Regioselectivity of the Metalation of Polymethoxylated Pivaloylaminobenzenes. Synthesis of Methoxy-2(1*H*)-quinolones Precursors of 2-Substituted-5,8-quinolinediones

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Synthesis of methoxy-2(1*H*)-quinolones precursors of 2-substituted-5,8-quinolinediones is described. A metalation, Heck coupling reaction and cyclisation sequence is used. Regioselectivity of the metalation of methoxypivaloylaminobenzenes is studied.

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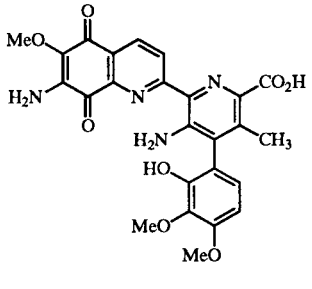
Within the framework of the synthesis of natural products [1] we were interested by the synthesis of Streptonigrin **1** an highly substituted 5,8-quinolinedione [2]. This alkaloid is well known to possess interesting antitumor activity [3] and it was recently found to be one of the most potent inhibitors of avian myelobastis virus reverse transcriptase (AMV-RT) [4]. Kubo observed that 6-methoxy-5,8-quinolinedione **2a** and 6-methoxy-7-methyl-5,8-quinolinedione **2b** were less toxic than **1** while activity against AMV-RT was comparable to that of **1**. A series of heterocyclic quinones was then synthesized [4]. The strategy we developed to prepare streptonigrin involves independent synthesis of each aryl part of the alkaloid followed by two successive biaryl cross-couplings [5]. We recently reported the synthesis of the quinoline moiety **2c** (R_2 = 2-pyridyl, R = NH_2, R_1 = H) [6]. The synthetic pathway consists in three main steps: metalation of a suitable methoxylated anilide followed by an Heck [7] coupling reaction and cyclisation. Quinolinequinone **2c** was then obtained after biaryl cross-coupling and by oxydative demethylation [8] (Scheme 2).

Scheme 1



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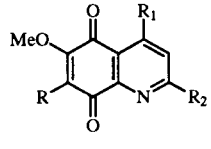
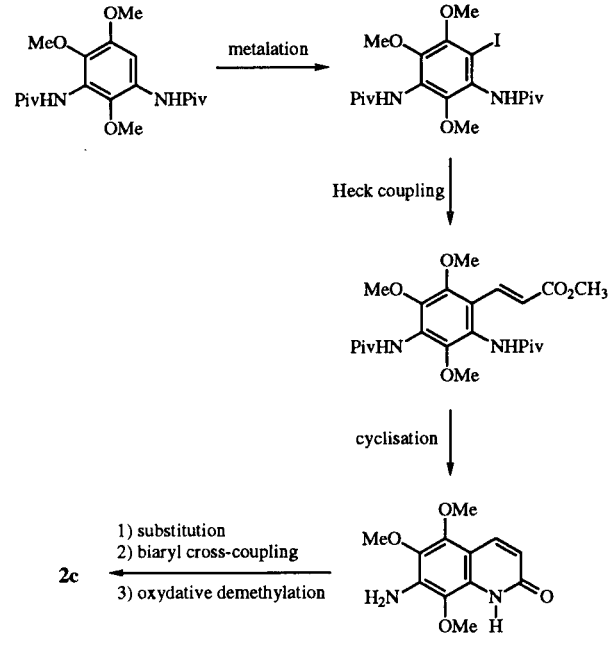


2a R = R_1 = R_2 = H
2b R = CH_3; R_1 = R_2 = H
2c R = NH_2; R_1 = H; R_2 = 2-pyridyl

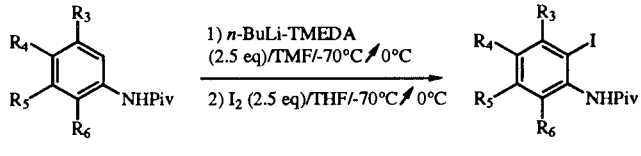
The methodology was applied to the synthesis of different methoxylated quinolines precursors of 5,8-quinolinediones. We wish to report here on the synthesis of 2(1*H*)-quinolones and more specially on the regioselectivity of metalation of methoxypivaloylaminobenzenes.

Scheme 2



In the benzene series, pivaloylamino and methoxy functions are *ortho*-directing groups for the metalation [9]. Moreover, when two substituents are in *meta* position of each other, metalation generally occurs between the two groups [10]. These observations are verified when methoxypivaloylaminobenzenes **3a-d** are functionalized in the conditions described in Scheme 3 (Table 1). However, when **3e** and **3f** (Schemes 4 and 5) were treated under the conditions described above (*n*-

Scheme 3



3 **4**

Table 1

Metalation of Methoxypivaloylaminobenzenes **3a-3d**

Entry		R_3	R_4	R_5	R_6	4 Yield [%]
1	**3a**	H	H	H	OMe	72
2	**3b**	OMe	H	H	OMe	77
3	**3c**	OMe	OMe	H	H	88
4	**3d**	OMe	OMe	NHPiv	OMe	86 [a]

[a] 3.5 Equivalents of complexed *n*-BuLi/TMEDA were used.

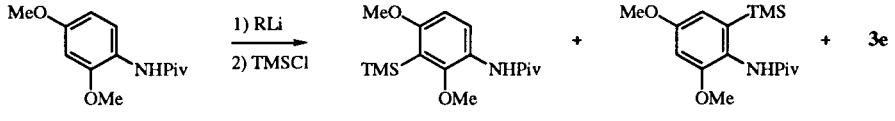
BuLi-TMEDA/THF/0°), only mixtures were obtained and no regioselective metalation was observed. Conditions for regioselective metalations of **3e** and **3f** were then studied.

When metalation of **3e** was carried out with *n*-BuLi/TMEDA (3.5 equivalents) as the reagent at 0° in THF with TMSCl as the electrophile, compound **5** substituted at C-3 was mainly obtained. The same reaction carried out at -70° affords the same product in 16% yield. The use of *sec*-BuLi at -70° afforded compound **6** (isomer of **5**) substituted at C-6 as the main product (Scheme 4). Moreover, when the reaction was carried out with *sec*-BuLi at -70° and the reaction mixture heated to 0°, the ratio of compound **5** increased. These observations led us to conclude that isomer **5** is the thermodynamic compound and isomer **6** is the kinetic one.

Metalation of 2,4,5-trimethoxypivaloylaminobenzene **3f** with *n*-BuLi (2 equivalents) gave a mixture of **3f** and of compounds substituted at C-3, **7** and at C-6, **8** in variable ratios but no marked regioselectivity was observed. Use of *sec*-BuLi allows us to improve the regioselectivity at C-3. The best regioselectivity was obtained with *sec*-BuLi (5 equivalents) complexed by TMEDA in THF at -70° (2 hours) followed by the reaction of TMSCl at -70° (Scheme 5).

Compound **3e** is metalated by *sec*-BuLi at -70° preferentially in the *ortho* position of the pivaloylamino group. For **3f**, one could expect the same regioselectivity under similar conditions, moreover, the C-6 position is placed between the pivaloylamino and the methoxy group. It could be observed that the major product was not the expected one **8** but **7**. The best conditions for metalation of **3f** to **7** are: *sec*-BuLi/TMEDA (5 equivalents), -70°, 2 hours followed by reaction with TMSCl (5 equivalents) at -70° for 2

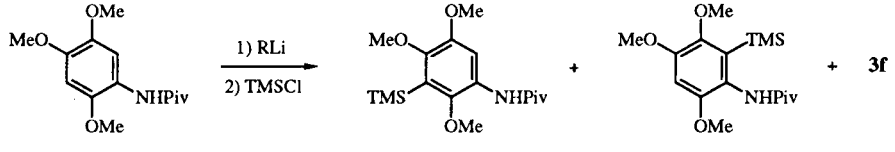
Scheme 4



3e **5** **6**

1) *n*-BuLi/TMEDA/THF/0°C/4 h 2) TMSCl/0°C/2 h	61%	14%	8%
1) *n*-BuLi/TMEDA/THF/-70°C/2 h 2) TMSCl/-70°C/2 h	16%	--	81%
1) *sec*-BuLi/TMEDA/THF/-70°C to 0°C/2 h 2) TMSCl/-70°C to 0°C/2 h	41%	35%	13%
1) *sec*-BuLi/TMEDA/THF/-70°C/2 h 2) TMSCl/-70°C/2 h	21%	72%	4%

Scheme 5



3f **7** **8**

1) *n*-BuLi/TMEDA/THF/0°C/4 h 2) TMSCl/0°C/2 h	25%	21%	41%
1) *sec*-BuLi/TMEDA/THF/-70°C/2 h 2) TMSCl/-70°C/2 h	69%	17%	12%
1) *tert*-BuLi/TMEDA/THF/-70°C/2 h 2) TMSCl/-70°C/2 h	4%	--	90%

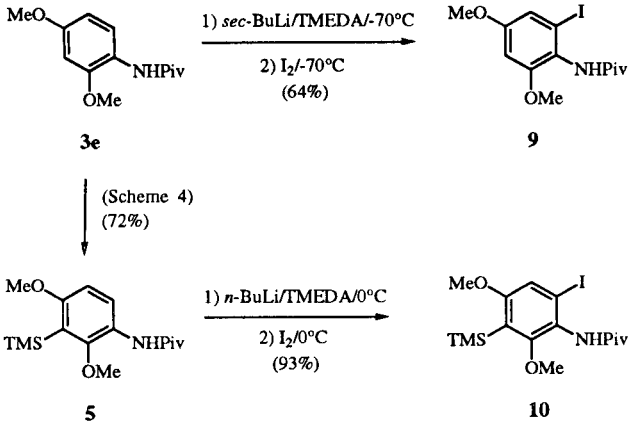
Table 2

Synthesis of Methyl *trans*-Cinnamates **12** and of 2(1*H*)-quinolones **13**

Entry No.	Compounds **4, 10, 11**					**12**		**13**	
		R_3	R_4	R_5	R_6		Yield [%]		Yield [%]
1	**4a**	H	H	H	OMe	**12a**	93	**13a**	87
2	**4b**	OMe	H	H	OMe	**12b**	96	**13b**	85
3	**4c**	OMe	OMe	H	H	**12c**	83	**13c**	75
4	**4d**	OMe	OMe	NHPiv	OMe	**12d**	92	**13d**	52 ($R_5 = NH_2$) [a]
5	**10**	H	OMe	TMS	OMe	**12e**	83	**13e**	41 (R_5 = H) [b]
6	**11**	OMe	OMe	TMS	OMe	**12f**	76	**13f**	65 (R_5 = H) [c]

[a] The first step is performed in a sealed tube. [b] *Ipso*-desilylation occurs in the second step. [c] The first step (Heck coupling) is performed in a sealed tube. *Ipso*-desilylation occurs in the second step (cyclisation).

Scheme 6



hours. Steric hindrance at the C-6 position could be an explanation to this fact and is in agreement with other results: with the less hindered linear *n*-butyllithium no regioselectivity was observed, with the very hindered *tert*-butyllithium very low yield is obtained.

The results described above were used to synthesize different iodo derivatives:

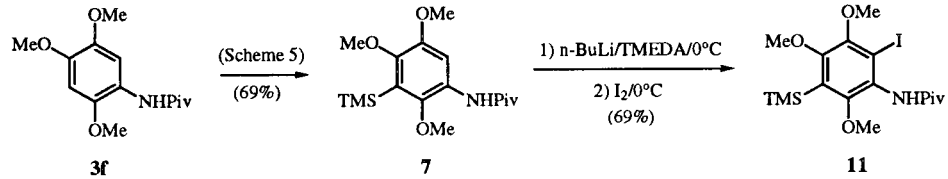
Reaction of 2,4-dimethoxypivaloylaminobenzene **3e** with *sec*-BuLi at -70° under the conditions described in Scheme 4 using iodine as an electrophile affords 2,4-dimethoxy-6-iodopivaloylaminobenzene **9** in 64% yield. On the other hand metalation of silylated compound **5** with *n*-BuLi at 0° afforded the tetrasubstituted *ortho*-iodopivaloylaminobenzene **10** in 93% yield (Scheme 6).

When treated with *n*-BuLi at 0° the trimethoxy derivative **7** affords the iodo derivative **11** in 69% yield (Scheme 7).

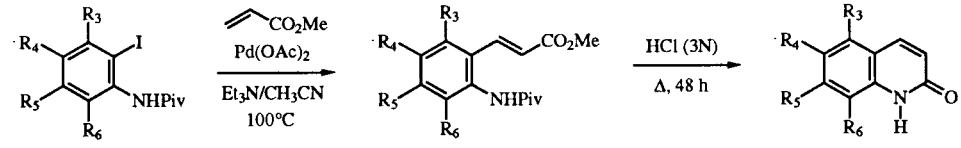
Obtaining the trimethylsilyl derivative does not represent a difficulty for the synthesis of our target molecules because of the possibility of *ipso*-desilylation in a subsequent step. On the contrary it gave the possibility of other substitutions on the benzene ring.

The quinoline ring was obtained in two steps from the iodo derivatives. The methyl methoxypivaloylaminocinnamates **12** were first prepared from the corresponding iodo derivatives by a Heck coupling reaction (Scheme 8) (Table 2). Cyclisation to 2(1*H*)-quinolones **13** was performed in acidic medium. Thus 2(1*H*)-quinolones were synthesized in 3 or 4 steps starting from methoxylated pivaloylaminobenzenes in fairly good overall yields (19% to 62%). The strategy could be used for the syn-

Scheme 7



Scheme 8



thesis of various substituted methoxyquinolines precursors of 5,8-quinolinequinones.

EXPERIMENTAL

All melting points were determinated on a Kofler apparatus and are uncorrected. The ^{1}H-nmr spectra were measured at 60 MHz in deuteriochloroform (or in DMSO) with tetramethylsilane (or HMDS) as an internal standard. Microanalyses are performed on a Carlo Erba 1160 apparatus and mass spectra on a Jeol JMS-AX 500.

Synthesis of Methoxypivaloylaminobenzenes **3**. General Procedure.

A solution of alkoxyamine (0.01 mole) and triethylamine (1 g, 0.01 mole) in anhydrous ether (50 ml) is cooled to 0°. Pivaloyl chloride (1.2 g, 0.01 mole) is added at 0° and the mixture is stirred for 16 hours at room temperature. After addition of water (100 ml), potassium carbonate is added (*p*H = 9-10). After decantation and extraction of the aqueous layer with dichloromethane, the organic layers are dried over magnesium sulfate and evaporated under reduced pressure.

2-Methoxypivaloylaminobenzene (**3a**).

This compound was obtained as a white solid, yield 98%, mp <50°; ^{1}H nmr (deuteriochloroform): δ 1.30 (s, 9H, *t*-Bu), 3.80 (s, 3H, OMe), 6.30 (m, 3H, H_3, H_4 and H_5), 8.17 (d, 1H, H_6, J = 3.05 Hz), 8.50 (br s, 1H, NH).

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.33; H, 8.37; N, 6.74.

2,5-Dimethoxypivaloylaminobenzene (**3b**).

This compound was obtained as a white solid, yield 95%, mp 54°; ^{1}H nmr (deuteriochloroform): δ 1.37 (s, 9H, *t*-Bu), 3.78 (s, 3H, OMe), 3.86 (s, 3H, OMe), 6.52 (dd, 1H, H_4, J = 9 Hz, J = 3 Hz), 6.80 (d, 1H, H_3, J = 9 Hz), 8.13 (br s, 1H, NH), 8.19 (d, 1H, H_6, J = 3 Hz).

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.81; H, 8.10; N, 5.90.

3,4-Dimethoxypivaloylaminobenzene (**3c**).

This compound was obtained as a white solid, yield 86%, mp 128°; ^{1}H nmr (deuteriochloroform): δ 1.33 (s, 9H, *t*-Bu), 3.77 (s, 3H, OMe), 3.80 (s, 3H, OMe), 6.67 (d, 1H, H_5, J = 9 Hz), 6.95 (dd, 1H, H_6, J = 9 Hz, J = 2 Hz), 7.42 (d, 1H, H_2, J = 2 Hz), 7.90 (br s, 1H, NH).

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.63; H, 8.17; N, 5.98.

2,4,5-Trimethoxy-1,3-dipivaloylaminobenzene (**3d**).

The 2,4,5-trimethoxy-*m*-phenylenediamine obtained from 3,5-dinitro-1,2,4-trimethoxybenzene (six steps from gaïacol, overall yield 31%) [11] by catalytic reduction (quantitative yield) was treated following the general procedure (triethylamine, 3.5 equivalents), pivaloyl chloride (3.5 equivalents) and anhydrous THF as the solvent. A white solid was obtained, yield 96%, mp 170°; ^{1}H nmr (deuteriochloroform): δ 1.30 (s, 9H, *t*-Bu), 1.35 (s, 9H, *t*-Bu), 3.65 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.85 (s, 3H, OMe), 7.08 (br s, 1H, NH), 8.02 (br s, 1H, NH), 8.18 (s, 1H, H_6).

Anal. Calcd. for $C_{19}H_{30}N_2O_5$: C, 62.27; H, 8.25; N, 7.64. Found: C, 62.28; H, 8.42; N, 7.70.

2,4-Dimethoxypivaloylaminobenzene (**3e**).

This compound was obtained as a white solid, yield 89%, mp 50-52°; ^{1}H nmr (deuteriochloroform): δ 1.33 (s, 9H, *t*-Bu), 3.78 (s, 3H, OMe), 3.87 (s, 3H, OMe), 6.35 to 6.55 (m, 2H, H_3 and H_4), 7.88 (br s, 1H, NH), 8.26 (d, 1H, H_6, J = 9 Hz).

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.72; H, 7.83; N, 5.86.

2,4,5-Trimethoxypivaloylaminobenzene (**3f**).

This product was obtained from 2,4,5-trimethoxyaniline [12] following the general procedure as a white solid, yield 91%, mp 80°; ^{1}H nmr (deuteriochloroform): δ 1.33 (s, 9H, *t*-Bu), 3.87 (s, 9H, 3*OMe), 6.52 (s, 1H, H_3), 7.93 (br s, 1H, NH), 8.17 (s, 1H, H_6).

Anal. Calcd. for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.91; H, 8.24; N, 5.19.

Metalation of Methoxypivaloylaminobenzenes **3a-3d**. General Procedure.

A solution of methoxypivaloylaminobenzene (0.01 mole) and 2.75 g of TMEDA (0.025 mole) in 50 ml of anhydrous THF is cooled to -70°. *n*-Butyllithium (10 ml of a 2.5 *M* solution in hexane [0.025 mole]) is added and the mixture heated to 0°. After stirring for two hours, the temperature is brought down again to -70° and 6.35 g of iodine (0.025 mole) in 10 ml THF is added. After 15 minutes the mixture is heated to 0° and stirred for 2 hours. A saturated solution of sodium thiosulfate is then added. After the usual workup the iodo derivative is purified by flash chromatography.

6-Iodo-2-methoxypivaloylaminobenzene (**4a**).

This compound was obtained as a white solid, yield 72%, mp 142°; ^{1}H nmr (deuteriochloroform): δ 1.35 (s, 9H, *t*-Bu), 3.80 (s, 3H, OMe), 7.00 to 7.50 (m, 4H, H_3, H_4, H_5 and NH).

Anal. Calcd. for $C_{12}H_{16}NO_2I$: C, 43.26; H, 4.84; N, 4.20. Found: C, 43.33; H, 4.78; N, 4.07.

6-Iodo-2,5-dimethoxypivaloylaminobenzene (**4b**).

This compound was obtained as a white solid, yield 77%, mp 120°; ^{1}H nmr (deuteriochloroform): δ 1.40 (s, 9H, *t*-Bu), 3.78 (s, 3H, OMe), 3.83 (s, 3H, OMe), 6.72 (d, 1H, J = 8 Hz), 6.93 (d, 1H, J = 8 Hz), 7.06 (br s, 1H, NH).

Anal. Calcd. for $C_{13}H_{18}NO_3I$: C, 42.99; H, 5.00; N, 3.86. Found: C, 42.88; H, 4.94; N, 3.86.

2-Iodo-3,4-dimethoxypivaloylaminobenzene (**4c**).

This compound was obtained as a white solid, yield 88%, mp 82°; ^{1}H nmr (deuteriochloroform): δ 1.37 (s, 9H, *t*-Bu), 3.82 (s, 3H, OMe), 3.85 (s, 3H, OMe), 6.87 (d, 1H, H_5, J = 9 Hz), 7.70 (br s, 1H, NH), 7.87 (d, 1H, H_6, J = 9 Hz).

Anal. Calcd. for $C_{13}H_{18}NO_3I$: C, 42.99; H, 5.00; N, 3.86. Found: C, 42.97; H, 4.88; N, 3.92.

6-Iodo-2,4-dimethoxy-3-trimethylsilylpivaloylaminobenzene (**10**).

The general procedure is used with 2,4-dimethoxy-3-trimethylsilylpivaloylaminobenzene (**5**) as the substrate. A white solid is obtained in 93% yield, mp 230°; ^{1}H nmr (deuteriochloroform): δ 0.28 (s, 9H, $SiMe_3$), 1.37 (s, 9H, *t*-Bu), 3.58 (s, 3H, OMe), 3.73 (s, 3H, OMe), 6.98 (br s, 1H, NH), 7.10 (s, 1H, H_5).

Anal. Calcd. for $C_{16}H_{26}NO_3SiI$: C, 44.14; H, 6.02; N, 3.22. Found: C, 44.08; H, 6.19; N, 3.11.

6-Iodo-2,4,5-trimethoxy-3-trimethylsilylpivaloylaminobenzene (**11**).

The general procedure is used with 2,4,5-trimethoxy-3-trimethylsilylpivaloylaminobenzene (**7**) as the substrate. A white solid is obtained in 69% yield, mp 194°; ^{1}H nmr (deuteriochloroform): δ 0.32 (s, 9H, $SiMe_3$), 1.38 (s, 9H, *t*-Bu), 3.55 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.82 (s, 3H, OMe), 7.03 (br s, 1H, NH).

Anal. Calcd. for $C_{17}H_{28}NO_4SiI$: C, 43.87; H, 6.06; N, 3.00. Found: C, 43.87; H, 6.15; N, 2.91.

6-Iodo-2,4,5-trimethoxy-1,3-dipivaloylaminobenzene (**4d**).

The general procedure is used with 3.5 equivalents of *n*-BuLi complexed with TMEDA and 3.5 equivalents of iodine. A white solid is obtained in 86% yield, mp >260°; ^{1}H nmr (deuteriochloroform): δ 1.35 (s, 9H, *t*-Bu), 1.37 (s, 9H, *t*-Bu), 3.45 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.82 (s, 3H, OMe), 7.1 and 7.2 (2*br s, 2H, 2*NH).

Anal. Calcd. for $C_{19}H_{29}N_2O_5I$: C, 46.35; H, 5.94; N, 5.69. Found: C, 46.47; H, 5.95; N, 5.59.

2,4-Dimethoxy-3-trimethylsilylpivaloylaminobenzene (**5**).

A solution of 1 g (4.2 mmoles) of 2,4-dimethoxypivaloylaminobenzene (**3e**) and 1.60 ml (10.5 mmoles) of TMEDA in 50 ml of anhydrous diethyl ether is cooled to -70°. *n*-Butyllithium (4.2 ml of a 2.5 *M* solution in hexane, 10.5 mmoles) is added and the mixture heated to 0°. After stirring for four hours, the temperature is brought down again to -70° and 1.34 ml (10.5 mmoles) of trimethylsilylchloride is added. The mixture is heated to 0° and stirred for 2 hours. Water is then added at 0°. Extraction of the reaction mixture with diethyl ether and evaporation *in vacuo*, gave a solid which was purified by flash chromatography (silica gel), eluent, hexane/diethyl ether 50:50. A white solid is obtained, yield 70%, mp 94°; ^{1}H nmr (deuteriochloroform): δ 0.33 (s, 9H, $SiMe_3$), 1.33 (s, 9H, *t*-Bu), 3.67 (s, 3H, OMe), 3.77 (s, 3H, OMe), 6.62 (d, 1H, H_5, J = 9 Hz), 7.85 (br s, 1H, NH), 8.26 (d, 1H, H_6, J = 9 Hz).

Anal. Calcd. for $C_{16}H_{27}NO_3Si$: C, 62.10; H, 8.79; N, 4.53. Found: C, 61.99; H, 8.92; N, 4.46.

2,4-Dimethoxy-6-trimethylsilylpivaloylaminobenzene (**6**).

A solution of 0.5 g (2.1 mmoles) of 2,4-dimethoxypivaloylaminobenzene (**3e**) and 1.12 ml (7.35 mmoles) of TMEDA in 50 ml of anhydrous THF is cooled to -70°. *sec*-Butyllithium (5.32 ml of a 1.4*M* solution in hexane, 7.35 mmoles) is added and the mixture stirred for two hours at -70°. Trimethylsilylchloride (0.94 ml 7.35 mmoles) is added and the mixture stirred for 2 hours. A mixture of water/ethanol/THF (1/1/1) is added at -70° and the temperature is brought up to 20°. Extraction of the reaction mixture with methylene chloride and evaporation *in vacuo*, gave a solid which was purified by flash chromatography (silica gel), eluent, hexane/diethyl ether 50:50 then diethyl ether. A white solid is obtained, yield 72%, mp 142°; ^{1}H nmr (deuteriochloroform): δ 0.27 (s, 9H, $SiMe_3$), 1.33 (s, 9H, t-Bu), 3.77 (s, 3H, OMe), 3.80 (s, 3H, OMe), 6.47 (d, 1H, J = 2.6 Hz), 6.58 (d, 1H, J = 2.6 Hz), 6.70 (br s, 1H, NH).

Anal. Calcd. for $C_{16}H_{27}NO_3Si$: C, 62.10; H, 8.79; N, 4.53. Found: C, 62.16; H, 9.03; N, 4.34.

6-Iodo-2,4-dimethoxypivaloylaminobenzene (**9**).

The same procedure as above is used with 1.865 g (7.35 mmoles) of iodine as electrophile dissolved in 10 ml of anhydrous THF. A saturated solution of sodium thiosulfate is added for the hydrolysis. After the usual workup the iodo derivative is purified by flash chromatography (silica gel), eluent, hexane/diethyl ether 50:50. A white solid is obtained, yield 64%, mp 94°; ^{1}H nmr (deuteriochloroform): δ 1.34 (s, 9H, *t*-Bu), 3.75 (s, 3H, OMe), 3.77 (s, 3H, OMe), 6.45 (d, 1H, J = 2.57 Hz), 6.87 (br s, 1H, NH), 6.94 (d, 1H, J = 2.57 Hz).

Anal. Calcd. for $C_{13}H_{18}NO_3I$: C, 42.99; H, 4.99; N, 3.86. Found: C, 43.35; H, 4.93; N, 3.56.

2,4,5-Trimethoxy-3-trimethylsilylpivaloylaminobenzene (**7**).

A solution of 0.5 g (1.87 mmoles) of 2,4,5-trimethoxypivaloylaminobenzene (**3f**) and 1.4 ml (9.35 mmoles) of TMEDA in 50 ml of anhydrous THF is cooled to -70°. *sec*-Butyllithium (6.8 ml of a 1.4*M* solution in hexane, 9.35 mmoles) is added and the mixture stirred for two hours at -70°. Trimethylsilylchloride (1.25 ml, 9.35 mmoles) is added and the mixture was stirred for 2 hours. A mixture of water/ethanol/THF (1/1/1) is added at -70° and the temperature is brought up to 20°. Extraction of the reaction mixture with methylene chloride and evaporation *in vacuo*, gave a liquid which was purified by flash chromatography (silica gel), eluent, hexane/diethyl ether 50:50, viscous orange liquid, yield 69%; ^{1}H nmr (deuteriochloroform): δ 0.37 (s, 9H, $SiMe_3$), 1.35 (s, 9H, *t*-Bu), 3.63 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.87 (s, 3H, OMe), 7.93 (br s, 1H, NH), 8.13 (s, 1H, H_6).

Anal. Calcd. for $C_{17}H_{29}NO_4Si$: C, 60.14; H, 8.61; N, 4.12. Found: C, 60.51; H, 9.14; N, 4.08.

2,4,5-Trimethoxy-6-trimethylsilylpivaloylaminobenzene (**8**).

This compound was obtained as a white solid, yield 21%, mp 122°; ^{1}H nmr (deuteriochloroform): δ 0.32 (s, 9H, $SiMe_3$), 1.30 (s, 9H, *t*-Bu), 3.77 (s, 6H, 2*OMe), 3.83 (s, 3H, OMe), 6.50 (s, 1H, H_3), 6.80 (br s, 1H, NH).

Anal. Calcd. for $C_{17}H_{29}NO_4Si$: C, 60.14; H, 8.61; N, 4.12. Found: C, 60.52; H, 8.74; N, 4.10.

Synthesis of Methyl *trans*-Methoxypivaloylaminocinnamates **12a-12c, 12e**. General Procedure.

A solution of iodomethoxypivaloylaminobenzene (0.02 mole), methyl acrylate (0.04 mole), triethylamine (0.025 mole) and palladium acetate (0.6 mmole) in acetonitrile (50 ml) as the solvent was stirred and refluxed over a period of 48 hours under argon. After cooling, the solution was diluted with methylene chloride (50 ml), washed with a saturated solution of sodium carbonate (50 ml), water (50 ml), dried over magnesium sulfate and evaporated under reduced pressure. Pure methyl *trans*-methoxypivaloylaminocinnamates **13a-13c** and **13e** were obtained after flash chromatography.

Methyl *trans*-3-Methoxy-2-pivaloylaminocinnamate (**12a**).

This compound was obtained as a white solid, yield 93%, mp 143°; ^{1}H nmr (deuteriochloroform): δ 1.36 (s, 9H, *t*-Bu), 3.75 (s, 3H, OMe), 3.82 (s, 3H, OMe), 6.32 (d, 1H, H_2 of =CH, J = 16 Hz), 6.76 to 7.30 (m, 4H, H_4, H_5, H_6 and NH), 7.62 (d, 1H, H_3 of =CH, J = 16 Hz).

Anal. Calcd. for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.69. Found: C, 66.21; H, 7.36; N, 4.69.

Methyl *trans*-3,6-Dimethoxy-2-pivaloylaminocinnamate (**12b**).

This compound was obtained as a white solid, yield 96%, mp 108°; ^{1}H nmr (deuteriochloroform): δ 1.40 (s, 9H, *t*-Bu), 3.77 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.85 (s, 3H, OMe), 6.76 (d, 1H, H_2 of =CH, J = 16 Hz), 6.76 to 6.87 (m, 2H, H_4 and H_5), 7.26 (br s, 1H, NH), 7.63 (d, 1H, H_3 of =CH, J = 16 Hz).

Anal. Calcd. for $C_{17}H_{23}NO_5$: C, 63.53; H, 7.21; N, 4.36. Found: C, 63.76; H, 7.00; N, 4.33.

Methyl *trans*-5,6-Dimethoxy-2-pivaloylaminocinnamate (**12c**).

This compound was obtained as a white solid, yield 83%, mp 88°; ^{1}H nmr (deuteriochloroform): δ 1.33 (s, 9H, *t*-Bu), 3.80 (s, 6H, 2*OMe), 3.87 (s, 3H, OMe), 6.53 (d, 1H, H_2 of =CH, J = 17 Hz), 6.87 (d, 1H, H_4, J = 9 Hz), 7.33 (br s, 1H, NH), 7.40 (d, 1H, H_5, J = 9 Hz), 7.68 (d, 1H, H_3 of =CH, J = 17 Hz).

Anal. Calcd. for $C_{17}H_{23}NO_5$: C, 63.53; H, 7.21; N, 4.36. Found: C, 63.26; H, 6.98; N, 4.30.

Methyl *trans*-3,5,6-Trimethoxy-2,4-dipivaloylaminocinnamate (**12d**).

The synthesis is identical to the general procedure but is conducted in a sealed tube at 100° over a period of 8 hours. It was obtained as a white solid, yield 92%, mp 195°; ^{1}H nmr (deuteriochloroform): δ 1.35 (s, 18H, 2**t*-Bu), 3.35 (s, 3H, OMe), 3.77 (s, 6H, 2*OMe), 3.82 (s, 3H, OMe), 6.65 (d, 1H, H_2 of =CH, J = 16 Hz), 7.33 (br s, 1H, NH), 7.56 (br s, 1H, NH), 7.59 (d, 1H, H_3 of =CH, J = 16 Hz).

Anal. Calcd. for $C_{23}H_{34}N_2O_7$: C, 61.32; H, 7.61; N, 6.22. Found: C, 61.35; H, 7.71; N, 6.12.

Methyl *trans*-3,5-Dimethoxy-4-trimethylsilyl-2-pivaloylaminocinnamate (**12e**).

This compound was obtained as a white solid, yield 83%, mp 156°; ^{1}H nmr (deuteriochloroform): δ 0.32 (s, 9H, $SiMe_3$), 1.38 (s, 9H, *t*-Bu), 3.58 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.78 (s, 3H, OMe), 6.32 (d, 1H, H_2 of =CH, J = 16 Hz), 6.80 (s, 1H, H_6), 7.16 (br s, 1H, NH), 7.55 (d, 1H, H_3 of =CH, J = 16 Hz).

Anal. Calcd. for $C_{20}H_{31}NO_5Si$: C, 61.04; H, 7.94; N, 3.56. Found: C, 61.26; H, 8.18; N, 3.71.

Methyl *trans*-3,5,6-Trimethoxy-4-trimethylsilyl-2-pivaloylaminocinnamate (**12f**).

The synthesis is identical to the general procedure but is conducted in a sealed tube at 140° over a period of 120 hours. This compound was obtained as a white solid, yield 76%, mp 175°; ^{1}H nmr (deuteriochloroform): δ 0.31 (s, 9H, $SiMe_3$) 1.33 (s, 9H, *t*-Bu), 3.55 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.83 (s, 3H, OMe), 6.71 (d, 1H, H_2 of =CH, J = 16 Hz), 7.25 (br s, 1H, NH), 7.47 (d, 1H, H_3 of =CH, J = 16 Hz).

Anal. Calcd. for $C_{21}H_{33}NO_6Si$: C, 59.55; H, 7.85; N, 3.30. Found: C, 59.52; H, 8.19; N, 3.23.

Cyclisation of the Methyl *trans*-Methoxypivaloylaminocinnamates **12a-12f** into 2(1*H*)-Quinolones **13a-13f**. General Procedure.

A solution of 0.01 mole of the *trans*-cinnamates **13a-13f** in 3*M* hydrochloric acid (50 ml) is refluxed over a period of 48 hours. After cooling and neutralization with solid potassium carbonate, the aqueous layers are extracted with methylene chloride (3*50 ml). After evaporation of the solvent under reduced pressure, the 2(1*H*)-quinolones **14a-14f** are purified by flash chromatography.

8-Methoxy-2(1*H*)-quinolone (**13a**).

This compound was obtained as a white solid, yield 87%, mp 109°; ^{1}H nmr (deuteriochloroform): δ 3.97 (s, 3H, OMe), 6.63 (d, 1H, H_3, J = 10 Hz), 6.83 to 7.30 (m, 3H, H_5, H_6, and H_7), 7.70 (d, 1H, H_4, J = 10 Hz), 9.50 (br s, 1H, NH).

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.57; H, 5.07; N, 7.87.

5,8-Dimethoxy-2(1*H*)-quinolone (**13b**).

This compound was obtained as a white solid, yield 85%, mp 153°; ^{1}H nmr (deuteriochloroform): δ 3.87 (s, 3H, OMe), 3.93 (s, 3H, OMe), 6.35 to 6.90 (m, 3H, H_3, H_6, and H_7), 8.05 (d, 1H, H_4, J = 10 Hz), 9.63 (br s, 1H, NH).

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.82. Found: C, 64.56; H, 5.40; N, 6.64.

5,6-Dimethoxy-2(1*H*)-quinolone (**13c**).

This compound was obtained as a white solid, yield 75%, mp 187°; ^{1}H nmr (deuteriochloroform): δ 3.82 (s, 6H, 2*OMe), 6.41 (d, 1H, H_3, J = 9 Hz), 6.96 (d, 1H, H_7, J = 9 Hz), 7.29 (d, 1H, H_8, J = 9 Hz), 7.91 (d, 1H, H_4, J = 9 Hz), 11.58 (br s, 1H, NH).

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.82. Found: C, 64.20; H, 5.20; N, 6.76.

7-Amino-5,6,8-trimethoxy-2(1*H*)-quinolone (**13d**).

This compound was obtained as a pale brown solid, yield 52%, mp 191°; ^{1}H nmr (deuteriochloroform): δ 3.63 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.82 (s, 3H, OMe), 5.44 (br s, 2H, NH_2), 6.10 (d, 1H, H_3, J = 10 Hz), 7.75 (d, 1H, H_4, J = 10 Hz).

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.82; H, 5.68; N, 10.93.

6,8-Dimethoxy-2(1*H*)-quinolone (**13e**).

This compound was obtained as a white solid, yield 41%, mp 155°; ^{1}H nmr (deuteriochloroform): δ 3.80 (s, 3H, OMe), 3.92 (s, 3H, OMe), 6.43 to 6.72 (m, 3H, H_3, H_5 and H_7), 7.57 (d, 1H, H_4, J = 9 Hz), 10.07 (br s, 1H, NH).

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.82. Found: C, 64.12; H, 5.55; N, 6.46.

5,6,8-Trimethoxy-2(1*H*)-quinolone (**13f**).

This compound was obtained as a pale brown solid, yield 65%, mp 167°; ^{1}H nmr (deuteriochloroform): δ 3.90 (s, 3H, OMe), 3.92 (s, 3H, OMe), 3.95 (s, 3H, OMe), 6.65 (d, 1H, H_3, J = 9 Hz), 6.73 (s, 1H, H_7), 8.02 (d, 1H, H_4, J = 9 Hz), 9.35 (br s, 1H, NH).

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.08; H, 5.88; N, 5.89.

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