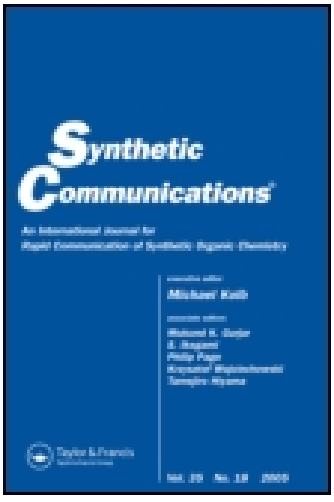

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Alternatives to N,N-Diethyl-2,4-dimethoxybenzamide as a Precursor for the Synthesis of 6,8-Dimethoxy-3-methyl-3,4-dihydro-1H-isochro

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Alternatives to *N,N*-Diethyl-2,4-dimethoxybenzamide as a Precursor for the Synthesis of 6,8-Dimethoxy-3-methyl-3,4-dihydro-1*H*-isochromen-1-one

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Abstract: Although the amide group of *N*,*N*-diethyl-2,4-dimethoxybenzamide facilitates directed *ortho*-metallation and subsequent allylation of the aromatic ring, it is not readily hydrolyzed prior to conversion into the title isochromenone. This article describes the use of 1-(2-allyl-4,5-dimethoxybenzoyl)-4-methylpiperazine and *N*,*N*-diethyl-2-(2-hydroxypropyl)-4,6-dimethoxybenzamide as alternative substrates for conversion into 6,8-dimethoxy-3-methyl-3,4-dihydro-1*H*-isochromen-1-one.

Keywords: 3,4-dihydro-1*H*-isochromen-1-one, directed *ortho* metallation, *N,N*-diethyl arylamide

INTRODUCTION

3,4-Dihydroisochromenones such as the naturally occurring compound (−)-mellein **1** are of particular interest to the scientific community as a result of their biological activities (Fig. 1).[1] The synthesis of these types of compounds has been achieved by many research groups.[2] Of interest to our group is the use of directed *ortho*-metallation (DOM) as a key step to accomplish their synthesis. Sibi and coworkers had previously employed DOM methodology to construct a variety of substituted isochromanones **2**

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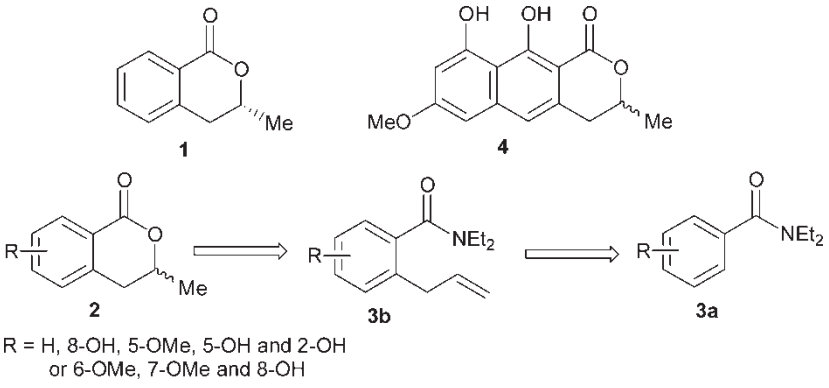


Figure 1. R = H, 8-OH, 5-OMe, 5-OH, and 2-OH or 6-OMe, 7-OMe, and 8-OH.

from appropriately substituted tertiary benzamides.[3] In their synthesis, the *N,N*-diethylamide functional group was used for the directed *ortho* metalation to introduce the allyl substituent (**3a**→**3b**). More recently, this methodology has also been used in the synthesis of the naturally occurring isochromanone semivioxanthin **4**.[4]

As part of our program[5] directed toward the synthesis of aromatic and heteroaromatic compounds using DOM,[6] we decided to implement this strategy for the synthesis of target molecule **5** (Fig. 2).

RESULTS AND DISCUSSION

The initial synthetic steps involved the methylation of commercially available 2,4-dihydroxybenzoic acid **7** followed by ester hydrolysis under basic conditions and conversion into the corresponding acid chloride (Scheme 1). Treatment of the carboxylic acid chloride with diethylamine resulted in the formation of the *N,N*-diethylamido compound **8** in good overall yields. Application of the Snieckus metallation methodology[3,6] using *s*-BuLi, followed by transmetalation of the lithium species with Mg and subsequent quenching with allyl bromide, afforded compound **6** in good yield.[7]

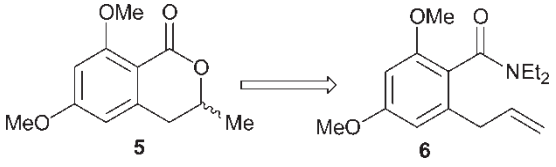
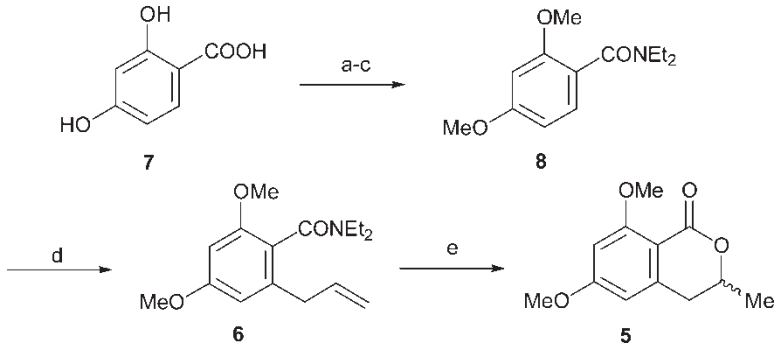


Figure 2. Retrosynthesis of 6,8-Dimethoxy-3-methyl-3,4-dihydro-1H-isochromene-1-one.

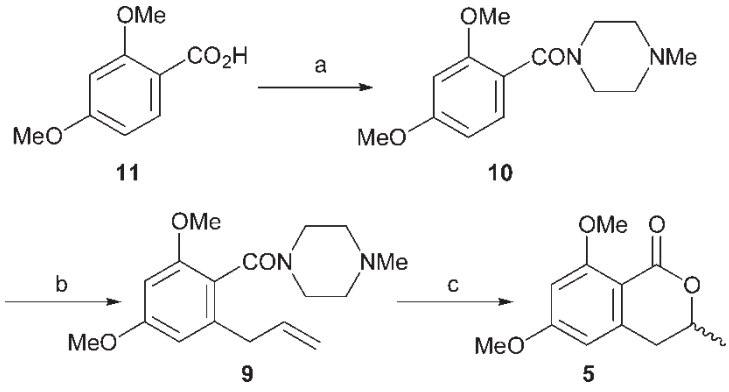


Scheme 1. (a) Me_2SO_4, K_2CO_3, quantitative; (b) KOH, 97%; (c) (i) $SOCl_2$, (ii) $HNEt_2$, quantitative over two steps; (d) (i) *s*-BuLi, (ii) $MgBr_2 \cdot Et_2O$, (iii) allyl bromide, 95%; (e) HCl or KOH, low yields of contaminated **5** obtained.[8]

With the *o*-allyl amide **6** in hand, we initially decided to hydrolyze the amide **6** using the acid-catalyzed route suggested by Sibi and coworkers.[3] It was expected that the ensuing acid would participate in an acid-induced reaction with the internal alkene to yield the desired lactone **5**, but this transformation proved to be less than straightforward in our hands. Unfortunately the hydrolysis was not always successful. When the lactone **5** was obtained it was in low yield, along with decomposition, and the reactions were often poorly reproducible.[8] Attempts at hydrolysis included the following procedures: (i) 6 M HCl, 90°C, 96 h (isochromanone **5**, 22%, recovered **6**, 75%); (ii) 6 M HCl, reflux, 24 h (mainly **6**), added further 6 M HCl and heated at reflux for 60 h (decomposition); (iii) 6.6 M HCl, 2-propanol, reflux, 144 h (lactone **5** 24%, recovered **6**, 50%); (iv) 10% KOH, $HOCH_2CH_2OH$, 90°C, 96 h (no product, alkene isomerization observed);[9a] (v) 6 M HCl, microwave, power 25–50%, 1 min (no product, DMF as co-solvent also had no effect).[9b]

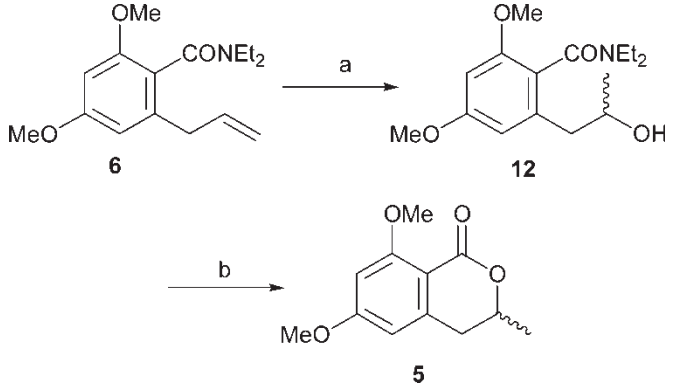
Reitz and Massey also described problems associated with the hydrolysis of 2,6-disubstituted benzamides, which they surmise were "essentially inert to hydrolysis except in the cases where intramolecular lactone formation is possible."[10] This reference seemed to confirm our fears that simple hydrolysis of the amide **6** and subsequent conversion into lactone **5** was going to be problematic. The problem also appears to be exacerbated by the presence of a methoxy substituent *ortho* to the tertiary amide.

Realizing that hydrolysis of the *N,N*-diethylamide was proving far from trivial, we synthesized the *N*-methylpiperazinylamide **9**,[11] as it was reported to be easier to hydrolyze, while still allowing the use of DOM methodology for the introduction of the required allyl substituent. The *N*-methylpiperazinylamide **10** was thus synthesized from carboxylic acid **11** in quantitative yield via the acid chloride (Scheme 2). Fortunately, straightforward acidic hydrolysis of **10** afforded isochromanone **5** in reproducible, moderate yields of up to 53%.



Scheme 2. (a) (i) $SOCl_2$, (ii) *N*-methylpiperazine, quantitative over two steps; (b) (i) *s*-BuLi, (ii) $MgBr_2 \cdot Et_2O$, (iii) allyl bromide, 70%; (c) 6 M HCl, heat, 53%.

Because the yields in converting **9** to **5** were still unsatisfactory, we sought an alternative method to accomplish this transformation. Work done by Watanabe et al.[12] and Salvadori et al.[7a] has demonstrated that compounds containing an alcohol functional group can participate successfully in the intramolecular hydrolysis of an *N,N*-diethylamide group to yield a variety of functionalized lactones. The alkene bond of **6** was thus oxymercurated with $Hg(OAc)_2$ in a THF–water mixture.[13,14] Reduction of the organomercury intermediate then afforded the secondary alcohol **12** as a 2:1 mixture of amide rotamers in 63% yield (Scheme 3).[15] It was hoped that the subsequent hydrolysis with intramolecular participation would be appreciably faster because of neighboring group participation,[16] and fortunately this time alkaline hydrolysis was highly successful. Compound **5** was isolated in 75% yield (94% based on recovered starting material) after workup and purification by chromatography.



Scheme 3. (a) (i) $Hg(OAc)_2$, H_2O, THF, (ii) $NaBH_4$, 63% over two steps; (b) KOH, EtOH, Δ, 75% (and 20% recovered **6**).

CONCLUSION

The inertness of the *N,N*-diethyl arylamide functionality, especially adjacent to an *ortho* methoxy substituent, leads to problems with hydrolysis. These can be overcome by using *N*-methylpiperazinyl benzamides as the DOM group or by allowing the reaction to proceed by using an internal hydroxyl nucleophile as in the transformation of **12** to **5**. Using these two methods allowed for the preparation of 6,8-dimethoxy-3-methyl-3,4-dihydro-1*H*-isochromen-1-one **5** in reasonable yields.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker AC-200 or Bruker DRX 400 spectrometer at the frequency indicated. Distortionless enhancement by polarization transfer (DEPT), carbon hydrogen (CH)-correlated, and heteronuclear multiple bond correlation (HMBC) spectra were run on some samples to enable complete assignments of all the signals. NMR spectroscopic assignments with the same superscript may be interchanged. Infrared spectra were recorded on either a Bruker IFS 25 or a Bruker Vector 22 Fourier transform spectrometer. Mass spectra were recorded on a Kratos MS 9/50, VG 70E MS, or VG 70 SEQ mass spectrometer. Macherey–Nagel kieselgel 60 (particle size 0.063–0.200 mm) was used for conventional silica-gel chromatography, and Macherey–Nagel kieselgel 60 (particle size 0.040–0.063 mm) was used for preparative flash chromatography. All solvents used for reactions and chromatography were distilled prior to use.

Methyl 2,4-dimethoxybenzoate,[17] 2,4-dimethoxybenzoic acid,[18] and *N,N*-diethyl-2,4-dimethoxybenzamide **8**[3] were prepared by reported procedures.

2-Allyl-*N,N*-diethyl-4,6-dimethoxybenzamide 6

N,N-Diethyl-2,4-dimethoxybenzamide **8** (0.683 g, 2.88×10^{-3} mol) was dissolved in dry THF (5 cm^3) and added dropwise by syringe over 5 min to a cooled solution (-78°C) of *s*-BuLi (5.5 cm^3, 4.2×10^{-3} mol) and tetramethylethylenediamine (TMEDA) (0.63 cm^3, 4.2×10^{-3} mol) in dry tetrahydrofuran (THF) (50 cm^3). The reaction mixture was stirred at -78°C under Ar for a further 30 min. Magnesium bromide etherate (2.23 g, 8.64×10^{-3} mol) was added, and the reaction mixture was allowed to warm slowly until all the white reagent had dissolved. The mixture was then recooled to -78°C and stirred for 40 min, after which allyl bromide (0.75 cm^3, 8.7×10^{-3} mol) was added by syringe. The reaction was then allowed to warm to rt over 14 h, during which time it went to a milky color. The organic solvent was washed with HCl (50 cm^3, 10%), which was extracted with CH_2Cl_2 (4×50 cm^3). The combined organic extracts were

dried ($MgSO_4$) and removed in vacuo to give a crude product, which was purified by silica-gel chromatography (50% EtOAc/hexane) to yield the product **6** as a yellow oil (0.76 g, 95%). The spectra of this compound compared well with those published in the literature.[4a]

6,8-Dimethoxy-3-methyl-3,4-dihydro-1*H*-isochromen-1-one 5

Method 1

Arylamide **6** (0.20 g, 7.2×10^{-4} mol) was dissolved in a solution of 1-propanol (10 cm^3) and concentrated HCl (15 cm^3) and heated under reflux for 6 d. After cooling, H_2O (50 cm^3) was added, and the crude organic compound was extracted with Et_2O (3×10 cm^3). The organic solvent was dried ($MgSO_4$) and removed under vacuum to give an impure residue. The desired compound **5** was obtained as a clear oil, which slowly became a semisolid (0.039 g, 24%) after silica-gel preparative layer chromatography (50% EtOAc/hexane). Unreacted starting material **6** (0.099 g, 50%) was also recovered. ^{1}H NMR (200 MHz; $CDCl_3$) δ_H 6.42 (1H, d, *J* 2.3, 5-H), 6.31 (1H, d, *J* 2.3, 7-H), 4.61–4.44 (1H, m, 3-H), 3.93 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 2.88–2.79 (2H, m, 4-H), 1.47 (3H, d, *J* 6.3, 3-CH_3); ^{13}C NMR (50 MHz; $CDCl_3$) δ_C 164.3 (C=O), 163.2, 162.7 (C-8 and C-6), 143.9 106.8 (C-8a and C-4a), 103.8 (C-5), 97.8 (C-7), 73.5 (C-3), 56.1, 55.6 ($2 \times OCH_3$), 36.6 (C-4), 20.7 (CH_3); IR (thin film) ν_{max}/cm^{-1} 1717 (C=O), 1603 (ArC=C); m/z (EI) M^+ (93%) 222.0901 ($C_{12}H_{14}O_4$ requires 222.0892), 205 (13), 178 (100), 161 (40), 148 (34), 135 (34), 120 (18), 77 (22), 43 (13). The ^{1}H NMR spectrum of this compound compared well with that published in the literature.[19]

Method 2

Arylamide **9** (0.050 g, 1.6×10^{-4} mol) was dissolved in a solution of 1-propanol (5 cm^3) and concentrated hydrochloric acid (7.5 cm^3) and heated under reflux for 4 d. H_2O (50 cm^3) was added, and a crude organic compound was extracted with CH_2Cl_2 (3×10 cm^3). The organic solvent was dried ($MgSO_4$) and removed under vacuum to give an impure residue. The product **5** was obtained as a clear oil (0.019 g, 53%), which slowly became a semisolid, after silica-gel preparative layer chromatography (50% EtOAc/hexane) of the crude material. Spectral data for this compound were identical to that obtained in the previous experiment.

Method 3

Alcohol **12** (0.074 g, 2.5×10^{-4} mol) was dissolved in a mixture of EtOH (2 cm^3) and aqueous NaOH solution (2 cm^3 H_2O, 1.0 g NaOH) and heated

at reflux for 144 h. The solvent was removed in vacuo, and the residue was acidified with concentrated HCl at 0°C. The aqueous layer was extracted with EtOAc ($4 \times 10\ cm^3$) and CH_2Cl_2 ($2 \times 10\ cm^3$). The combined organic extracts were washed with H_2O ($10\ cm^3$), dried ($MgSO_4$), and removed in vacuo. The residue was purified by silica-gel preparative layer chromatography (30% EtOAc/hexane) to afford isochromanone **5** (0.042 g, 75%), which slowly became a semisolid, and starting material **12** (0.015 g, 20%). The NMR spectra of compound **5** obtained in this experiment were identical to those obtained earlier.

1-(2,4-Dimethoxybenzoyl)-4-methylpiperazine 10

$SOCl_2$ ($0.96\ cm^3$, 1.32×10^{-2} mol, 1.2 mol equiv.) was added dropwise over 15 min to 2,4-dimethoxybenzoic acid **11** (2.00 g, 1.10×10^{-2} mol) dissolved in C_6H_6 ($100\ cm^3$) and DMF ($0.25\ cm^3$). The reaction mixture was heated at reflux for 2 h under an Ar atmosphere. After cooling to rt using an ice bath, *N*-methylpiperazine ($3.65\ cm^3$, 3.29×10^{-2} mol) was added, and the reaction mixture became cloudy as a precipitate formed. The mixture was stirred for a further 2 h, after which H_2O ($100\ cm^3$) was added. The organic layer was then extracted with Et_2O ($3 \times 50\ cm^3$). Subsequent drying ($MgSO_4$) and removal of the solvent in vacuo resulted in the crude material, which afforded the product **10** (2.90 g, quantitative) as a yellow oil after silica-gel column chromatography (50% EtOAc/hexane). ^{1}H NMR (200 MHz; $CDCl_3$) δ_H 7.17 (1H, d, *J* 8.2, 6′-H), 6.53–6.45 (2H, m, 3′-H and 5′-H), 3.80 (6H, br s, $2 \times OCH_3$), 3.35–3.28 (4H, m, $4 \times$ 2-H), 2.48–2.35 (4H, m, $4 \times$ 3-H), 2.30 (3H, br s, NCH_3); ^{13}C NMR (50 MHz; $CDCl_3$) δ_C 167.3 (C═O), 161.2, 156.2 (C-2′ and C-4′), 128.7 (C-6′), 117.8 (C-1′), 104.5 (C-5′), 97.9 (C-3′), 55.0, 54.9, 54.7, 54.2 ($2 \times OCH_3$ and $2 \times$ C-2), 46.3, 45.5 ($2 \times$ C-3)[a], 41.0 (NCH_3)[a]; IR (thin film) ν_{max}/cm^{-1} 1633 (C═O), 1616 (ArC═C); m/z (EI) M^+ (26%) 264.1475 ($C_{14}H_{20}N_2O_3$ requires 264.1474), 207 (33), 194 (25), 182 (17), 165 (100), 99 (94), 83 (65), 70 (60), 56 (32).

1-(2-Allyl-4,5-dimethoxybenzoyl)-4-methylpiperazine 9

Amide **10** (1.80 g, 6.81×10^{-3} mol) was dissolved in dry THF ($20\ cm^3$) and added dropwise over 5 min to a cooled solution (−78°C) of *s*-BuLi ($18.1\ cm^3$, 0.75 M, 1.36×10^{-2} mol, 2 mol equiv.) and TMEDA ($2.05\ cm^3$, 1.36×10^{-2} mol, 2 mol equiv.) in dry THF ($100\ cm^3$). The reaction was stirred at −78°C under Ar for a further 30 min. $MgBr_2 \cdot Et_2O$ (5.3 g, 2.0×10^{-2} mol) was added, and the reaction mixture was allowed to warm slowly until all the inorganic reagent had dissolved. The mixture was then cooled to −78°C and stirred for 40 min, after which allyl bromide ($1.80\ cm^3$, 2.0×10^{-2} mol) was added by syringe. The reaction was then

allowed to warm to rt over 14 h, during which time the amide started to precipitate out of solution. The reaction mixture was made basic with careful addition of an aqueous NaOH solution (10%) and was then extracted with CH_2Cl_2 ($3 \times 50\ cm^3$). The combined organic extracts were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by silica-gel column chromatography (50–100% EtOAc/hexane) to afford the product **9** as a pale yellow oil (1.45 g, 70%). ^{1}H NMR (200 MHz; $CDCl_3$) δ_H 6.38 (1H, d, *J* 2.2, 3′-H)[a], 6.33 (1H, d, *J* 2.2, 5′-H)a, 5.99–5.79 (1H, m, CH_2CH=CH_2), 5.13–5.02 (2H, m, CH_2CH=CH_2), 3.83–3.77 (2H, m, NCH_2)b, 3.79 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.36–3.18 (4H, m, CH_2CH=CH_2 and NCH_2)[b], 2.53–2.78 (4H, m, $2 \times NCH_2$), 2.30 (3H, br s, NCH_3); ^{13}C NMR (50 MHz; $CDCl_3$) δ_C 166.8 (C=O), 160.5, 156.4 (C-4′ and C-6′), 138.7 (C-2′), 136.0 (CH_2CH=CH_2), 117.7 (C-1′), 115.9 (CH_2CH=CH_2), 105.7 (C-3′), 95.8 (C-5′), 55.0, 55.0, 54.8, 54.3 ($2 \times OCH_3$ and $2 \times NCH_2$), 46.0, 45.7 ($2 \times NCH_2$), 40.8 (NCH_3)[c], 37.1 (CH_2CH=CH_2)[c]; IR (thin film) ν_{max}/cm^{-1} 1630 (C=O), 1606 (ArC=C); m/z (EI) M^+ (35%) 304.1796 ($C_{17}H_{24}N_2O_3$ requires 304.1787), 247 (5), 205 (100), 177 (16), 99 (91), 85 (27), 83 (41), 70 (50), 56 (29).

N,*N*-Diethyl-2-(2-hydroxypropyl)-4,6-dimethoxybenzamide 12

Arylamide **6** (0.200 g, 7.21×10^{-4} mol) and $Hg(OAc)_2$ (0.23 g, 7.2×10^{-4} mol) were dissolved in a THF ($10\ cm^3$)/water ($3\ cm^3$) mixture to yield a yellow solution. The mixture was stirred for 18 h, during which time the color faded gradually. An aqueous NaOH solution ($5\ cm^3$, 3 M) was added, followed by $NaBH_4$ in a NaOH solution ($3\ cm^3$, 3 M in 3 M NaOH). The reaction mixture was stirred for 30 min, after which the mercury was allowed to settle. Saturated NaCl solution ($10\ cm^3$) was added, and the organic layer was decanted carefully. The organic solvent was dried ($MgSO_4$), removed in vacuo, and purified by silica-gel preparative layer chromatography (50% EtOAc/hexane) to yield the product **12** as a clear oil (0.133 g, 63%). The product was a mixture of diastereomers (ratio 67:33) due to the hindered rotation about the amide C-N bond. ^{1}H NMR (200 MHz; $CDCl_3$, assignments for major diastereomer) δ_H 6.39 (1H, d, *J* 2.1, 3-H)a, 6.32 (1H, d, *J* 2.1, 5-H)[a], 4.53 (1H, br s, D_2O exchangeable, OH), 3.95–3.85 (1H, m, 2′-H), 3.80 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.58 (2H, q, *J* 7.2, NCH_2CH_3), 3.25–3.05 (2H, m, NCH_2CH_3), 2.71 (1H, dd, *J* 13.6 and 3.5, 1′-H), (1H, dd, *J* 13.6 and 6.5, 1′-H), 2.39 (1H, dd, *J* 13.6 and 10.0, 1′-H), 1.27–1.15 (3H, m, CH_3), (1.02), (1.00) (3H, $2 \times$ t, *J* 7.2, CH_2CH_3); ^{1}H NMR (200 MHz; $CDCl_3$, assignments for minor diastereomer indicating only different signals) 6.40 (1H, d, *J* 2.1, 3-H)[a], 6.35 (1H, d, *J* 2.1, 5-H)[a], 4.21–4.05 (1H, m, 2′-H), 2.54 (1H, dd, *J* 13.6 and 3.5, 1′-H); ^{13}C NMR (50 MHz; $CDCl_3$, assignments in for major diastereomer) δ_C 169.2 (C=O), 160.9, 156.2 (C-4′ and C-6′), 139.2 (C-2), 119.1 (C-1), 105.7 (C-3),

96.4 (C-5), 68.7, (C-2′), 55.3, 55.2 (2 × OCH_3), 43.1, 42.9 (2 × NCH_2), 39.1, (C-1′), 24.7, (C-3′), 13.9, 12.7 (2 × CH_2CH_3); ^{13}C NMR (50 MHz; $CDCl_3$, assignments for minor diastereomer) δ_C 168.2 (C═O), 160.0, 157.6 (C-4′ and C-6′), 137.2 (C-2), 119.2 (C-1), 107.0 (C-3), 96.4 (C-5), 66.6 (C-2′), 55.3, 55.2 (2 × OCH_3), 42.7 42.1 (2 × NCH_2), 38.8 (C-1′), 22.7 (C-3′), 13.7, 12.7 (2 × CH_2CH_3); IR (thin film) ν_{max}/cm^{-1} 3396br (OH), 1630 (C═O), 1607 (ArC═C); m/z (EI) M^+ (2%) 295.1789 ($C_{16}H_{25}NO_4$ requires 295.1777), 277 (2), 251 (27), 236 (100), 223 (23), 220 (16), 205 (49), 195 (48), 179 (63), 177 (7), 162 (3).

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