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Stereochemical Variations on the Colchicine Motif. Part 4. A Remote Metalation Approach toward a Colchicine Analog with a Five-Membered B-Ring

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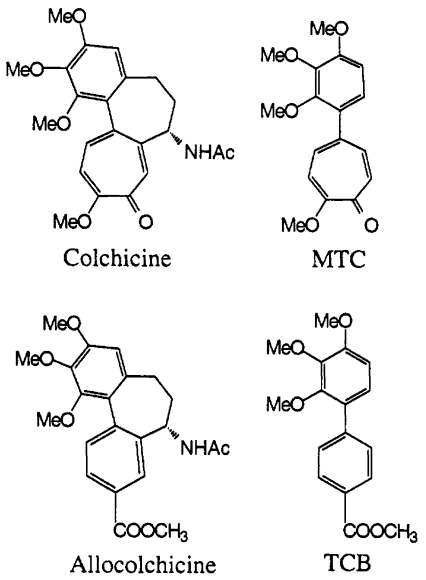
Attempts to prepare a colchicine analog with a 5-membered B-ring by remote metalation of *N,N*-diethyl-3,4,5-trimethoxy-2-(5′-methoxy-4′-oxo-2′,5′,7′-cycloheptatrienyl)-benzamide (**2**) led to ring contraction of the methoxytropone ring to the *p*-methoxycarbonylphenyl derivative (**3**). Dynamic ^{1}H NMR investigations showed that the biaryl amide **2** exists as a mixture of diastereomers due to hindered rotation around both aryl–aryl and aryl–amide bonds, with rotational barriers of ca. 63 kJ mol^{-1}. The colchicine and allocolchicine analogs **2** and **3** do not notably affect tubulin polymerization, despite the structural similarities with active analogs. The reduced tubulin binding activity of **2** and **3** may be a result of increasing steric bulk.

Colchicine, an antimitotic drug, and its structural analogs (Scheme 1), are known to exert their major biological effect by binding to the cytoskeletal protein tubulin. This interaction leads to depolymerisation of the microtubules and hence mitotic arrest. Colchicine and its derivatives have been extensively studied from both chemical and biological aspects.[2] From structure–activity relationship studies it can be concluded that the A- and C-rings are essential for high-affinity binding. The B-ring is not required for tubulin binding as the analog in which the B-ring is absent (MTC, Scheme 1) binds rapidly to tubulin. Substitution of the methoxytropone ring C with a *p*-methoxycarbonylphenyl ring results in allocolchicine, which retains tubulin-binding activity. The biphenyl analog TCB (Scheme 1) possesses tubulin-binding activity similar to that of MTC.[3] We have been interested in the structural requirements of colchicinoids for binding to tubulin, in particular the dynamic stereochemistry of the pivot bond joining the A and C rings. The absolute configuration for this bond is S_a and the torsional angle is close to 54° in colchicine and most active analogs. One way to modify the dihedral angle of the pivot bond is to change the number of atoms in the B-ring. In a previous publication a highly twisted analog with an eight-membered B-ring was shown to inhibit microtubule assembly.[1c] Recently one analog with a six atom B-ring has been reported to bind rapidly and reversibly to tubulin.[4] Colchicine analogs with less than six atoms in the B-ring have not been described. The remote aromatic metalation developed by Snieckus constitutes a short and convenient route to fluorenones.[5] This work deals with such an approach towards colchicine analogs with five atoms in the B-ring. Synthesis, NMR spectroscopy, tubulin binding experiments and the dynamic stereochemistry of amide analogs of MTC and TCB are presented.



Scheme 1.

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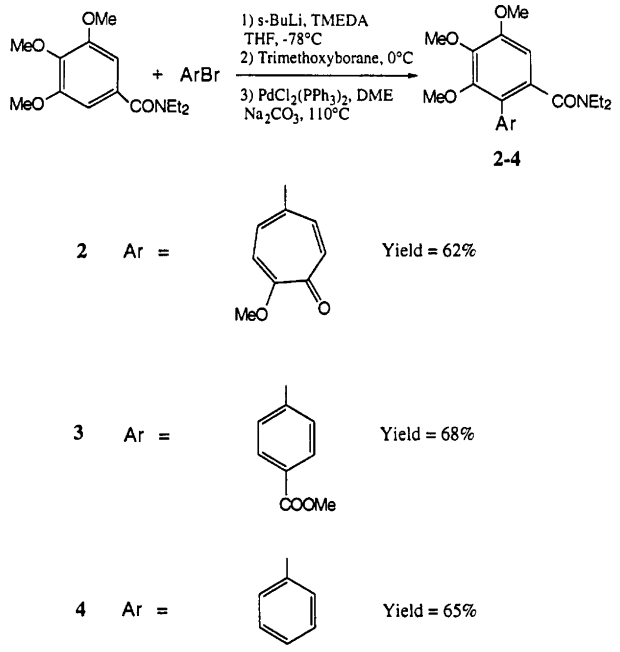
Results and discussion

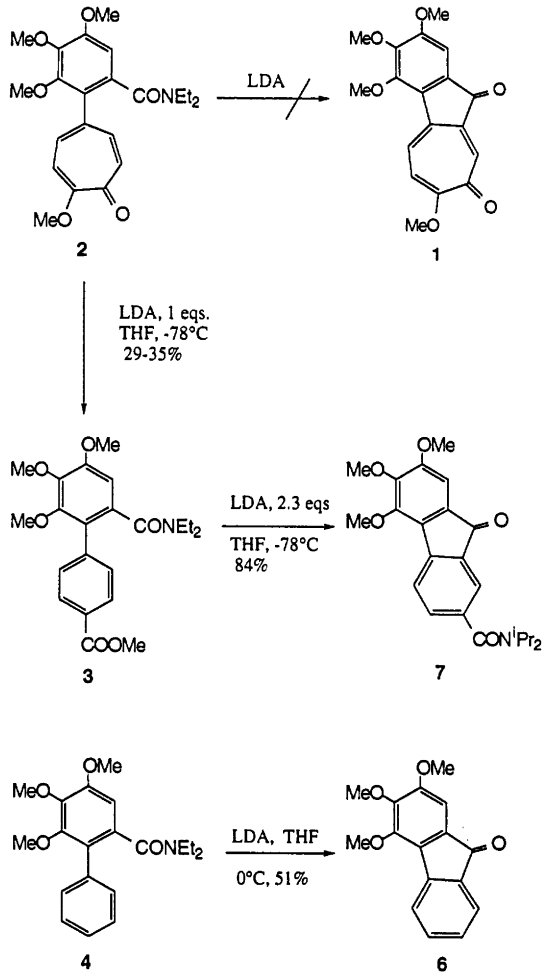
Syntheses. The initial purpose of this work was to prepare the tricyclic ketone **1** by remote metalation of *N,N*-diethyl-3,4,5-trimethoxy-2-(4-methoxy-5′-oxo-1,3,6′-cycloheptatrienyl)benzamide (**2**). The bicyclic amides **2**, **3** and **4** were prepared by palladium-catalyzed cross-coupling[6] (Scheme 2). The organoboranes were generated *in situ* from *N,N*-diethyl-3,4,5-trimethoxybenzamide (**5**) and cross-coupled with aryl bromides in rather good yields.

However, treatment of **2** with one equivalent lithium diisopropylamide (LDA) at −78 °C induced ring contraction of the methoxytropone ring to the *p*-methoxycarbonylphenyl derivative **3** (Scheme 3). The transformation of tropones into benzene derivatives upon treatment by nucleophiles is a well known reaction.[7] Ring contraction of tropones that carry a nucleofugal[8] substituent typically occurs with hard anionic nucleophiles, especially OH^-. For tropones substituted at the α carbon with a mesomerically electron-donating group, such as methoxy, the ring contraction is considered to be suppressed in favor of substitution of the methoxy group. The transformation of **2** by LDA into **3** is therefore unexpected and hard to rationalize. Use of *t*-BuLi did not lead to the desired product or to ring contraction, instead most of the starting material was recovered.

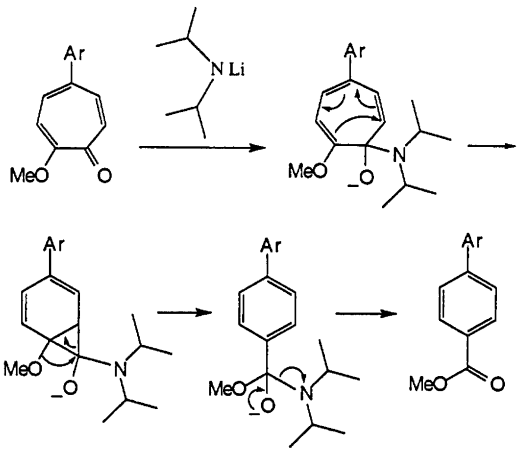
A tentative mechanism is presented in Scheme 4. The electrocyclic ring closure of the initial hydroxide anion adduct is followed by loss of the nucleofuge. In this case the amide is lost in lieu of the methoxide. Normally the methoxide, being the weakest base of the two substituents, is expected to be the preferred leaving group. The explanation for this abnormal behavior could be that, in the non-polar aprotic solvent THF, the difference in base strength for the two potential leaving groups may be less important. Unfavorable steric interaction in the tetrahedral intermediate may also be removed by loss of the more hindered amide nucleofuge.



Scheme 2.



Scheme 3.



Scheme 4.

Treatment of **3** with 2.3 equivalents of LDA at −78 °C resulted in ring closure and concomitant substitution of the ester function by diisopropylamide (Scheme 3). Use of less than 2 equivalents of LDA in the reaction results in mixtures of products and recovered starting material. Attempts to induce the cyclization with *t*-BuLi were unsuccessful. The desired tricyclic ester could not be isolated under any conditions.

Solution studies of **2** *and* **3**. In order to study the dynamic stereochemistry of compounds **2** and **3** a variable-temperature ^{1}H NMR investigation was undertaken. For the MTC analog **2** it was found that several signals in the NMR spectra were affected by exchange processes. When the temperature was lowered to 248 K, 6-H appears as two double doublets indicating the existence of two diastereomeric conformations (Fig. 1). By integration, the two diastereomers were determined to exist in a 91 : 9 ratio ($\Delta G^\circ_{249K} = 4.77$ kJ mol^{-1}) in $CDCl_3$. The corresponding ratio in acetonitrile was 69 : 31 ($\Delta G^\circ_{254K} = 1.67$ kJ mol^{-1}). The *N*-methylene protons are affected by multiple splitting. All four protons are non-equivalent and, in addition, doubled into two sets with the same populations as those of the 6-H. Thus eight multiplets are observed as shown by the COSY spectra (Fig. 2). The methyl groups give rise to four triplets. 1-OMe is split into two singlets. When the temperature was raised to 303 K the 6-H signals coalesced to one double doublet, the methylene protons to two broad multiplets, the methyls into two triplets, and finally the 1-OMe into one singlet.

Several restricted rotations with respect to single bonds must be considered in the discussion of this phenomenon. The most important ones are indicated in Fig. 3. The C–N rotation, process 3, is slow ($\Delta G^\ddagger \geqslant 63$ kJ mol^{-1}). This makes the ethyl groups non-equivalent. Process 4, the N–Et rotation, is considered to be fast ($\Delta G^\ddagger < 34$ kJ mol^{-1}),[10] as is the rotation of the C–O bond of the methoxy groups, process 5 ($\Delta G^\ddagger \leqslant 21$ kJ mol^{-1}). The restricted rotation with respect to both processes 1 and 2 results in two diastereomers. Geminal diastereotopism has been observed before in *ortho*-substituted, tertiary benzamides.[11] The barrier for interconversion of one diastereomer into the other was determined to be $\Delta G^\ddagger_{270K} = 60.2$ kJ mol^{-1} in acetonitrile and $\Delta G^\ddagger_{264K} = 61.5$ kJ mol^{-1} in $CDCl_3$. The barriers to rotation for processes 1 and 2 were calculated, using the MM2-91 force field, to be 57.3 and 56.1 kJ mol^{-1}, respectively ($\Delta E^\ddagger$), i.e., the barriers are of the same order of magnitude. Negative $\Delta S^\ddagger$ values are usually observed for rotation in atropisomeric systems.[12] Thus, the calculated values are in good agreement with the experimental results. The observed rate process is therefore assumed to be the combined result of process 1 and process 2.

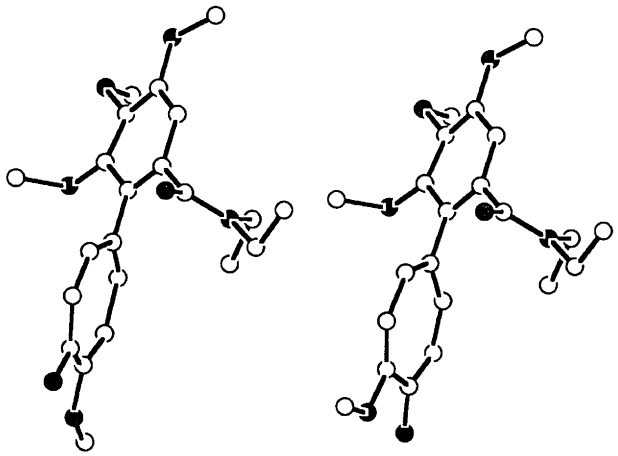


Fig. 1. Compound **2** in its two diastereomeric conformations. Hydrogen atoms are omitted.

The analysis for the allocolchicine analog **3** is more straightforward as the Ar substituent (Fig. 3) is symmetrical. Geminal non-equivalence was observed in the *N*-ethyl groups at 253 K. The protons *ortho* to the pivot bond in the *p*-methoxycarbonylphenyl ring were equivalent at the same temperature, indicating that process 1 must be fast or that accidental isochronism occurs. In addition the 1-OMe appeared as a singlet at the same temperature. By use of the MM2-91 force field, the barrier to rotation for processes 1 and 2 was calculated to be 40.2 and 70.7 kJ mol^{-1}, respectively ($\Delta E^\ddagger$). A variable-temperature NMR study[13] in acetonitrile, using the methylene signals as probes, gave the barrier to rotation for process 2 as $\Delta G^\ddagger_{313K} = 63.2$ kJ mol^{-1}. The lower barrier for compound **2** compared with **3** may be a result of the rather floppy tropolone ring,[1b] which thus is susceptible to considerable departure from a planar structure. This may result in avoided steric interaction in the transition state for process 2. Alternatively, the observed rate processes for the two compounds **2** and **3** may be of different origin, i.e., process 2 in compound **3** and process 1 in compound **2**.

Binding to tubulin of **2**, **3** *and* **4**. The effect on assembly of microtubules *in vitro* was determined in a temperature-controlled spectrophotometer by measuring the change in absorbance at 450 nm.[14] All compounds were found to be inactive in this assay. It has been shown that the tubulin binding activity of colchicine is lowered by increasing bulk in the B-ring.[2c] The fact that compounds **2** and **3** are inactive, despite their structural similarities to MTC and TCB, may be a result of the increased steric bulk.

Experimental

Spectra. ^{1}H and ^{13}C NMR spectra were recorded on Varian XL-300 or Bruker DRX 400 spectrometers, using the solvent peak, usually $CDCl_3$, as an internal shift standard. The dynamic NMR experiment is described by Sandström.[13] Temperature calibration of the NMR spectrometer was performed with methanol according to the method described by van Geet.[15] The populations and

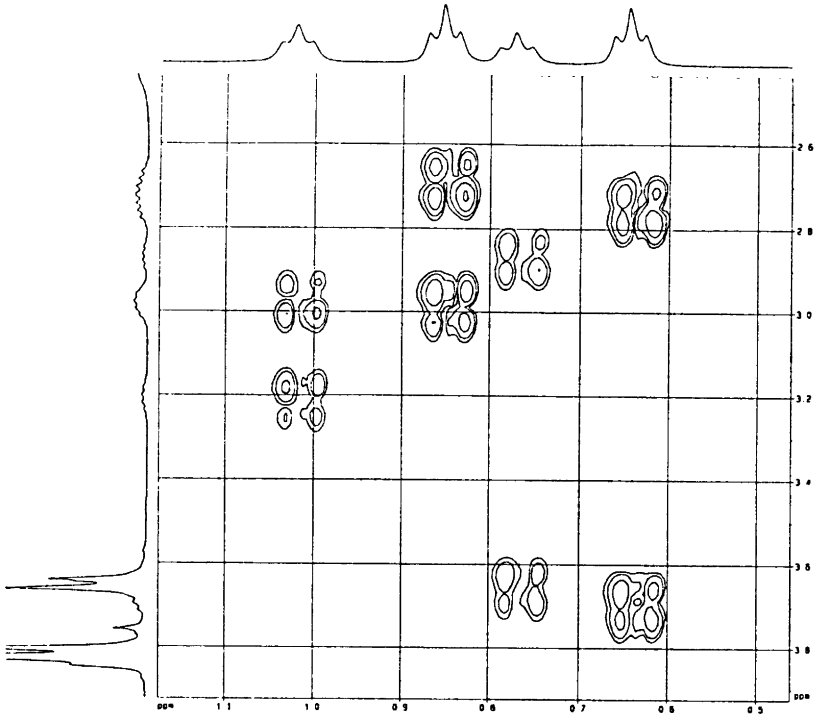


Fig. 2. COSY spectrum of compound **2** at 248 K in acetonitrile, showing correlations between the *N*-methylene and the methyl protons.

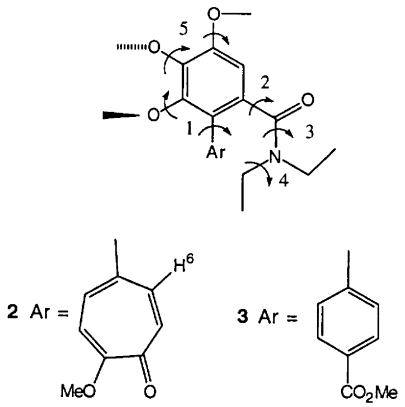


Fig. 3. Possible rotational modes in the observed exchange processes for compounds **2** and **3**.

rate constants were evaluated by visual fitting of the experimental spectra to spectra calculated by the McConnell classical formalism.[16] The evaluations of T_2 and $\delta\nu$ values for bandshape calculations were performed as previously described.[17] Errors in activation parameters have been given as ± 4 kJ mol^{-1} based on the assumption that the temperature could be determined with an accuracy of ± 1.0 K.[18]

Tubulin binding assay. The effect on assembly of microtubules was determined as described earlier using a temperature-controlled spectrophotometer by measuring the change in light scattering at 450 nm.[14]

Molecular mechanics (MM) analysis was performed using the MM2(91) force field[19] implemented in the MacMimic program package.[20]

Syntheses: general. DMF, diethyl ether, diethylamine, TMEDA, THF, DME and trimethoxyborane were dried and distilled prior to use. All reactions were performed under an argon atmosphere. 5-Bromtropolone was prepared according to a published procedure.[21]

N,N-*Diethyl-3,4,5-trimethoxybenzamide* (**5**). To an ice cooled solution of 3,4,5-trimethoxybenzoic acid (3.0 g, 14.2 mmol) and DMF (0.1 ml) in 100 ml dry ether, oxalyl chloride (7.0 ml, 80.2 mmol) was added with stirring. After 4 h the solution became clear and the solvents and excess oxalyl chloride were evaporated off. Carbon tetrachloride was then added and evaporated off to get rid of residual oxalyl chloride. The residue was dissolved in dry ether (10 ml), and diethylamine (5.5 ml, 53 mmol) was slowly added with stirring to the ice-cooled solution. After 24 h the mixture was filtered, extracted with ether, washed consecutively with 1 M HCl, water, dried (Na_2SO_4) and concentrated to give 3.7 g of **5** as a white solid. Yield 97–99%. m.p. 53–54 °C. ^{1}H NMR ($CDCl_3$): δ 6.55 (2 H, s), 3.87 (6 H, s), 3.85 (3 H, s), 3.6–3.2 (4 H, br m), 1.3–1.1 (6 H, br t).

N,N-*Diethyl-3,4,5-trimethoxy-2-(p-methoxycarbonylphenyl)benzamide* (**3**). To a -78 °C solution of *N,N*-diethyl-3,4,5-trimethoxybenzamide (**5**) (0.52 g, 1.95 mmol) and TMEDA (0.35 ml, 2.3 mmol) in THF

(12 ml) was added *s*-BuLi (1.7 ml, 1.3 M, 2.2 mmol) with stirring. Trimethoxyborane (0.3 ml, 2.7 mmol) was added after 40 min, the temperature was raised to 0 °C and the stirring was continued for 1.2 h. The solvent was evaporated off and DME (20 ml), methyl 4-bromobenzoate (0.50 g, 2.3 mmol), $PdCl_2(PPh_3)_2$ (100 mg) and aqueous sodium carbonate (1.8 ml, 2 M, 3.6 mmol) were added. The flask was immersed in a preheated oil bath (110 °C), refluxed for 4 h, cooled to ambient temperature and stirred overnight. Water was added to the mixture and it was extracted twice with chloroform. The organic phases were dried (Na_2SO_4) and concentrated to a yellow oil. Purification with flash chromatography (ethyl acetate–heptane 1 : 1) yielded 536 mg of **3** as a white solid. Yield 68%. M.p. 110–111 °C. ^{1}H NMR ($CDCl_3$): δ 8.02 (2 H, d, 8.6 Hz), 7.48 (2 H, d, 8.6 Hz), 6.69 (1 H, s), 3.92(4) (3 H, s), 3.92(1) (3 H, s), 3.90 (3 H, s), 3.70–3.59 (1 H, m), 3.56 (3 H, s), 3.10–2.97 (1 H, m), 2.92–2.81 (1 H, m), 2.69–2.55 (1 H, m), 0.85–0.80 (3 H, t, 7.1 Hz), 0.75–0.71 (3 H, t, 7.1 Hz). ^{13}C NMR ($CDCl_3$): δ 169.77, 167.45, 154.02, 151.58, 143.13, 140.54, 133.11, 130.73, 129.48, 129.33, 124.82, 106.16, 61.51, 61.51, 56.56, 52.53, 42.72, 38.62, 14.09, 12.26 HRMS $C_{22}H_{27}NO_6$: calc. 401.18384, found 401.1837.

N,N-*Diethyl-3,4,5-trimethoxy-2-phenylbenzamide* (**4**). The title compound was prepared from *N,N*-diethyl-3,4,5-trimethoxybenzamide (**5**) and bromobenzene according to the method given for **3**. Yield 85 mg, 65%. M.p. 108–109 °C. ^{1}H NMR ($CDCl_3$): δ 7.41–7.27 (5 H, m), 6.69 (1 H, s), 3.94 (3 H, s), 3.90 (3 H, s), 3.79–3.68 (1 H, m), 3.57 (3 H, s), 3.12–3.00 (1 H, m), 2.88–2.77 (1 H, m), 2.68–2.57 (1 H, m), 0.86–0.81 (3 H, t, 7.1 Hz), 0.73–0.68 (3 H, t, 7.1 Hz). ^{13}C NMR ($CDCl_3$): δ 170.10, 153.52, 151.66, 143.08, 135.55, 133.25, 130.57, 128.23, 127.66, 125.96, 105.99, 61.49, 61.43, 56.52, 42.58, 38.38, 14.02, 12.15. HRMS $C_{22}H_{25}NO_4$: calc. 343.17835, found 343.1783.

N,N-*Diethyl-3,4,5-trimethoxy-2-(4-methoxy-5-oxo-1,3,6-cycloheptatrienyl) benzamide* (**2**). The title compound was prepared from *N,N*-diethyl-3,4,5-trimethoxybenzamide (**5**) and 5-bromomethoxytropone accordingly to the method given for **3**. Yield 123 mg, 62%. Amorphous yellow substance. ^{1}H NMR ($CDCl_3$): δ 7.29–7.10 (3 H, m), 6.74 (1 H, d, 10.5 Hz), 6.64 (1 H, s), 3.93 (3 H, s), 3.91 (3 H, s), 3.88 (3 H, s), 3.80–3.70 (1 H, m), 3.67 (3 H, s), 3.15–2.65 (3 H, m), 0.92 (3 H, t, 7.0 Hz), 0.81 (3 H, t, 7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 180.47, 169.48, 165.12, 154.30, 151.30, 143.01, 140.56, 140.56, 135.93, 134.66, 132.86, 126.07, 112.48, 105.81, 61.52, 61.52, 56.78, 56.58, 42.94, 38.72, 14.29, 12,77 HRMS. $C_{22}H_{27}NO_6$: calc. 401.18384, found 401.1838.

2,3,4-Trimethoxyfluorenone (**6**). To a solution of *N,N*-diethyl-3,4,5-trimethoxy-2-phenylbenzamide (**4**) (90 mg, 0.26 mmol), in dry THF (5 ml) at 0 °C, a THF solution of LDA (2 ml, 0.65 M) was added dropwise with stirring. After 16 h water was added and the THF was evaporated off. The mixture was extracted with diethyl ether and the combined organic phases were washed consecutively with 2 M HCl and water, dried ($MgSO_4$) and concentrated to a yellow oil. Purification of the oil by flash chromatography (ethyl acetate–heptane 1 : 1) afforded 36 mg of **6** as yellow crystals. Yield 51%. M.p. 114–115 °C. ^{1}H NMR ($CDCl_3$): δ 7.68(1 H, unresolved dd, 7.4 Hz), 7.56 (1 H, unresolved dd, 7.3 Hz), 7.42 (1 H, ddd, 7.5, 7.3, 1.2 Hz), 7.18 (1 H, ddd, 7.5, 7.4, 0.9 Hz), 7.07 (1 H, s), 4.01 (3 H, s), 3.96 (3 H, s), 3.91 (3 H, s). ^{13}C NMR ($CDCl_3$): δ 193.60, 154.98, 149.86, 148.45, 143.78, 135.30, 134.64, 130.37, 130.26, 128.14, 124.38, 123.29, 104.70, 61.52, 61.13, 56.84. HRMS $C_{16}H_{14}O_4$: calc. 270.08921, found 270.0912.

2,3,4-Trimethoxy-7-diisopropylcarbamoylfluorenone (**7**). To a solution of *N,N*-diethyl-3,4,5-trimethoxy-2-(*p*-methoxycarbonylphenyl)benzamide (**3**) (114 mg, 0.28 mmol), in dry THF (5 ml) at −78 °C, a THF solution of LDA (1 ml, 0.65 M) was added dropwise with stirring. After 4 h water was added and the THF was evaporated off, the product was extracted with chloroform, washed consecutively with 2 M HCl and water, dried (Na_2SO_4) and concentrated to a yellow oil. Purification of the oil by flash chromatography (ethyl acetate–heptane 1 : 1) afforded 93 mg of **7** as yellow crystals. Yield 84%. M.p. 142–143 °C. ^{1}H NMR ($CDCl_3$): δ 7.69 (1 H, dd, 7.61, 0.64 Hz), 7.49 (1 H, dd, 1.61, 0.64 Hz), 7.39 (1 H, dd, 7.61, 1.61 Hz), 7.07 (1 H, s), 4.02 (3 H, s), 3.96 (3 H, s), 3.91 (3 H, s), 3.90–3.50 (2 H, unresolved m), 1.70–0.90 (12 H, unresolved m). ^{13}C NMR ($CDCl_3$): δ 192.81, 170.26, 155.27, 149.98, 148.52, 143.93, 138.83, 134.63, 132.77, 130.42, 129.86, 123.31, 121.65, 104.75, 61.54, 61.19, 56.86, 21.17. HRMS $C_{23}H_{27}O_5N$: calc. 397.18892, found 397.1876.

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