 4.45 (br s, 1H, OH), 5.28 (m, 2H, O-CH_2-O), 5.40-5.65 (m, 2H, CH=CH); ^{13}C nmr (deuteriochloroform): δ -1.5 ($SiMe_3$), 15.6-15.9 (2'-CH_3), 17.8-17.9 ($C_{6'}$), 18.0 (CH_2-Si), 20.3-21.3 (2 CH(CH_3)$_2$), 36.2-36.8 ($C_{3'}$), 38.6-39.2 ($C_{2'}$), 46.6-47.0 (2 *C*H(CH_3)$_2$), 53.5 (2-OCH_3), 59.9 (3-OCH_3), 67.4-67.5 (O-*C*H_2-CH_2), 71.2-71.6 (CH-OH), 90.3-90.4 (O-CH_2-O), 110.7-110.8 (C_5), 126.0-126.4 ($C_{5'}$), 129.1-129.5 ($C_{4'}$), 130.4 ($C_{3'}$), 151.5-151.6, 151.9, 152.9, 154.0-154.1; ir: ν 3441, 2957, 1724, 1589, 1471 cm^{-1}.

Anal. Calcd. for $C_{27}H_{48}N_2O_7Si$: C, 59.97; H, 8.95; N, 5.18. Found: C, 60.2; H, 8.8; N, 5.0.

General Procedure for Oxidation of Alcohols.

To a solution of alcohol (0.5 mmole) in dichloromethane (7 ml) was added molecular sieves (0.32 g) and pyridinium chlorochromate (0.325 g, 1.5 mmoles). The mixture was well stirred at room temperature and the reaction was followed by tlc. When the oxidation was complete the reaction mixture was diluted in ether and filtered through Celite. After drying over sodium sulphate, the solvents were removed to afford a crude product, which was purified by column chromatography on silica gel.

5-Benzoyl-6-chloro-2,3-dimethoxy-4-pyridyl *N,N*-Diisopropylcarbamate (**10a**).

Oxidation of **8d** (0.211 g, 0.5 mmole) gave after purification by column chromatography on silica gel with a mixture of dichloromethane and ether (96:4) as an eluent 0.187 g (89%) of **10a** as a colorless oil; ^{1}H nmr (deuteriochloroform): δ 0.99 and 1.06 (2 d, 12H, J = 6.8 Hz, 2 CH(CH_3)$_2$), 3.70 and 3.74 (2 sept, 2H, J = 6.8 Hz, 2 *C*H(CH_3)$_2$), 3.87 (s, 3H, 3-OCH_3), 4.04 (s, 3H, 2-OCH_3), 7.38-7.57 (m, 3H, phenyl), 7.85-7.91 (m, 2H, phenyl); ir: ν 2969, 1730, 1677, 1597, 1476 cm^{-1}.

Anal. Calcd. for $C_{21}H_{25}ClN_2O_5$: C, 59.93; H, 5.99; N, 6.66. Found: C, 59.9; H, 5.7; N, 6.5.

5-Acetyl-6-(*N,N*-diisopropylcarbamoyloxy)-2,3-dimethoxy-4-pyridyl *N,N*-Diisopropylcarbamate (**10b**).

Oxidation of **8g** (0.235 g, 0.5 mmole) gave after purification by column chromatography on silica gel with a mixture of dichloromethane and ether (94:6) as an eluent 0.187 g (80%) of **10b** as a white powder, mp 115-116°; ^{1}H nmr (deuteriochloroform): δ 1.27 (d, 24H, J = 6.8 Hz, 4 CH(CH_3)$_2$), 2.42 (s, 3H, $COCH_3$), 3.78 (s, 3H, 3-OCH_3), 3.92 and 3.99 (2 sept, 4H, J = 6.8 Hz, 4 *C*H(CH_3)$_2$), 3.94 (s, 3H, 2-OCH_3); ir: ν 2972, 1716, 1600, 1479, 1417 cm^{-1}.

Anal. Calcd. for $C_{23}H_{37}N_3O_7$: C, 59.08; H, 7.98; N, 8.99. Found: C, 59.1; H, 7.9; N, 8.7.

5-Benzoyl-6-(*N,N*-diisopropylcarbamoyloxy)-2,3-dimethoxy-4-pyridyl *N,N*-Diisopropylcarbamate (**10c**).

Oxidation of **8h** (0.266 g, 0.5 mmole) gave after purification by column chromatography on silica gel with a mixture of dichloromethane and ether (95:5) as an eluent 0.260 g (98%) of **10c** as a yellow oil; ^{1}H nmr (deuteriochloroform): δ 1.07 (d, 24H, J = 6.8 Hz, 4 CH(CH_3)$_2$), 3.73 (sept, 4H, J = 6.8 Hz, 4 *C*H(CH_3)$_2$), 3.83 (s, 3H, 3-OCH_3), 4.02 (s, 3H, 2-OCH_3), 7.30-7.50 (m, 3H, phenyl), 7.85-7.89 (m, 2H, phenyl); ^{13}C nmr (deuteriochloroform): δ 19.9 and 20.7 (4 CH(CH_3)$_2$), 46.0 and 46.5 (4 CH(CH_3)$_2$), 54.1 (2-OCH_3), 60.0 (3-OCH_3), 115.1 (C_5), 127.9 ($C_{3'}$), 129.6 ($C_{2'}$), 132.7 ($C_{4'}$), 133.6 (C_3), 137.3 ($C_{1'}$), 148.3, 150.5, 150.7, 151.3, 157.2 (C_2), 190.5 (*C*O-Ph).

Anal. Calcd. for $C_{28}H_{39}N_3O_7$: C, 63.50; H, 7.42; N, 7.93. Found: C, 63.3; H, 7.4; N, 7.9.

5-Benzoyl-2,3-dimethoxy-6-isopropoxy-4-pyridyl *N,N*-Diisopropylcarbamate (**10d**).

Oxidation of **8j** (0.223 g, 0.5 mmole) gave after purification by column chromatography on silica gel with a mixture of dichloromethane and ether (99:1) as an eluent 0.122 g (55%) of **10d** as a yellow powder, mp 105-107°; ^{1}H nmr (deuteriochloroform): δ 1.07 (d, 6H, J = 6.2 Hz, 2 O-CH(*CH*$_3$)$_2$), 1.07 (d, 12H, J = 6.8 Hz, N-CH(*CH*$_3$)$_2$), 3.76 (sept, 2H, J = 6.8 Hz, N-*CH*(CH$_3$)$_2$), 3.77 (s, 3H, 3-OCH_3), 3.95 (s, 3H, 2-OCH_3), 5.11 (sept, 1H, J = 6.2 Hz, O-*CH*(CH$_3$)$_2$), 7.33-7.46 (m, 3H, phenyl), 7.77-7.82 (m, 2H, phenyl); ir: ν 2975, 1721, 1672, 1579, 1472, 1418 cm^{-1}.

Anal. Calcd. for $C_{24}H_{32}N_2O_6$: C, 64.85; H, 7.26; N, 6.30. Found: C, 64.8; H, 7.4; N, 6.2.

2,3-Dimethoxy-5-(2,4-dimethyl-1-oxohexyl)-6-isopropoxy-4-pyridyl *N,N*-Diisopropylcarbamate (**10e**).

Oxidation of **8k** (0.234 g, 0.5 mmole) gave after purification by column chromatography on silica gel with a mixture of dichloromethane and ether (98:2) as an eluent 0.094 g (40%) of **10e** as a colorless oil; ^{1}H nmr (deuteriochloroform): δ 0.79-1.80 (m, 14H), 1.26 and 1.32 (d, 12H, J = 6.7 Hz, 2 N-CH(*CH*$_3$)$_2$), 1.32 (d, 6H, J = 6.2 Hz, O-CH(*CH*$_3$)$_2$), 3.26 (m, 1H, CH-CO), 3.76 (s, 3H, 3-OCH_3), 3.89 and 4.01 (2 sept, 2H, J = 6.7 Hz, 2 N-*CH*(CH$_3$)$_2$), 3.95 (s, 3H, 2-OCH_3), 5.27 (sept, 1H, J = 6.2 Hz, O-*CH*(CH$_3$)$_2$); ^{13}C nmr (deuteriochloroform): δ 11.1-11.3 ($C_{6'}$), 15.5-16.8 (2'-CH_3), 18.5-19.7 (4'-CH_3), 20.3-21.1 (2 N-CH(*CH*$_3$)$_2$), 22.0 (O-CH(*CH*$_3$)$_2$), 28.9-30.3 ($C_{4'}$), 31.7-31.8 ($C_{5'}$), 39.0-40.1 ($C_{3'}$), 43.8 ($C_{2'}$), 46.5-47.0 (2 N-*CH*(CH$_3$)$_2$), 53.6 (2-OCH_3), 60.1 (3-OCH_3), 69.1 (O-*CH*(CH$_3$)$_2$), 111.2 (C_5), 129.8 (C_3), 151.3, 151.6, 153.9 (C_6), 156.2 (C_2), 204.8-205.0 (CO ketone).

Anal. Calcd. for $C_{25}H_{42}N_2O_6$: C, 64.35; H, 9.07; N, 6.00. Found: C, 64.2; H, 9.3; N, 5.8.

5-Benzoyl-2,3-dimethoxy-6-{[2-(trimethylsilyl)ethoxy]-methoxy}-4-pyridyl *N,N*-Diisopropylcarbamate (**10f**).

Oxidation of **8l** (0.267 g, 0.5 mmole) gave after purification by column chromatography on silica gel with a mixture of dichloromethane and ether (98:2) as an eluent 0.234 g (88%) of **10f** as a yellow oil; ^{1}H nmr (deuteriochloroform): δ -0.11 (s, 9H, $SiMe_3$), 0.79 (t, 2H, J = 8.4 Hz, CH_2-Si), 1.03 and 1.07 (2d, 12H, J = 7.5 Hz, 2 CH(CH_3)$_2$), 3.45 (t, 2H, J = 8.4 Hz, O-*C*H_2-CH_2), 3.74 (sept, 2H, J = 7.5 Hz, 2 *C*H(CH_3)$_2$), 3.79 (s, 3H, 3-OCH_3), 3.98 (s, 3H, 2-OCH_3), 5.43 (s, 2H, O-CH_2-O), 7.34-7.49 (m, 3H, phenyl), 7.85-7.89 (m, 2H, phenyl); ^{13}C nmr (deuteriochloroform): δ -1.7 ($SiMe_3$), 17.7 (CH_2-Si), 20.0 and 20.7 (2 CH(CH_3)$_2$), 46.5 and 46.6 (2 *C*H(CH_3)$_2$), 53.8 (2-OCH_3), 60.0 (3-OCH_3), 66.8 (O-*C*H_2-CH_2), 90.1 (O-CH_2-O), 109.6 (C_5), 128.0 ($C_{3'}$), 129.5 ($C_{2'}$), 130.6 (C_3), 132.8 ($C_{4'}$), 137.7 ($C_{1'}$), 150.8, 151.3, 152.9, 156.5, 191.5 (*C*O-Ph).

Anal. Calcd. for $C_{27}H_{40}N_2O_7Si$: C, 60.88; H, 7.57; N, 5.26. Found: C, 60.6; H, 7.5; N, 5.0.

2,3-Dimethoxy-5-[(4*E*)-2-methyl-1-oxo-4-hexenyl]-6-{[2-(trimethylsilyl)ethoxy]methoxy}-4-pyridyl *N,N*-Diisopropylcarbamate (**10g**).

Oxidation of **8m** (0.27 g, 0.5 mmole) gave after purification by column chromatography on silica gel with a mixture of dichloromethane and ether (99:1) as an eluent 0.17 g (63%) of **10g** as a colorless oil; ^{1}H nmr (deuteriochloroform): δ 0.00 (s, 9H, $SiMe_3$), 0.96 (t, 2H, J = 8.4 Hz, CH_2-Si), 1.09 (d, 3H, J = 6.9 Hz, 2'-CH_3), 1.28 and 1.29 (2 d, 12H, J = 6.7 Hz, 2 N-CH(CH_3)$_2$), 1.62 (d, 2H, J = 4.9 Hz, CH_3-CH=CH), 1.94-2.08 and 2.38-2.47 (2 m, 2H, CH=CH-CH_2), 3.07-3.20 (m, 1H, CH-CO), 3.74 (t, 2H, J = 8.4 Hz, O-CH_2-CH_2), 3.77 (s, 3H, 3-OCH_3), 3.93 and 4.06 (2 sept, 2H, J = 6.7 Hz, N-CH(CH_3)$_2$), 3.96 (s, 3H, 2-OCH_3), 5.26-5.48 (m, 2H, CH=CH), 5.55 (s, 2H, O-CH_2-O); ^{13}C nmr (deuteriochloroform): δ -1.5 ($SiMe_3$), 15.3 (2'-CH_3), 17.9-18.0 ($C_{6'}$ and CH_2-Si), 20.3 and 21.1 (2 N-CH(CH_3)$_2$), 35.5 ($C_{3'}$), 46.3 ($C_{2'}$), 46.6 and 47.0 (2 N-CH(CH_3)$_2$), 53.9 (2-OCH_3), 60.1 (3-OCH_3), 67.4 (O-CH_2-CH_2), 90.5 (O-CH_2-O), 111.1 (C_5), 126.9 ($C_{5'}$), 128.5 (C4'), 130.7 (C_3), 151.4 and 151.5 (C_4 and OCON-*i*-Pr_2), 152.9 (C_6), 156.3 (C_2), 203.8 (CO ketone).

Anal. Calcd. for $C_{27}H_{46}N_2O_7Si$: C, 60.19; H, 8.61; N, 5.20. Found: C, 60.4; H, 8.6; N, 5.0.

General Procedure for the Cleavage of *N,N*-Diisopropylcarbamates **10d-g**.

N,N-Diisopropylcarbamate (0.3 mmole) was refluxed in 6 ml of a 5 *N* solution of potassium hydroxide in methanol. After 20 hours, the mixture was cooled, methanol was evaporated, and diluted acetic acid was added. The solution was treated by sodium hydrogenocarbonate, extracted with dichloromethane, and dried over magnesium sulphate. Solvent removal afforded a crude product which was purified by chromatography on silica gel.

5-Benzoyl-2,3-dimethoxy-6-isopropoxypyrid-4(1*H*)-one (**11a**).

Cleavage of carbamate **10d** (0.133 g, 0.3 mmole) gave after purification by column chromatography on silica gel with a mixture of dichloromethane and ether (99:1) as an eluent 0.084 g (88%) of **11a** as a yellow solid, mp 63-64°; ^{1}H nmr (deuteriochloroform): δ 0.93 (d, 6H, J = 6.2 Hz, O-CH(CH_3)$_2$), 3.83 (s, 3H, 3-OCH_3), 3.97 (s, 3H, 2-OCH_3), 5.07 (sept, 1H, J = 6.2 Hz, O-C*H*(CH_3)$_2$), 7.32-7.51 (m, 5H, phenyl), 12.70 (s, 1H, NH); ir: ν 2970, 2933, 1631, 1576, 1451, 1423 cm^{-1}.

Anal. Calcd. for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.3; H, 6.05; N, 4.35.

2,3-Dimethoxy-5-(2,4-dimethyl-1-oxohexyl)-6-isopropoxy-4(1*H*)-pyridone (**11b**).

Cleavage of carbamate **10e** (0.14 g, 0.3 mmole) gave after purification by column chromatography on silica gel with a mixture of dichloromethane and ether (99:1) as an eluent 0.061 g (60%) of **11b** as a colorless oil; ^{1}H nmr (deuteriochloroform): δ 0.81-2.0 (m, 14H), 1.42 (d, 6H, J = 6.2 Hz, O-CH(CH_3)$_2$), 3.81 (s, 3H, 3-OCH_3), 3.89-4.05 (m, 1H, C*H*-CO), 3.99 (s, 3H, 2-OCH_3), 5.45 (sept, 1H, J = 6.2 Hz, O-C*H*(CH_3)$_2$), 14.40 and 14.43 (2 s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 11.2 ($C_{6'}$), 17.8-18.8 (2'-CH_3), 19.1-19.3 (4'-CH_3), 22.0-22.1 (O-CH(CH_3)$_2$), 29.7 ($C_{4'}$), 32.0-32.3 ($C_{5'}$), 39.4-40.0 ($C_{3'}$), 41.5-41.6 ($C_{2'}$), 53.7 (2-OCH_3), 60.6 (3-OCH_3), 69.8 (O-C*H*(CH_3)$_2$), 100.7-100.9 (C_5), 124.6 (C_3), 158.1, 165.9 (C_4), 211.0-211.2 (CO ketone).

Anal. Calcd. for $C_{18}H_{29}NO_5$: C, 63.69; H, 8.61; N, 4.13. Found: C, 63.9; H, 8.6; N, 3.9.

5-Benzoyl-2,3-dimethoxy-6-{[2-(trimethylsilyl)ethoxy]methoxy}-4-(1*H*)-pyridone (**11c**).

Cleavage of carbamate **10f** (0.16 g, 0.3 mmole) gave after purification by column chromatography on silica gel with a mixture of dichloromethane and ether (97:3) as an eluent 0.077 g (63%) of **11c** as a colorless oil; ^{1}H nmr (deuteriochloroform): δ -0.05 (s, 9H, $SiMe_3$), 0.74 (t, 2H, J = 8.4 Hz, CH_2-Si), 3.20 (t, 2H, J = 8.4 Hz, O-CH_2-CH_2), 3.85 (s, 3H, 3-OCH_3), 3.98 (s, 3H, 2-OCH_3), 5.32 (s, 2H, O-CH_2-O), 7.36-7.61 (m, 5H, phenyl), 12.35 (s, 1H, NH); ir: ν 2953, 1626, 1574, 1471, 1452 cm^{-1}.

Anal. Calcd. for $C_{20}H_{27}NO_6Si$: C, 59.24; H, 6.71; N, 3.45. Found: C, 59.5; H, 6.9; N, 3.3.

2,3-Dimethoxy-5-[(4*E*)-2-methyl-1-oxo-4-hexenyl]-6-{[2-(trimethylsilyl)ethoxy]methoxy}-4(1*H*)-pyridone (**11d**).

Cleavage of carbamate **10g** (0.162 g, 0.3 mmole) gave after purification by column chromatography on silica gel with a mixture of dichloromethane and light petroleum (3:1) as an eluent 0.063 g (51%) of **11d** as a colorless oil; ^{1}H nmr (deuteriochloroform): δ 1.01 (t, 2H, J = 8.4 Hz, CH_2-Si), 1.16 (d, 3H, J = 6.8 Hz, 2'-CH_3), 1.64 (d, 3H, J = 5.1 Hz, CH_3-CH=CH), 1.98-2.12 and 2.42-2.52 (2 m, 2H, CH=CH-CH_2), 3.72-3.88 (m, 1H, CH-CO), 3.81 (t, 2H, J = 8.4 Hz, O-CH_2-CH_2), 3.81 (s, 3H, 3-OCH_3), 3.98 (s, 3H, 2-OCH_3), 5.30-5.55 (m, 2H, CH=CH), 5.67 (s, 2H, O-CH_2-O), 14.25 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ -1.6 ($SiMe_3$), 16.4 (2'-CH_3), 17.8 and 18.0 (CH_2-Si and $C_{6'}$), 36.6 ($C_{3'}$), 44.3 ($C_{2'}$), 53.8 (2-OCH_3), 60.5 (3-OCH_3), 68.0 (O-CH_2-CH_2), 91.3 (O-CH_2-O), 100.5 (C_5), 125.2 (C_3), 127.1 ($C_{5'}$), 128.2 ($C_{4'}$), 157.1 and 157.9 (C_2 and C_6), 165.5 (C_4), 209.8 (CO ketone).

Anal. Calcd. for $C_{20}H_{33}NO_6Si$: C, 58.37; H, 8.08; N, 3.40. Found: C, 58.2; H, 8.2; N, 3.2.

5,6-Dimethoxy-4-hydroxy-3-benzoyl-2(1*H*)-pyridone (**12**).

Method A.

To a solution of **11a** (44 mg, 0.13 mmole) in dichloromethane (3 ml) was added a solution of boron trichloride (1 *M* in dichloromethane, 2.6 ml) under a dry argon atmosphere. The mixture was stirred for 2 hours at room temperature, and then hydrolyzed at -70°. The solution was made slightly basic with a saturated sodium hydrogenocarbonate solution. Extraction with dichloromethane, drying over magnesium sulphate, and solvent removal afforded a crude product which was purified by column chromatography on silica gel with a mixture of dichloromethane and methanol (98:2) as an eluent to yield 12 mg (30%) of **12** as a white powder. This product was identical with **12** which was prepared by Method B.

Method B.

Pyridone **11c** (67 mg, 0.16 mmole) was dissolved in 5 ml of a solution of concentrated hydrochloric acid in methanol (1:10) and refluxed for 1 hour. Methanol was evaporated and the reaction mixture was made slightly basic with a saturated solution of sodium hydrogenocarbonate. Extraction with dichloromethane, drying over magnesium sulphate, and solvent removal afforded a crude product which was purified by column chromatography on silica gel with a mixture of

dichloromethane and methanol (98:2) as an eluent to yield 25 mg (42%) of **12** as a white powder, mp 172-174°; ^{1}H nmr (deuteriochloroform): δ 3.69 (s, 3H, 5-OCH_3), 3.79 (s, 3H, 6-OCH_3), 7.38-7.58 (m, 5H, phenyl), 12.0 (br s, 2H, 2 OH); ^{13}C nmr (deuteriochloroform): δ 56.5 (5-OCH_3), 61.3 (6-OCH_3), 99.9 (C_3), 121.6 (C_5), 127.6 ($C_{2'}$ and $C_{3'}$), 130.9 ($C_{4'}$), 140.5 ($C_{1'}$), 157.3 (C_6), 161.5 (C_2), 167.1 (C_4), 199.4 (*C*O-Ph); ir: ν 3448, 2932, 1654, 1594, 1441 cm^{-1}; ms: (70 eV, electron impact) m/z 275 (M^+, 100%), 105 ($PhCO^+$, 78%).

Anal. Calcd. for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 60.9; H, 5.0; N, 4.8.

5,6-Dimethoxy-4-hydroxy-3-[(2*RS*,4*E*)-2-methyl-1-oxo-4-hexenyl]-2(1*H*)-pyridone: (±)-Harzianopyridone (**1**).

Pyridone **11d** (35 mg, 0.085 mmole) was dissolved in 5 ml of a solution of concentrated hydrochloric acid in methanol (1:10) and refluxed for 1 hour. Methanol was evaporated and the reaction mixture was made slightly basic with a saturated solution of sodium hydrogenocarbonate, extracted with dichloromethane and dried over magnesium sulphate. Solvent removal afforded a product which was purified by chromatography on a silica gel column with a mixture of dichloromethane and ether (98:2) as an eluent to yield 17 mg (70%) of **1** as a white powder, mp 121-122° (lit [1a] mp 125° for racemized natural harzianopyridone; lit [1c] mp 77-78° for natural (-)-harzianopyridone); ^{1}H nmr (deuteriochloroform): δ 1.15 (d, 3H, J = 6.8 Hz, 2'-CH_3), 1.65 (d, 3H, J = 5.0 Hz, CH_3-CH=CH), 1.98-2.13 and 2.40-2.51 (2 m, 2H, CH=CH-CH_2), 3.82 (s, 3H, 5-OCH_3), 3.93 (sext, J = 7 Hz, CH-CO), 4.15 (s, 3H, 6-OCH_3), 5.39-5.52 (m, 2H, CH=CH); ^{13}C nmr (deuteriochloroform): δ 16.3 (2'-CH_3), 18.0 ($C_{6'}$), 36.1 ($C_{3'}$), 43.3 ($C_{2'}$), 57.0 (6-OCH_3), 61.5 (5-OCH_3), 100.2 (C_3), 121.9 (C_5), 128.6 ($C_{4'}$), 156.1 (C_6), 161.6 (C_2), 209.4 ($C_{1'}$ ketone); ir: ν 2930, 1653, 1595, 1445, 1321, 1286, 1201, 1164, 995 cm^{-1}; ms: (70 eV, electron impact) m/z 281 (M^+, 30%), 263 (M^+ -H_2O, 8%), 248 (7%), 198 (M^+ -C_6H_{11}, 100%), 171 (13%); hrms Calcd. for $C_{14}H_{19}NO_5$: 281.1263. Found: 281.1260 (M^+, 30%), 198.0380 (M^+ -C_6H_{11}, 100%). These data are in agreement with those reported [1] for natural harzianopyridone.

Anal. Calcd. for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 60.0; H, 6.6; N, 4.6.

REFERENCES AND NOTES

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

[2] Natural harzianopyridone exhibits an optical activity, as reported in reference [1c]: $[\alpha]_D$ = -12.3° (*c* 1.0, MeOH, 22°), but its absolute configuration remains undefined.

[3a] R. Jansen and G. Höfle, *Tetrahedron Letters*, **24**, 5485 (1983), and references cited therein; [b] F. P. Schmidtchen and H. Rapoport, *J. Am. Chem. Soc.*, **99**, 7014 (1977); [c] K. H. Chung, K. Y. Cho, Y. Asami, N. Takahashi and S. Yoshida, *Z. Naturforsch.*, **44c**, 609 (1989).

[4a] S. Omura, H. Tomoda, K. Kimura, D.-Z. Zhen, H. Kumagai, K. Igarashi, N. Imamura, Y. Takahashi, Y. Tanaka and Y. Iwai, *J. Antibiot.*, **41**, 1769 (1988); [b] S. Omura, H. Koda, N. Imamura, Y. Tanaka and Y. Iwai, *Japan Kokai Tokkyo Koho*, JP O1, 199, 582 [89, 199, 582]; *Chem. Abstr.*, **112**, 215205n (1990); [c] K. Oshino, H. Kumagai, H. Tomoda and S. Omura, *J. Antibiot.*, **43**, 1064 (1990); [d] H. Kumagai, H. Nishida, N. Imamura, H. Tomoda, S. Omura and J. Bordner, *J. Antibiot.*, **43**, 1553 (1990).

[5] T. Otsuka, S. Takase, H. Terano and M. Okuhara, *J. Antibiot.*, **45**, 1970 (1992).

[6a] F. Trécourt, M. Mallet, O. Mongin, B. Gervais and G. Quéguiner, *Tetrahedron*, **49**, 8373 (1993); [b] A. Godard, F. Marsais, N. Plé, F. Trécourt, A. Turck and G. Quéguiner, *Heterocycles*, **40**, 1055 (1995).

[7] For a review on directed ortho metalation of pyridines and some other π-deficient azaaromatics, see: G. Quéguiner, F. Marsais, V. Snieckus and J. Epsztajn, Advances in Heterocyclic Chemistry, Vol **52**, A. R. Katritzky, ed, Academic Press, Inc., San Diego, 1991, pp 187-304.

[8] F. Trécourt, M. Mallet, O. Mongin and G. Quéguiner, *J. Org. Chem.*, **59**, 6173 (1994), and references cited therein.

[9] D. T. Deyo, J. D. Aebi and D. H. Rich, *Synthesis*, 608 (1988).

[10] J.-M. Jacquelin, Y. Robin, A. Godard and G. Quéguiner, *Can. J. Chem.*, **66**, 1135 (1988).

[11a] E. J. Corey and J. W. Suggs, *Tetrahedron Letters*, **31**, 2647 (1975); [b] G. Piancatelli, A. Scettri and M. D'Auria, *Synthesis*, 245 (1982).

[12] T. Sala and M. V. Sargent, *J. Chem. Soc., Perkin Trans. 1*, 2593 (1979).

[13] W. Wang and V. Snieckus, *J. Org. Chem.*, **57**, 424 (1992).

[14] J. Bizot, *Bull. Soc. Chim. France*, 151 (1967).

[15] The 2,4-dimethylhexanal used was a mixture of four stereoisomers (two chiral centers): H. C. Brown, G. W. Kabalka, M. W. Rathke and M. M. Rogic, *J. Am. Chem. Soc.*, **90**, 4165 (1968).