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Mendeleev Commun., 2010, **20**, 321–322
Mendeleev Communications

A simple synthesis of the lamellarin analogues from 3-nitro-2-trifluoromethyl-2*H*-chromenes and 1-benzyl-3,4-dihydroisoquinolines

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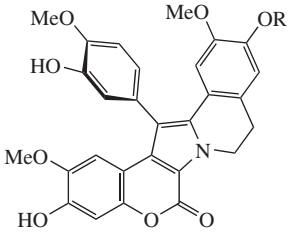
DOI: 10.1016/j.mencom.2010.11.006

The basic structural framework of lamellarin alkaloids, 8,9-dihydro-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinoline derivatives, was accessed in good yields by the Grob reaction between 3-nitro-2-trifluoromethyl-2*H*-chromenes and dihydropapaverine or drotaverine in refluxing isobutanol.

The pyrrolo[2,1-*a*]isoquinoline ring constitutes the basic structural framework of the well-known lamellarin alkaloids **1** (for example, lamellarins L and U), a family of marine natural products, which exhibit a wide range of bioactivities such as cytotoxicity and antitumor activity, reversal of multidrug resistance (MDR), HIV-1 integrase inhibition, immunomodulation, and antibiotic activity, making these compounds a particularly important subject for research.[1]

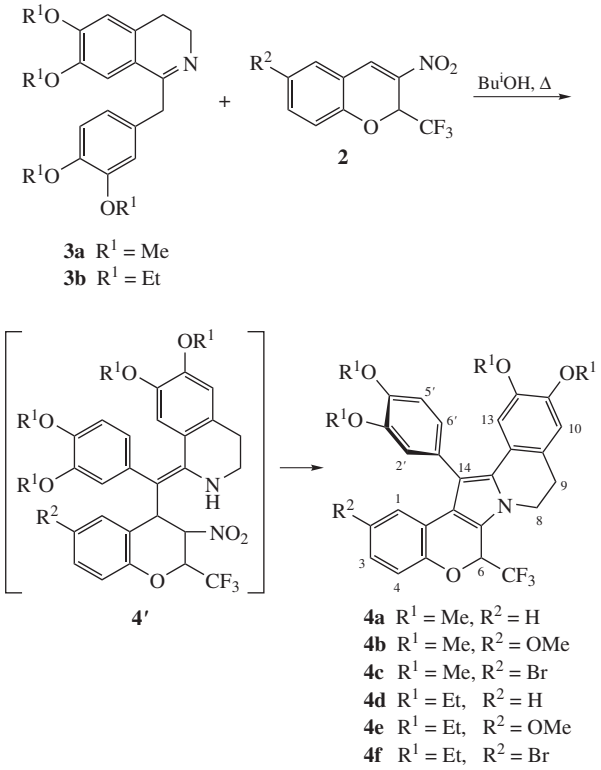


1

R = H (lamellarin L)
R = Me (lamellarin U)

Trifluoromethylated heterocycles represent another group of biologically interesting compounds, many of which have found use as agrochemicals and drugs.[2] Trihalomethylated 2*H*-chromenes possess unique chemical reactivity within both nucleophilic and cycloaddition reactions due to their highly reactive double bond. Owing to this, 3-nitro-2-trihalomethyl-2*H*-chromenes have attracted our attention as excellent building blocks for the preparation of a variety of benzopyran derivatives.[3] Recently, we reported a new synthetic route to the lamellarin skeleton using the Grob reaction between 3-nitro-2-trifluoromethyl-2*H*-chromenes **2** and 1,3,3-trimethyl-3,4-dihydroisoquinolines.[4] Here we report an extension of this cyclization for the synthesis of other lamellarin analogues (Scheme 1) derived from 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (dihydropapaverine **3a**, R^1 = Me) and 1-(3,4-diethoxybenzyl)-6,7-diethoxy-3,4-dihydroisoquinoline (drotaverine **3b**, R^1 = Et). The hydrochloride of the latter is a well-known spasmolytic agent widely used in medicine and known as No-Spa. We anticipated that these new analogues prepared from **2** and **3a**,**b** and differing from lamellarins **1** by replacement of the oxo group with CF_3 one can serve as a basis for the search of new physiologically active compounds.

Recently, it was reported that the reaction of 3-nitrocoumarins with 1-benzyl-3,4-dihydroisoquinolines gave the target lamellarins in only 5–6% yields.[5] This may have been stipulated with the tautomeric composition of 1-benzyldihydroisoquinolines existing mainly in an unreactive imine form.[6] However, we found that compounds **3** reacted with chromenes **2** in a desired manner under reflux in isobutanol for 45 min to produce compounds **4a**–**f** in 64–92% yields.† This reaction proceeds by a tandem intermolecular nucleophilic addition and a subsequent intramolecular displacement of the NO_2 group by the NH group,



Scheme 1

† *General procedure.* A mixture of the corresponding chromene **2** (1.0 mmol) and dihydropapaverine **3a** (0.34 g, 1.0 mmol) or drotaverine **3b** (0.40 g, 1.0 mmol) was refluxed in isobutanol (2 ml) for 45 min. After that, the mixture was concentrated under reduced pressure and the solid formed was recrystallized from isobutanol–hexane (2:1) to give compounds **4** as a colourless powder.

thus affording lamellarin derivatives **4** along with elimination of water and hyponitrous acid $H_2N_2O_2$ (the Grob reaction).[7] Since compounds **3a**,**b** are prone to air oxidation, all operations should be performed in an inert atmosphere. Note that the intermediates **4′** could not be isolated and underwent spontaneous cyclization to form the fused pyrrole ring (see Scheme 1). Reactions of 3-nitro-2-trichloromethyl- and 3-nitro-2-phenyl-2*H*-chromenes with 1-benzyl-3,4-dihydroisoquinolines did not give the corresponding lamellarin derivatives even under more drastic conditions.

The structures of **4a**–**f** were characterized by ^{1}H, ^{19}F, ^{13}C NMR spectra and elemental analyses.‡ A characteristic feature of the ^{1}H NMR spectra is the presence of quartet at δ 5.69–5.75 ppm with $^3J_{H,F}$ 6.0–6.4 Hz in $CDCl_3$ for H-6 proton (δ 6.49–6.64 ppm, $^3J_{H,F}$ 6.8–6.9 Hz in [$^2H_6$]DMSO). Both NMR spectroscopy and X-ray crystallography revealed that the aromatic group on the pyrrole ring is orthogonal to the rest of the relatively planar pentacyclic system of lamellarins **1**.[8] Keeping this fact in mind and in making the ^{1}H NMR assignments, we have assumed that the ring current of the phenyl ring attached at C-14 causes shielding of the protons at C-1 and C-13. Note that in all cases, the ^{1}H NMR spectra of **4** recorded at 298 K displayed broad signals for the aromatic protons H-2′, H-5′ and H-6′. This phenomenon may be attributed to the restricted rotation of the aryl moiety about the C-14–C-1′ bond leading to rotamer formation.

In conclusion, a series of new CF_3-containing lamellarin derivatives, 8,9-dihydro-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]-isoquinolines, was obtained in high yields *via* the Grob reaction between 3-nitro-2-trifluoromethyl-2*H*-chromenes, and dihydropapaverine or drotaverine in refluxing isobutanol.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2010.11.006.

‡ *14-(3′,4′-Dimethoxyphenyl)-11,12-dimethoxy-6-trifluoromethyl-8,9-dihydro-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinoline* **4a**. Yield 78%, mp 177–178 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.05 (t, 2H, CH_2, *J* 5.9 Hz), 3.36, 3.86, 3.95 (all s, 3H, MeO), 3.7–4.0 (m, 4H, MeO, C*H*HN), 4.07 (dt, 1H, CH*H*N, *J* 12.2 and 5.9 Hz), 5.75 (q, 1H, H-6, $^3J_{H,F}$ 6.2 Hz), 6.57 (s, 1H, H-13), 6.69 (s, 1H, H-10), 6.72 (ddd, 1H, H-3, *J* 8.0, 7.0 and 1.5 Hz), 6.92 (d, 1H, H-1, *J* 7.7 Hz), 6.98 (dd, 1H, H-4, *J* 8.0 and 1.5 Hz), 7.00 (td, 1H, H-2, *J* 7.5 and 1.5 Hz), 6.8–7.2 (m, 3H, Ar). ^{19}F NMR (376 MHz, $CDCl_3$) δ: 83.35 (br. d, CF_3, *J* 6.2 Hz). ^{1}H NMR (400 MHz, [$^2H_6$]DMSO) δ: 3.00 (t, 2H, CH_2, *J* 5.5 Hz), 3.21, 3.73, 3.82 (all s, 3H, MeO), 3.6–3.9 (m, 4H, MeO, C*H*HN), 4.37 (dt, 1H, CH*H*N, *J* 12.5 and 5.5 Hz), 6.43 (s, 1H, H-13), 6.56 (q, 1H, H-6, $^3J_{H,F}$ 6.9 Hz), 6.6–6.8 (br. s, 1H, Ar), 6.74 (ddd, 1H, H-3, *J* 8.2, 7.5 and 2.0 Hz), 6.87 (d, 1H, H-1, *J* 7.5 Hz), 6.89 (s, 1H, H-10), 6.95–7.02 (m, 2H, H-2, H-4), 7.0–7.3 (br. s, 2H, Ar). ^{19}F NMR (376 MHz, [$^2H_6$]DMSO) δ: 85.35 (d, CF_3, $^3J_{F,H}$ 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.97, 41.98, 55.18, 55.92, 56.04 (2C), 70.03 (q, C-6, $^2J_{C,F}$ 34.1 Hz), 107.41, 111.01, 111.69 (br. s), 114.01 (br. s), 115.11, 115.21, 116.07, 116.34, 120.32, 121.60, 122.31, 122.76, 123.30 (q, CF_3, $^1J_{C,F}$ 287.5 Hz), 123.33 (br. s), 123.90, 126.39, 128.91, 129.00, 147.34, 147.58, 148.46, 149.43, 149.99. IR (KBr, ν/cm^{-1}): 1610, 1578, 1542, 1515, 1505, 1485. Found (%): C, 66.75; H, 4.87; N, 2.89. Calc. for $C_{30}H_{26}F_3NO_5$ (%): C, 67.03; H, 4.88; N, 2.61.

*14-(3′,4′-Diethoxyphenyl)-11,12-diethoxy-6-trifluoromethyl-8,9-dihydro-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinoline* **4d**. Yield 81%, mp 154–155 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17, 1.42, 1.52 (all t, 3H, Me, *J* 7.0 Hz), 1.3–1.5 (br. s, 3H, Me), 2.96–3.08 (m, 2H, CH_2), 3.52–3.64 (m, 2H, CH_2N), 3.92–4.02 (m, 2H, CH_2O), 4.06 (q, 4H, $2CH_2O$, *J* 7.0 Hz), 4.17 (br. q, 2H, CH_2O, *J* 7.0 Hz), 5.74 (q, 1H, H-6, $^3J_{H,F}$ 6.2 Hz), 6.60 (br. s, 1H, H-13), 6.68 (s, 1H, H-10), 6.70 (ddd, 1H, H-3, *J* 8.2, 7.5 and 2.0 Hz), 6.90 (d, 1H, H-1, *J* 7.6 Hz), 6.96 (d, 1H, H-4, *J* 8.2 Hz), 6.98 (td, 1H, H-2, *J* 8.0 and 1.4 Hz), 6.7–7.2 (br. m, 3H, Ar). ^{19}F NMR (376 MHz, $CDCl_3$) δ: 83.33 (br. s, CF_3). ^{1}H NMR (400 MHz, [$^2H_6$]DMSO) δ: 1.05, 1.29, 1.38 (all t, 3H, Me, *J* 7.0 Hz), 1.15–1.35 (br. s, 3H, Me), 2.94–3.01 (m, 2H, CH_2), 3.40–3.55 (m, 2H, CH_2N), 3.7–4.4 (br. m, 8H, $4CH_2O$), 6.45 (br. s, 1H, H-13), 6.55 (q, 1H, H-6, $^3J_{H,F}$ 6.8 Hz), 6.6–6.8 (br. s, 1H, Ar), 6.73 (ddd, 1H, H-3, *J* 8.2, 7.2 and 1.7 Hz), 6.85 (d, 1H, H-1, *J* 7.5 Hz), 6.86 (s, 1H, H-10), 6.96 (dd, 1H, H-4, *J* 8.2 and 1.2 Hz), 6.99 (td, 1H, H-2, *J* 8.0 and 1.3 Hz), 6.92–7.22 (br. s, 2H, Ar). ^{19}F NMR (376 MHz, [$^2H_6$]DMSO) δ: 85.33 (d, CF_3, $^3J_{F,H}$ 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.49, 14.75, 14.84, 14.87, 28.92, 41.97, 63.62, 64.15 (br. s), 64.44 (br. s), 64.63, 70.03 (q, C-6, $^2J_{C,F}$ 34.0 Hz), 108.95, 113.08, 113.13, 113.85 (br. s), 114.95, 115.21, 115.62 (br. s), 115.98, 116.38, 120.36, 121.71, 122.26, 122.76, 123.28 (q, CF_3, $^1J_{C,F}$ 287.0 Hz), 123.70, 126.27, 128.98, 129.01, 146.89, 147.15, 148.02, 149.16, 149.94. IR (KBr, ν/cm^{-1}): 1608, 1581, 1553, 1542, 1504, 1515, 1475. Found (%): C, 68.58; H, 6.01; N, 2.30. Calc. for $C_{34}H_{34}F_3NO_5$ (%): C, 68.79; H, 5.77; N, 2.36.

For characteristics of compounds **4b**,**c**,**e**,**f**, see Online Supplementary Materials.

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Received: 14th April 2010; Com. 10/3504