Tetrahedron Letters 49 (2008) 5376–5379

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A facile route to the pentacyclic lamellarin skeleton via Grob reaction between 3-nitro-2-(trifluoromethyl)-2*H*-chromenes and 1,3,3-trimethyl-3,4-dihydroisoquinolines

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ARTICLE INFO

Article history:
Received 5 May 2008
Revised 17 June 2008
Accepted 26 June 2008
Available online 3 July 2008

Keywords:
Lamellarin skeleton
Grob reaction
3-Nitro-2-(trifluoromethyl)-2*H*-chromenes
1,3,3-Trimethyl-3,4-dihydroisoquinolines

ABSTRACT

The basic structural framework of lamellarin alkaloids, 8,9-dihydro-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinoline derivatives, has been obtained in good yields via Grob reaction between 3-nitro-2-(trifluoromethyl)-2*H*-chromenes and 1,3,3-trimethyl-3,4-dihydroisoquinolines in refluxing isobutanol. When the reaction was carried out in toluene at room temperature, only Michael adducts, as a mixture of two diastereomers, were isolated.

Recently, considerable interest has been devoted to the synthesis of partially fluorinated heterocycles, many of which have found use as agrochemicals and drugs.[1] However, reports on the use of 2-(trifluoromethyl)-2*H*-chromenes as substrates for organic synthesis are very scarce, although 2*H*-chromene (2*H*-1-benzopyran) and its derivatives belong to an important class of oxygen-containing heterocyclic compounds that are common in plants and exhibit a wide spectrum of useful properties. Structures containing a benzopyran framework have antitumor, antibacterial, and antiinflammatory activity and inhibit HIV-1 reverse transcriptase, interleukin-1 production, and protein kinases and can cleave DNA.[2] In addition, they are also useful intermediates in the synthesis of complex natural products, such as pterocarpans.[3] In continuation of our studies on the chemical properties of 3-nitro-2-(trihalomethyl)-2*H*-chromenes (**1**, X = F, Cl),[4] which turned out to be highly reactive substrates in reactions with N-, S-, and C-nucleophiles,[5] we decided to investigate their reaction with 1,3,3-trimethyl-3,4-dihydroisoquinolines **2**, which are capable of reacting with electrophilic substrates as C-nucleophiles or 1,3-C,N-dinucleophiles via the enamine tautomeric form.[6] 3,4-Dihydroisoquinolines are another group of biologically interesting compounds, which exhibit diverse biological properties including anticonvulsant, antimicrobiological, and antitumor activities.[7] Although much attention has been paid to the chemistry of 1,3,3-trimethyl-3,4-dihydroisoquinolines **2**, mainly due to their use as excellent building blocks for the preparation of a variety of complex heterocyclic compounds,[6] their reactions with 2*H*-chromenes have not been described in the literature.

A reaction involving the addition of secondary enaminoesters to nitroolefins followed by intramolecular displacement of the nitro group by the amino group to yield pyrroles was disclosed by Grob et al.[8] This method makes use of easily prepared reagents and is particularly suitable for a combinatorial approach to the synthesis of substituted pyrroles.[9] Since imines, which exist in equilibrium with their enamines, have been shown to react with β-nitrostyrene to give the corresponding pyrroles,[10] it was expected that Michael addition of enamines derived from 1,3,3-trimethyl-3,4-dihydroisoquinolines **2** to a powerful Michael acceptor, such as chromenes **1**, followed by ring closure and aromatization (Grob reaction) could provide a direct route to 8,9-dihydro-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolines **3** (Fig. 1).

This heterocyclic system constitutes the basic structural framework of the recently discovered lamellarin alkaloids **4**,[11] a class of marine natural products, a few of which show cytotoxic and immunomodulatory activity that may prove highly effective in the treatment of multidrug resistant tumours.[12] In addition, the lamellarins represent a new and promising series of topoisomerase

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0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.06.122

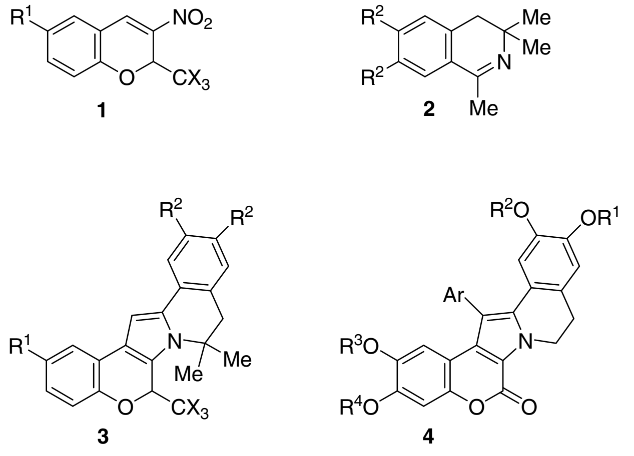


Figure 1.

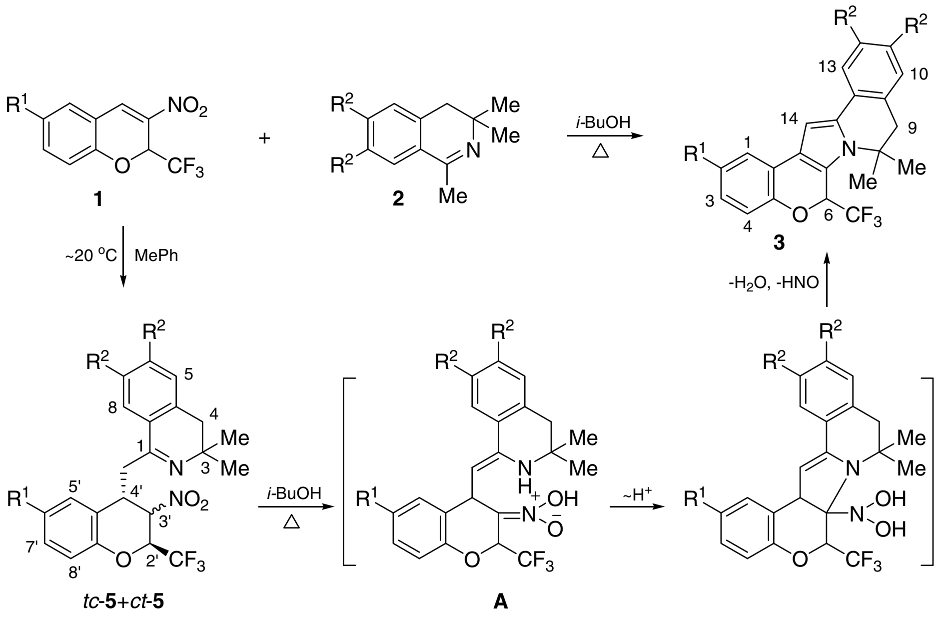
I inhibitors.[13] Therefore, the development of efficient new methods leading to this heterocyclic framework is highly desirable.[14] Very recently, it was reported that the reaction of 3-nitrocoumarins with 1-benzyldihydroisoquinolines gave the desired lamellarins in only 5–6% yields.[15] In this context, we anticipated that, if the reaction occurred with chromenes **1**, the pentacyclic lamellarin ring system would be constructed successfully in one chemical operation and a series of novel lamellarin derivatives would be accessible. We now report our work in this area as a preliminary communication.

We found that chromenes **1**, as the nitroolefin components, reacted with dihydroisoquinolines **2**, as the enamine components, in toluene at room temperature for 1 h to give Michael adducts **5a–f** as a mixture of trans–cis and cis–trans-isomers (ca. 1:1) in good to high combined yields (Scheme 1 and Table 1). The double bond of **1** is so reactive that no catalyst was necessary. Notably, the chroman products **5** contain three contiguous stereogenic centres, but in all cases, only two diastereomers could be observed by ^{1}H NMR spectroscopy of the crude reaction mixtures. The structures of **5** were characterized by ^{1}H, ^{19}F, ^{13}C NMR and elemental analyses.

Table 1
Synthesis of compounds **3** and **5**

R^1	R^2	Adduct	Yield (%)	Product **3**	Yield (%) method A	Yield (%) method B
H	H	**5a**	68	**3a**	58	48
H	Me	**5b**	73	**3b**	67	60
H	MeO	**5c**	81	**3c**	56	25
MeO	MeO	**5d**	84	**3d**	77	42
Br	Me	**5e**	39	**3e**	52	26
Br	MeO	**5f**	86	**3f**	75	61

The most diagnostic parameter for structural assignment was the coupling constants between protons H-2′ and H-3′ and H-3′ and H-4′. In the cis–trans-isomer (ct-isomer) **5** the coupling constants $J_{2',3'} = J_{3',4'} = 1.5$ Hz are significantly smaller and typical of a gauche conformation. The cis–trans configuration was verified by comparison of spectral data obtained for ct-**5** with those reported in the literature. Earlier, $J_{2,3} = J_{3,4} = 1.2–1.8$ Hz values were reported for cis–trans adducts formed in reactions of thiols and indoles with chromenes **1**[5a,b,e] and $J_{2,3} = J_{3,4} = 2.2$ Hz for *cis-trans*-2-(4-chlorophenyl)-4-(indol-3-yl)-3-nitrochroman, whose structure was confirmed by X-ray diffraction analysis.[16] Additional evidence for the cis–trans configuration was obtained from the chemical shift in the narrow range δ 86.5–86.6 ppm (C_6F_6) and the coupling constant of the doublet for the CF_3 group ($^3J_{F,H} = 5.7–5.9$ Hz), which agrees well with the literature data for cis–trans adducts of chromenes **1** with thiols[5a,b] and azoles.[5e] The trans–cis configuration (tc-isomer) was also evident from the experimental coupling constants $J_{2',3'} \approx J_{3',4'} \approx 4.5$ Hz, which correlate with the literature data for trans–cis adducts of thiols with chromenes **1**.[5a,b] A characteristic difference between the two stereoisomers is based on the chemical shift of the H-2′ proton, which was shifted downfield by 0.7–0.8 ppm in tc-isomer compared to ct-isomer. This is due to the deshielding effect of the NO_2 group, which is *cis* to H-2′ in the tc-isomer.[17] Note that in some cases, the ^{1}H NMR spectra of the Michael adducts recorded at 298 K displayed broad signals for the aliphatic and aromatic protons. This phenomenon may be attributed to the restricted rotation of the dihydroisoquinoline moiety about the C–C bond leading to rotamer formation.



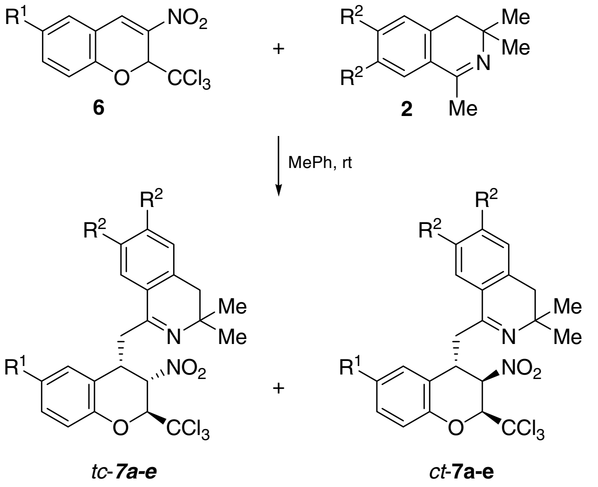
Scheme 1.

When chromans **5a–f** as a mixture of tc- and ct-diastereomers were heated at reflux in isobutanol for 1 h, pentacycles **3a–f** were obtained in good yields (method A). The progress of the reaction was monitored by TLC, and the results are summarized in Table 1. Among different solvents (alcohols, acetonitrile), isobutanol appeared to give the best results. In accordance with the proposed mechanism,[8b] the Michael adduct **5** undergoes intramolecular displacement of the nitro group by the NH group, thus affording lamellarin system **3** via elimination of water and hyponitrous acid. It was also found that **1** and **2** could be employed directly under these conditions to give **3a–f** in 25–61% yields (method B), however, better yields and easier purification of compounds **3** were achieved if the transformation was performed in a two-step approach (method A). Thus, compounds **3** and **5** could be synthesized from the same starting material simply by the choice of the reaction conditions (Scheme 1).

To the best of our knowledge, pentacycles **3** represent the first lamellarin derivatives reported to date bearing a CF_3 substituent instead of a carbonyl group. The structures of **3a–f** were confirmed with the help of spectral and analytical data.[18] For example, the ^{1}H NMR spectrum of compound **3b** in $CDCl_3$ showed two AX doublets ($J_{AX} = 15.4$ Hz) at δ 2.70 and 3.13 ppm for the CH_2 group and a quartet at δ 6.14 ppm ($^{3}J_{H,F} = 6.1$ Hz) due to the H-6 proton. The pyrrole ring proton resonated at δ 6.77 ppm. In the ^{19}F NMR spectrum the CF_3 group of **3b** appeared as a doublet with $^{3}J_{F,H} = 6.1$ Hz at 86.43 ppm (C_6F_6). The ^{13}C NMR spectrum of **3b** exhibited a quartet ($^{1}J_{C,F} = 288.0$ Hz) at 123.60 ppm for the carbon of the CF_3 group and a quartet ($^{2}J_{C,F} = 32.6$ Hz) at 71.22 ppm for the C–CF_3 atom. This confirmed that the CF_3 group is bonded to the sp^3 hybridized carbon atom. In addition, another feature of interest was the appearance of a quartet ($^{6}J_{C,F} = 2.4$ Hz) at 26.43 ppm due to one of the Me-8 groups, indicating that the Me-8 and CF_3 groups were spatially close to each other.

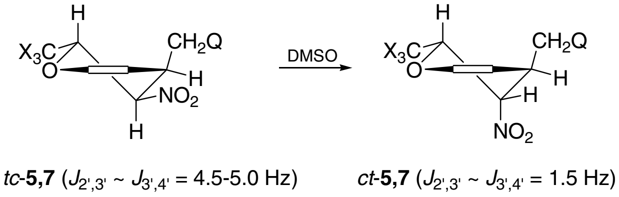
We next investigated the reaction of 3-nitro-2-(trichloromethyl)-2*H*-chromenes **6** with dihydroisoquinolines **2** in order to prepare CCl_3-containing pentacycles of type **3**. When 2-CCl_3-chromenes **6** were reacted in toluene at room temperature for 1 h, the reaction proceeded smoothly to give, both prior to and after recrystallization, an unequal mixture of trans–cis and cis–trans chromans **7a–e** substantially favouring the trans–cis isomer (85:15). This result shows that the isomer ratio depends on the steric effects of the trihalomethyl group (Scheme 2).

The structures of compounds **7** compared well with the results of elemental analysis, ^{1}H, ^{13}C NMR and IR spectroscopy. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis. In this case, the coupling constants for the tc-isomers are $J_{2',3'} \approx J_{3',4'} \approx 5.0$ Hz and those for the ct-isomers are $J_{2',3'} = J_{3',4'} = 1.5$ Hz. It should be noted that on dissolution in DMSO-d_6, the ratio of the isomers changed to tc-**7**:ct-**7** = 35:65 (for compounds **5** in DMSO-d_6 it was tc-**5**:ct-**5** = 15:85). Isomerization to this extent is evident immediately on dissolution (after 1–2 min), and at constant temperature there was no subsequent change in the percentage isomerization. This is associated with epimerization at the C-3 atom and indicates the higher thermodynamic stability of the cis–trans isomer of 2-CX_3-chromans **5** and **7**, especially for **5** (X = F). Of the four possible diastereomers (trans–trans, cis–cis, trans–cis, and cis–trans), the dihydroisoquinoline fragment and trihalomethyl substituent are trans to each other only in the last two isomers, which probably control the stereochemistry of the Michael addition (Scheme 3).



$R^1 = R^2 =$ H (**7a**, 60%); $R^1 =$ H, $R^2 =$ MeO (**7b**, 71%);
$R^1 =$ MeO, $R^2 =$ MeO (**7c**, 62%); $R^1 =$ Br, $R^2 =$ Me (**7d**, 52%);
$R^1 =$ Br, $R^2 =$ MeO (**7e**, 58%)

Scheme 2.



tc-**5**:*ct*-**5** = 55:45 ($CDCl_3$), *tc*-**5**:*ct*-**5** = 15:85 (DMSO-d_6);
tc-**7**:*ct*-**7** = 85:15 ($CDCl_3$), *tc*-**7**:*ct*-**7** = 35:65 (DMSO-d_6)

Scheme 3.

Unfortunately, attempts to cyclise trichloromethylated Michael adducts **7** in the usual manner (methods A and B) gave only tarry multicomponent reaction mixtures from which no fused pyrroles **3** could be isolated. Thus, the reaction turned out to be very sensitive to the nature of the CX_3 substituent and afforded pyrroles **3** only when the 2-CF_3-chromenes **1** were used. This is probably a result of the equilibrium between the nitro and *aci* forms of the Michael adduct. It seems that the CF_3 group, due to its powerful electron-withdrawing character, favours a preponderance of the latter form **A** (Scheme 1), from which the pyrroles **3** are derived. Another reason may be a weak C(4′)–CH_2 linkage in **7**, since partial decomposition in DMSO-d_6 took place and starting materials **2** and **6** were observed in the ^{1}H NMR spectra. It should be noted that the reaction of 3-nitro-2-phenyl-2*H*-chromene with **2** (R^2 = MeO) also stops at the Michael addition stage and all our attempts to synthesize the corresponding lamellarin derivative failed.

In conclusion, the reaction of 3-nitro-2-(trifluoromethyl)-2*H*-chromenes **1** with 1,3,3-trimethyl-3,4-dihydroisoquinolines **2** provides a simple and convenient preparative procedure for 8,9-dihydro-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolines **3**, which may be considered as new pentacyclic lamellarin derivatives. The resulting products are of considerable interest as precursors in the synthesis of other biologically and medicinally important organic materials. Further studies on the synthetic application of this reaction are currently in progress in our group and will be published elsewhere.

Acknowledgement

This work was financially supported by the Russian Foundation for Basic Research (Grant 06-03-04004).

References and notes

1. (a) *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Filler, R., Kobayashi, Y., Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, 1993; (b) Hiyama, T. *Organofluorine Compounds: Chemistry and Application*; Springer: Berlin, 2000.
2. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.
3. (a) Engler, T. A.; Reddy, J. P.; Combrink, K. D.; Velde, D. V. *J. Org. Chem.* **1990**, *55*, 1248–1254; (b) Murugesh, M. G.; Subburaj, K.; Trivedi, G. K. *Tetrahedron* **1996**, *52*, 2217–2228; (c) Engler, T. A.; LaTessa, K. O.; Iyengar, R.; Chai, W.; Agrios, K. *Bioorg. Med. Chem.* **1996**, *4*, 1755–1769.
4. Korotaev, V. Yu.; Kutyashev, I. B.; Sosnovskikh, V. Ya. *Heteroat. Chem.* **2005**, *16*, 492–496.
5. (a) Korotaev, V. Yu.; Sosnovskikh, V. Ya.; Kutyashev, I. B.; Kodess, M. I. *Lett. Org. Chem.* **2005**, *2*, 616–620; (b) Korotaev, V. Yu.; Sosnovskikh, V. Ya.; Kutyashev, I. B.; Kodess, M. I. *Izv. Akad. Nauk, Ser. Khim.* **2006**, 309–321; Korotaev, V. Yu.; Sosnovskikh, V. Ya.; Kutyashev, I. B.; Kodess, M. I. *Russ. Chem. Bull., Int. Ed.* **2006**, *55*, 317–330; (c) Korotaev, V. Yu.; Sosnovskikh, V. Ya.; Kutyashev, I. B.; Kodess, M. I. *Izv. Akad. Nauk, Ser. Khim.* **2006**, 1945–1955; Korotaev, V. Yu.; Sosnovskikh, V. Ya.; Kutyashev, I. B.; Kodess, M. I. *Russ. Chem. Bull., Int. Ed.* **2006**, *55*, 2020–2031; (d) Korotaev, V. Yu.; Kutyashev, I. B.; Sosnovskikh, V. Ya.; Kodess, M. I. *Mendeleev Commun.* **2007**, *17*, 52–53; (e) Korotaev, V. Yu.; Sosnovskikh, V. Ya.; Kutyashev, I. B. *Izv. Akad. Nauk, Ser. Khim.* **2007**, 1985–1990; Korotaev, V. Yu.; Sosnovskikh, V. Ya.; Kutyashev, I. B. *Russ. Chem. Bull., Int. Ed.* **2007**, *56*, 2054–2059.
6. (a) Shklyaev, Yu. V.; Maslivets, A. N. *Zh. Org. Khim.* **1996**, *32*, 319; Shklyaev, Yu. V.; Maslivets, A. N. *Russ. J. Org. Chem.* **1996**, *32*, 302; (b) Sviridov, V. D.; Chkanikov, N. D.; Galakhov, M. V.; Shklyaev, Yu. V.; Shklyaev, V. S.; Aleksandrov, B. B.; Gavrilov, M. S. *Izv. Acad. Nauk SSSR, Ser. Khim.* **1990**, 1405–1410; Sviridov, V. D.; Chkanikov, N. D.; Galakhov, M. V.; Shklyaev, Yu. V.; Shklyaev, V. S.; Aleksandrov, B. B.; Gavrilov, M. S. *Bull. Acad. Sci. USSR. Div. Chem. Sci.* **1990**, *39*, 1268–1273; (c) Tyutin, V. Yu.; Chkanikov, N. D.; Shklyaev, Yu. V.; Shklyaev, V. S.; Kolomiets, A. F.; Fokin, A. V. *Izv. Acad. Nauk, Ser. Khim.* **1992**, 1888–1891; Tyutin, V. Yu.; Chkanikov, N. D.; Shklyaev, Yu. V.; Shklyaev, V. S.; Kolomiets, A. F.; Fokin, A. V. *Bull. Russ. Acad. Sci. Div. Chem. Sci.* **1992**, *41*, 1474–1477; (d) Sviridov, V. D.; Chkanikov, N. D.; Shklyaev, Yu. V.; Kolomiets, A. F.; Fokin, A. V. *Khim. Geterotsikl. Soedin.* **1990**, 1689; Sviridov, V. D.; Chkanikov, N. D.; Shklyaev, Yu. V.; Kolomiets, A. F.; Fokin, A. V. *Chem. Heterocycl. Compd.* **1990**, *26*, 1405.
7. (a) Shamma, M. *The Isoquinoline Alkaloids*; Academic Press: New York, 1972; (b) Bentley, K. W. *The Isoquinoline Alkaloids*; Harwood Academic Publishers, 1998.
8. (a) Grob, C. A.; Camenisch, K. *Helv. Chim. Acta* **1953**, *36*, 49–58; (b) Grob, C. A.; Schad, H. P. *Helv. Chim. Acta* **1955**, *38*, 1121–1127.
9. (a) Gómez-Sánchez, A.; Mancera, M.; Rosado, F. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1199–1205; (b) Revial, G.; Lim, S.; Viossat, B.; Lemoine, P.; Tomas, A.; Duprat, A. F.; Pfau, M. *J. Org. Chem.* **2000**, *65*, 4593–4600; (c) Baldoli, C.; Cremonesi, G.; Croce, P. D.; La Rosa, C.; Licandro, E. *Heterocycles* **2004**, *64*, 491–497; (d) Alizadeh, A.; Rezvanian, A.; Bijanzadeh, H. R. *Synthesis* **2008**, 725–728.
10. Lim, S.; Jabin, I.; Revial, G. *Tetrahedron Lett.* **1999**, *40*, 4177–4180.
11. (a) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264–287; (b) Andersen, R. J.; Faulkner, D. J.; Cun-heng, H.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1985**, *107*, 5492–5495; (c) Ham, J.; Kang, H. *Bull. Korean Chem. Soc.* **2002**, *23*, 163–166; (d) Krishnaiah, P.; Reddy, V. L. N.; Venkataramana, G.; Ravinder, K.; Srinivasulu, M.; Raju, T. V.; Ravikumar, K.; Chandrasekar, D.; Ramakrishna, S.; Venkateswarlu, Y. *J. Nat. Prod.* **2004**, *67*, 1168–1171.
12. (a) Banwell, M.; Flynn, B.; Hockless, D. *Chem. Commun.* **1997**, 2259–2260; (b) Reddy, M. V. R.; Rao, M. R.; Rhodes, D.; Hansen, M. S. T.; Rubins, K.; Bushman, F. D.; Venkateswarlu, Y.; Faulkner, D. J. *J. Med. Chem.* **1999**, *42*, 1901–1907; (c) Reddy, S. M.; Srinivasulu, M.; Satyanarayana, N.; Kondapi, A. K.; Venkateswarlu, Y. *Tetrahedron* **2005**, *61*, 9242–9247.
13. Tardy, C.; Facompré, M.; Laine, W.; Baldeyrou, B.; García-Gravalos, D.; Francesch, A.; Mateo, C.; Pastor, A.; Jiménez, J. A.; Manzanares, I.; Cuevas, C.; Bailly, C. *Bioorg. Med. Chem.* **2004**, *12*, 1697–1712.
14. (a) Banwell, M. G.; Flynn, B. L.; Hamel, E.; Hockless, D. C. R. *Chem. Commun.* **1997**, 207–208; (b) Handy, S. T.; Zhang, Y.; Bregman, H. *J. Org. Chem.* **2004**, *69*, 2362–2366; (c) Nyerges, M.; Tőke, L. *Tetrahedron Lett.* **2005**, *46*, 7531–7534; (d) Cironi, P.; Manzanares, I.; Albericio, F.; Álvarez, M. *Org. Lett.* **2003**, *5*, 2959–2962; (e) Marfil, M.; Albericio, F.; Álvarez, M. *Tetrahedron* **2004**, *60*, 8659–8668; (f) Ploypradith, P.; Jinaglueng, W.; Pavaro, C.; Ruchirawat, S. *Tetrahedron Lett.* **2003**, *44*, 1363–1366; (g) Fujikawa, N.; Ohta, T.; Yamaguchi, T.; Fukuda, T.; Ishibashi, F.; Iwao, M. *Tetrahedron* **2006**, *62*, 594–604; (h) Ploypradith, P.; Petchmanee, T.; Sahakitpichan, P.; Litvinas, N. D.; Ruchirawat, S. *J. Org. Chem.* **2006**, *71*, 9440–9448.
15. Ploypradith, P.; Mahidol, C.; Sahakitpichan, P.; Wongbundit, S.; Ruchirawat, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 866–868.
16. Lin, C.; Hsu, J.; Sastry, M. N. V.; Fang, H.; Tu, Z.; Liu, J.-T.; Ching-Fa, Y. *Tetrahedron* **2005**, *61*, 11751–11757.
17. *3,3,6,7-Tetramethyl-1-[3-nitro-2-(trifluoromethyl)chroman-4-yl]methyl-3,4-dihydroisoquinoline* **5b**: Yield 73%, mp 116–117 °C; IR (KBr) 1618, 1583, 1565, 1491, 1371 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) (tc, 50%) δ 1.13, 1.17, 2.26, 2.27 (all s, 3H, Me), 2.59 (AB-system, 2H, CH$_2$-4, J = 16.1 Hz), 3.05 (dd, 1H, C*H*H, J = 16.7, 8.4 Hz), 3.27 (dd, 1H, CH*H*, J = 16.7, 5.6 Hz), 4.30 (dt, 1H, H-4′, J = 8.0, 5.0 Hz), 5.28 (quint, 1H, H-2′, J = 5.0 Hz), 5.85 (t, 1H, H-3′, J = 4.4 Hz), 6.92 (s, 1H, H-5), 7.00–7.30 (m, 4H, arom.), 7.17 (s, 1H, H-8), (ct, 50%) δ 1.18, 1.21, 2.27, 2.28 (all s, 3H, Me), 2.65 (bs, 2H, CH$_2$-4), 2.78 (dd, 1H, C*H*H, J = 16.8, 12.0 Hz), 3.35 (dd, 1H, CH*H*, J = 16.8, 3.1 Hz), 4.05 (bd, 1H, H-4′, J = 12.0 Hz), 4.58 (bq, 1H, H-2′, J = 6.0 Hz), 5.56 (bs, 1H, H-3′), 6.96 (s, 1H, H-5), 7.00–7.30 (m, 4H, arom.), 7.17 (s, 1H, H-8); ^{19}F NMR (376 MHz, CDCl$_3$) (tc, 50%) δ 85.06 (d, CF$_3$, J = 6.6 Hz), (ct, 50%) δ 86.45 (d, CF$_3$, J = 5.9 Hz); ^{1}H NMR (400 MHz, DMSO-d_6) (ct, 84%) δ 1.11, 1.14, 2.22, 2.23 (all s, 3H, Me), 2.63 (bs, 2H, CH$_2$-4), 3.23 (dd, 1H, C*H*H, J = 17.6, 3.8 Hz), 3.32 (dd, 1H, CH*H*, J = 17.6, 11.1 Hz), 4.01 (dd, 1H, H-4′, J = 11.1, 3.8 Hz), 5.53 (bq, 1H, H-2′, J = 6.2 Hz), 5.57 (bs, 1H, H-3′), 7.02 (s, 1H, H-5), 7.03 (dd, 1H, H-8′, J = 8.3, 1.2 Hz), 7.08 (td, 1H, H-6′, J = 7.5, 1.2 Hz), 7.25 (ddd, 1H, H-7′, J = 8.3, 7.3, 1.5 Hz), 7.35 (s, 1H, H-8), 7.46 (bd, 1H, H-5′, J = 7.0 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) (ct, 84%) δ 88.12 (d, CF$_3$, J = 6.3 Hz), (tc, 16%) δ 87.78 (d, CF$_3$, J = 7.0 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) (tc + ct) δ 19.60, 19.64, 19.78, 19.80, 27.65, 27.71, 28.05, 28.19, 32.01, 33.62, 35.73, 38.24, 38.26, 41.53, 53.91, 54.17, 70.58 (q, *C*–CF$_3$, $^{2}J_{C,F}$ = 34.1 Hz), 73.53 (q, *C*–CF$_3$, $^{2}J_{C,F}$ = 32.5 Hz), 78.51, 80.88, 117.03, 117.17, 122.13 (q, CF$_3$, $^{1}J_{C,F}$ = 280.9 Hz), 122.31, 122.88, 122.95, 123.03, 123.04 (q, CF$_3$, $^{1}J_{C,F}$ = 283.0 Hz), 125.11, 125.12, 125.28, 125.77, 126.50, 128.33, 128.79, 128.92, 129.75, 130.11, 133.96, 134.25, 134.84, 135.00, 139.71, 140.28, 151.96, 152.10, 158.82, 158.96. Anal. Calcd for $C_{24}H_{25}F_3N_2O_3$: C, 64.57; H, 5.64; N, 6.27. Found: C, 64.53; H, 5.70; N, 6.24.
18. *8,8,11,12-Tetramethyl-6-(trifluoromethyl)-8,9-dihydro-6H-chromeno[4′,3′:4,5]-pyrrolo[2,1-a]isoquinoline***3b**: Yield 67%, mp 178–179 °C; IR (KBr) 1635, 1616, 1592, 1560, 1532, 1498 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.34, 1.78, 2.27, 2.30 (all s, 3H, Me), 2.70 (d, 1H, C*H*H, J = 15.4 Hz), 3.13 (d, 1H, CH*H*, J = 15.4 Hz), 6.14 (q, 1H, H-6, J = 6.1 Hz), 6.77 (s, 1H, H-14), 6.93 (s, 1H, H-10), 7.00 (dd, 1H, H-4, J = 7.8, 1.3 Hz), 7.02 (td, 1H, H-2, J = 7.4, 1.3 Hz), 7.10 (td, 1H, H-3, J = 7.6, 1.7 Hz), 7.38 (s, 1H, H-13), 7.45 (dd, 1H, H-1, J = 7.4, 1.7 Hz); ^{19}F NMR (376 MHz, CDCl$_3$) δ 86.43 (d, CF$_3$, J = 6.1 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 19.59, 19.63, 26.43 (q, Me-8, $^{6}J_{C,F}$ = 2.4 Hz), 27.98, 44.87, 58.32, 71.22 (q, *C*–CF$_3$, $^{2}J_{C,F}$ = 32.6 Hz), 98.55, 115.68, 115.89, 118.94, 120.81, 122.31, 122.53, 123.60 (q, CF$_3$, $^{1}J_{C,F}$ = 288.0 Hz), 123.91, 126.12, 126.79, 127.47, 129.15, 134.54, 135.30, 135.38, 149.43; MS (EI): *m/z* 397 [M]$^{+}$ (16), 328 [M−CF$_3$]$^{+}$ (100), 285 (24), 157 (20), 149 (12), 142 (11). Anal. Calcd for $C_{24}H_{22}F_3NO$: C, 72.53; H, 5.58; N, 3.52. Found: C, 72.62; H, 5.67; N, 3.50.