3-Nitrochromene Derivatives as 2π Components in 1,3-Dipolar Cycloadditions of Azomethine Ylides

Miklós Nyerges,*[a] Andrea Virányi,[a] Gabriella Marth,[a] András Dancsó,[b] Gábor Blaskó,[b] László Tőke[a]

[a] Organic Chemical Technology Research Group of the Hungarian Academy of Sciences, Budapest University of Technology and Economics, 1521 Budapest P.O.B. 91, Hungary

[b] EGIS Pharmaceuticals Ltd., 1475 Budapest P.O.B. 100, Hungary
Fax +361(463)3648; E-mail: mnyerges@mail.bme.hu

Received 26 August 2004

Abstract: The 1,3-dipolar cycloaddition of 2-aryl-3-nitrochromenes with various azomethine ylides has been investigated. The structure and stereochemistry of cycloadducts were studied in detail by NMR spectroscopic methods.

Key words: azomethine ylids, chromenes, cycloadditions, pyrroles

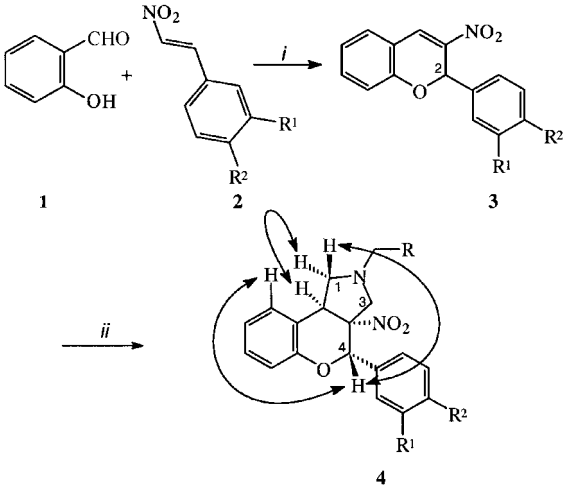
1,3-Dipolar cycloadditions of azomethine ylides represent one of the most convergent approaches for the construction of pyrrolidine rings.[1] The ease of generation of 1,3-dipoles, the rapid accumulation of polyfunctionality in a relatively small molecular framework coupled with the highly regio- and stereoselective nature of their cycloaddition reactions, has resulted in a number of syntheses which utilize such a reaction as the key step.[2] Recently, we have demonstrated the usefulness of the intermolecular 1,3-dipolar cycloaddition of azomethine ylides in the synthesis of aza-cephalotaxine analogues[3] or alkaloid derivatives with a spiro-indolenine framework.[4] This method gives a rapid access to the pyrrolo[3,2-*c*]quinoline ring system of martinellines[5] and to pyrrolo[3,4-*c*]quinolines.[6]

The abundance of naturally occuring chromene and chromane derivatives and their interesting physiological properties along with the known selective dopamine D_3 receptor antagonist action of some benzopirano[3,4-*c*]-pyrrolidine derivatives[7] suggested the study of easily available 2-aryl-3-nitrochromene derivatives (**3**) as 2π components in 1,3-dipolar cycloadditions of azomethine ylides.

The 3-nitrochromene derivatives (**3a**–**e**) were prepared by modification of the method described by Yao[8] from the corresponding 2-aryl-nitroethylenes (**2a**–**e**)[9] by the treatment with salicylaldehyde, in the presence of DABCO, without any solvent in a single step.

In the first set of experiments we used the most simple non-stabilized azomethine ylides, which were generated from paraformaldehyde and sarcosine or *N*-benzyl-glycine using the decarboxylation method.[10] The reaction of 3-nitrochromenes (**3a**–**e**) with these unstable intermediates in refluxing toluene proceeds smoothly to give the expected 3a-nitro-4-aryl-benzopirano[3,4-*c*]-pyrrolidines (**4a**–**j**).

The results, summarized in Table 1, showed that dipolarophiles **2** with more electron-donating substituents on the 2-aryl group are less reactive than without or with electron-withdrawing substituents in accordance with our earlier experiments with β-nitro-styrenes.



Scheme 1 *Reagents and conditions*: i. DABCO, 40 °C; ii. $CH_3NHCH_2CO_2H$ (R = H) or $BnNHCH_2CO_2H$ (R = Ph), $(CH_2O)_n$, toluene, reflux

The structures of compounds **4** were elucidated by NMR spectroscopy using ^1H, ^{13}C, ^1H-^1H COSY, ^1H-^{13}C HSQC, ^1H-^{13}C HMQC techniques. The relative stereochemistry of these cycloadducts **4** was established on **4a** and **4h** mostly by $^1H\{^1H\}$ NOE studies. The most important proof of their stereochemistry were the NOE enhancements indicated with arrows in Scheme 1.

Thermally generated dipoles from imines of glycine or other α-amino acid esters undergo stereoselective cycloadditions with highly activated cyclic dipolarophiles such as maleimides leading to the exclusive formation of *endo*-adducts of *E*,*E*-ylides.[12] However, their cycloadditions with less reactive olefin dipolarophiles such as maleates and fumarates were found to be no longer stereoselective.[13] Activation with a wide range of metal salt/tertiary amine combinations proved to be effective for increasing the rate of cycloaddition of aryl imines to less

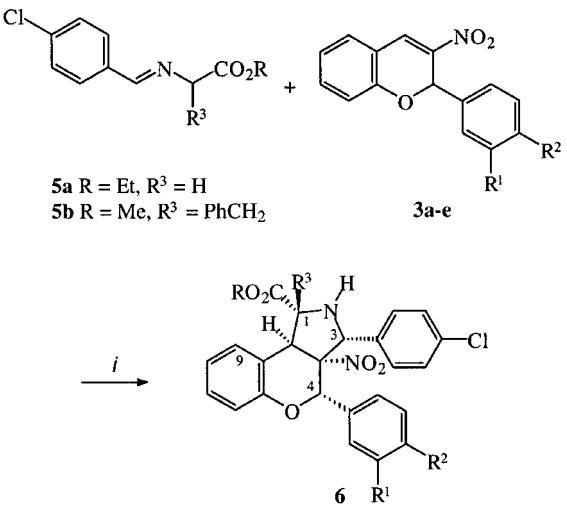
SYNLETT 2004, No. 15, pp 2761–2765
Advanced online publication: 08.11.2004
DOI: 10.1055/s-2004-835655; Art ID: D25504ST

Table 1 Reaction Times and Yields of Compounds **4a**–**j**[11]

Entry	R^1	R^2	Nitrochromene	R	Product	Time (h)	Yield (%)
1	H	H	**3a**	Me	**4a**	3	93
2	H	H	**3a**	Bn	**4b**	5	72
3	H	MeO	**3b**	Me	**4c**	5	94
4	H	MeO	**3b**	Bn	**4d**	5	85
5	H	Cl	**3c**	Me	**4e**	5	89
6	H	Cl	**3c**	Bn	**4f**	5	83
7	MeO	MeO	**3d**	Me	**4g**	12	75
8	MeO	MeO	**3d**	Bn	**4h**	16	68
9	NO_2	H	**3e**	Me	**4i**	1	84
10	NO_2	H	**3e**	Bn	**4j**	1	79

reactive dipolarophiles, allowing the reaction to be run at room temperature with excellent regio- and stereocontrol.[14] The cycloaddition of **3a**–**e** with the azomethine ylides derived from the imines of ethyl glycinate or phenylalanine ethylester in the presence of AgOAc and Et_3N occurred smoothly at room temperature giving pure benzopirano[3,4-*c*]-pyrrolidine derivatives **5** in 60–77% yield (Scheme 2, Table 2).[15] Representative ^1H NMR and ^{13}C NMR data for compound **6c**, which verify the structure, are collected in Table 3. Assignments and stereochemistry were confirmed as noted above in the case of compounds **4**.

1,3-Dipolar cycloadditions of azomethine ylides derived from isoquinolinium salt **8** by deprotonation have previously been studied in detail by us.[16] Reaction with suitably active dipolarophiles afford pyrrolo[2,1-*a*]isoquinoline cycloadducts in practically quantitative yield as single diastereoisomers. The cycloaddition of **3a**–**e** with the



Scheme 2 *Reagents and conditions*: AgOAc, Et_3N, toluene, r.t.

Table 2 Reaction Times and Yields of Compounds **6a**–**j**

Entry	R^1	R^2	Nitrochromene	R	R^3	Product	Yield (%)
1	H	H	**3a**	Et	H	**6a**	72
2	H	H	**3a**	Me	$PhCH_2$	**6b**	75
3	H	MeO	**3b**	Et	H	**6c**	60
4	H	MeO	**3b**	Me	$PhCH_2$	**6d**	65
5	H	Cl	**3c**	Et	H	**6e**	70
6	H	Cl	**3c**	Me	$PhCH_2$	**6f**	72
7	MeO	MeO	**3d**	Et	H	**6g**	61
8	MeO	MeO	**3d**	Me	$PhCH_2$	**6h**	62
9	NO_2	H	**3e**	Et	H	**6i**	77
10	NO_2	H	**3e**	Me	$PhCH_2$	**6j**	75
11	H	H	**3a**	Et	H	**6a**	72

Table 3 Selected ^{1}H NMR and ^{13}C NMR Chemical Shifts, H-H Couplings and Measured NOE and HMQC Connectivities for Compound **6c**

	δ_H	$^1H\{^1H\}$ NOE connections	δ_C	HMQC correlations
1	4.12, br s	H-9, H-4, H-3, H-9b, OCH_2, H-3	68.3	H-9b
3	4.94, d[a]	H-4, H-1, Ar^3-2′and 6′H	69.4	Ar^3-2′ and 6′H, H-4
3a	–	–	96.6	H-3, H-4, H-9b
4	5.49, s	Ar^3-2′and 6′H, Ar^4-2′ and 6′H, H-9b	75.2	Ar^4-2′ and 6′H, H-9b
9b	4.79, d[b]	H-9, Ar^3-2′and 6′H, Ar^4-2′and 6′H, H-1	45.6	H-9, H-4, H-1

[a] J = 7.4 Hz.
[b] J = 3.8 Hz.

azomethine ylide derived from isoquinolinium salt **7** at ambient temperature with the exclusion of air gave rise to the formation of cycloadducts **8a**–**c** in virtually quantitative yield as a single diastereoisomer (Scheme 3. Table 4).[17] However, as observed during the early experiments the solution of **8**, in the presence of oxygen, transforms into pyrrole derivative **9** at room temperature in a short period of time.

Table 4 Reaction Times and Yields of Compounds **8a**,**b**,**d**

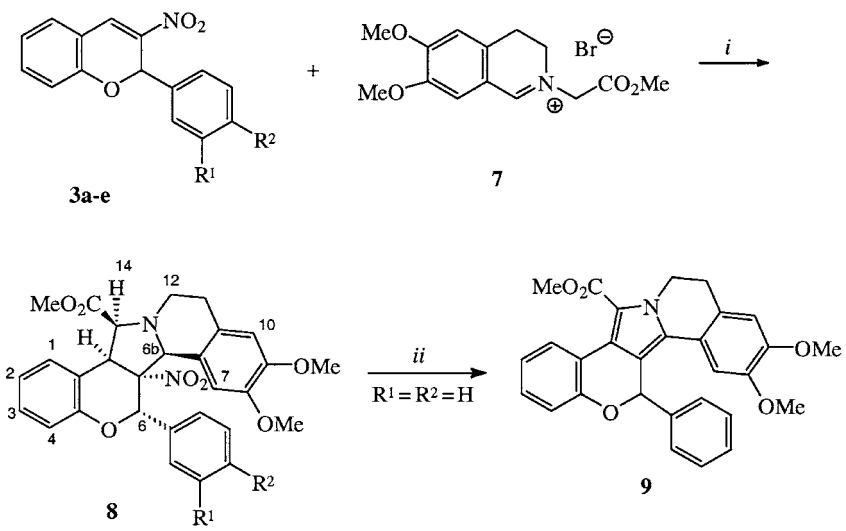
Entry	R^1	R^2	Nitro-chromene	Product	Yield (%)
1	H	H	**3a**	**8a**	92
2	H	MeO	**3b**	**8b**	95
3	MeO	MeO	**3d**	**8d**	93

The structures of compounds **8** were elucidated again by NMR spectroscopy: the ^{1}H-^{1}H NOE experiments proved the *all-cis* relationships of 6-, 6b-, 14-, 14a-protons. The strongly shielded aromatic H-7 proton, probably results as a consequence of the anisotropy of the aromatic ring connected at C-6 exhibiting a chemical shift of δ = 6.10 ppm, further corroborated the proposed structure. Selected NMR data are collected in Table 5.

In summary, the use of 3-nitrochromene derivatives as 2π components in 1,3-dipolar cycloadditions of azomethine ylides allows the assembly of polysubstituted benzopirano[3,4-*c*]-pyrrolidines from simple precursors in one-pot reaction. The further study of other reactive chromene derivatives in these cycloadditions along with the possible conversions of the formed cycloadducts is in progress.

Acknowledgment

This work was financially supported by the *National Fund for Science and Research, Hungary* (OTKA Project No. T 046196). N.M. thanks the *Hungarian Academy of Sciences* for a Bolyai J. fellowship.



Scheme 3 *Reagents and conditions:* i. Et_3N, EtOH, r.t.; ii. O_2, $CDCl_3$, r.t.

Table 5 Selected ^{1}H NMR and ^{13}C NMR Chemical Shifts, H-H Couplings and Measured NOE and HMQC Connectivities for Compound **8b**

	δ_H	$^1H\{^1H\}$ NOE connections[a]	δ_C	HMQC correlations
6	5.77, s	Ar^6-2′ and 6′H, H-7, H-6b, H-14, H-14a	75.8	Ar^6-2′ and 6′H, H-6b
6a	–	–	90.4	H-6b
6b	4.86, s	H-7, H-6, H-14, H-14a, H-12α	65.7	H-7, H-12, H-14
7	6.10, s	H-6, H-6b, 8-OMe	109.8	H-6b
14	4.11, d[a]	–	67.7	H-12, H-14a
14a	4.12, d[a]	–	47.2	H-1, H-14

[a] J = 11.3 Hz.

References

(1) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A.; Pearson, W. H., Eds.; John Wiley and Sons, Inc.: New York, **2002**.

(2) (a) Garner, P.; Ho, W. B.; Grandhee, S. K.; Youngs, W. J.; Kennedy, V. O. *J. Org. Chem.* **1991**, *56*, 5893. (b) Garner, P.; Ho, W. B.; Shin, C. *J. Am. Chem. Soc.* **1993**, *115*, 10742. (c) Monn, J. A.; Valli, M. J. *J. Org. Chem.* **1994**, *59*, 2773. (d) Pham, V. C.; Charlton, J. L. *J. Org. Chem.* **1995**, *60*, 8051. (e) Fiswick, C. W. G.; Foster, R. J.; Carr, R. E. *Tetrahedron Lett.* **1996**, *37*, 3915. (f) Daubié, C.; Mutti, S. *Tetrahedron Lett.* **1996**, *37*, 3915. (g) Selvakumar, N.; Azhagan, A. M.; Srinivas, D.; Krishna, G. G. *Tetrahedron Lett.* **2002**, *43*, 9175. (h) Coldham, I.; Crapnell, K. M.; Fernandez, J.-C.; Moseley, J. D.; Rabot, R. *J. Org. Chem.* **2002**, *67*, 6181. (i) Pandey, G.; Laha, J. K.; Lakshmaiah, G. *Tetrahedron* **2002**, *58*, 3525.

(3) (a) Nyerges, M.; Bitter, I.; Kádas, I.; Tóth, G.; Tőke, L. *Tetrahedron* **1995**, *51*, 11489. (b) Nyerges, M.; Rudas, M.; Szántay, C. Jr.; Bitter, I.; Tőke, L. *Tetrahedron* **1997**, *53*, 3269.

(4) Fejes, I.; Nyerges, M.; Szöllőssy, Á.; Blaskó, G.; Tőke, L. *Tetrahedron* **2001**, *57*, 1129.

(5) (a) Fejes, I.; Nyerges, M.; Tőke, L. *Tetrahedron Lett.* **2000**, *41*, 7951. (b) Nyerges, M.; Fejes, I.; Tőke, L. *Synthesis* **2002**, 1823.

(6) (a) Nyerges, M.; Virányi, A.; Tőke, L. *Heterocycl. Commun.* **2003**, 239. (b) Virányi, A.; Nyerges, M.; Blaskó, G.; Tőke, L. *Synthesis* **2003**, 2655.

(7) Dubuffet, T.; Newman-Tancerdi, A.; Cussac, D.; Audinot, V.; Loutz, A.; Millan, M. J.; Lavielle, G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2059.

(8) (a) Yan, M.-C.; Jang, Y.-J.; Yao, C.-F. *Tetrahedron Lett.* **2001**, *42*, 2717. (b) Yan, M.-C.; Jang, Y.-J.; Kuo, W.-Y.; Tu, Z.; Shen, K.-H.; Cuo, T.-S.; Ueng, C.-H.; Yao, C.-F. *Heterocycles* **2002**, *57*, 1033.

(9) Worral, D. E. *Org. Synth., Coll. Vol. I* **1941**, 413.

(10) (a) Tsuge, O.; Kanemasa, S.; Ohe, M.; Takenaka, S. *Chem. Lett.* **1986**, 973. (b) Tsuge, O.; Kanemasa, S.; Ohe, M.; Takenaka, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4079. (c) Nyerges, M.; Balázs, L.; Bitter, I.; Kádas, I.; Kövesdi, I.; Tőke, L. *Tetrahedron* **1995**, *51*, 6783. (d) Joucla, M.; Mortier, J. *Bull. Soc. Chim. Fr.* **1988**, 579.

(11) **General Procedure:** A mixture of sarcosine (2.5 equiv) or *N*-benzyl-glycine (2.5 equiv), paraformaldehyde (6 equiv), and the corresponding 3-nitrochromene derivatives (**3a**–**e,** 1 equiv) was heated under reflux in toluene (10 mL for 1 mmol of dipolarophile). The water formed was removed by the aid of a Dean–Stark trap. After completion of the reaction (judged by TLC) the reaction mixture was filtered through a pad of Celite and the solvent was evaporated in vacuo. The residue crystallized from Et_2O to give **4a**–**j**. The reaction times and yields (based on the dipolarophiles) are summarized in Table 1. All new compounds afforded correct elemental analyses and spectroscopic data, for example:
2-Methyl-3a-nitro-4-phenyl-benzopirano[3,4-*c*]-pyrrolidine (4a): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.44 (5 H, m, Ph-H), 7.23 (2 H, m, Ar-H), 7.04 (2 H, m, Ar-H), 5.01 (1 H, s, H-4), 4.03 (1 H, t, J = 8.5 Hz, H-9*b*), 3.62 (1 H, d, J = 11.4 Hz, H-3), 3.50 (1 H, t, J = 8.5 Hz, H-1), 2.85 (1 H, d, J = 11.4 Hz, H-3), 2.71 (1 H, t, J = 8.5 Hz, H-1), 2.41 (3 H, s, *N*Me). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 154.0 (q, C-5*a*), 134.0 (Ph-1′C), 129.4 (CH, C-7), 128.5 (2 × CH, Ph-2′ and 6′C), 128.3 (CH, C-9), 127.8 (CH, Ph-4′C), 126.8 (2 × CH, Ph-3′ and 5′C), 122.6 (q, C-9*a*), 122.5 (CH, C-8), 117.6 (CH, C-6), 95.9 (q, C-3*a*), 80.1 (CH, C-4), 62.8 (CH_2), 61.8 (CH_2), 43.3 (CH, H-9*b*), 41.3 (NCH_3). IR (KBr): 2976, 2947, 2823, 1535, 1489, 1479, 1452, 1371, 1254, 1238, 1149, 1045, 1024 cm^{-1}.
2-Benzyl-4-(4-chlorophenyl)-3a-nitro-benzopirano[3,4-*c*]-pyrrolidine (4f): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.37–7.23 (8 H, m, Ar-H), 7.21 (1 H, t, J = 7.5 Hz, H-7), 7.16 (2 H, d, J = 8.5 Hz, Ar^4-3′ and 5′H), 7.02 (1 H, t, J = 7.5 Hz, H-8), 7.00 (1 H, d, J = 7.5 Hz, H-6), 5.03 (1 H, s, H-4), 3.97 (1 H, t, J = 8.4 Hz, H-9*b*), 3.71 (1 H, d, J = 12.9 Hz, CH_2Ph), 3.57 (1 H, d, J = 12.9 Hz, CH_2Ph), 3.46 (1 H, t, J = 8.4 Hz, H-1), 3.41 (1 H, d, J = 11.4 Hz, H-3), 2.87 (1 H, d, J = 11.4 Hz, H-3), 2.86 (1 H, t, J = 8.4 Hz, H-1). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 154.0 (q, C-5*a*), 137.6 (Bn-1′C), 135.5 (q, Ar^4-4′C), 132.8 (q, Ar^4-1′C), 128.9 (2 × CH), 128.8 (2 × CH), 128.7 (2 × CH), 128.4 (2 × CH), 128.1 (CH, C-9), 127.8 (Bn-4′C), 123.1 (CH, C-8), 122.9 (q, C-9*a*), 117.8 (CH, C-6), 94.9 (q, C-3*a*), 79.6 (CH, C-4), 60.7 (CH_2), 59.2 (CH_2), 59.1 (CH_2), 42.6 (CH, H-9*b*). IR (KBr): 3061, 3025, 2968, 2920, 2824, 1537, 1490, 1455, 1380, 1260, 1233, 1210, 1153, 1092, 1057, 1014 cm^{-1}.

(12) Grigg, R.; Gunaratne, H. Q. N.; Sridharan, V.; Thianpatanagul, S. *Tetrahedron Lett.* **1983**, *24*, 4363.

(13) Grigg, R.; Kemp, J. *Tetrahedron Lett.* **1980**, *21*, 2461.

(14) (a) Tsuge, O.; Kanemasa, S.; Yoshioka, M. J. *J. Org. Chem.* **1988**, *53*, 1384. (b) Nyerges, M.; Rudas, M.; Tóth, G.; Herényi, B.; Bitter, I.; Tőke, L. *Tetrahedron* **1995**, *51*, 13321. (c) Kanemasa, S. *Synlett* **2002**, 1371. (d) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400.

(15) **General Procedure:** The corresponding 3-nitrochromene derivatives (**3a**–**e**, 10 mmol) were dissolved in dry toluene (50 mL) and ethyl (4-chlorobenzylideneamino)acetate (2.47 g, 11 mmol) or methyl 2-(4-chlorobenzylideneamino)-3-phenyl-propionate (3.32 g, 11 mmol), silver acetate (2.50 g, 15 mmol), and Et_3N (1.11 g, 1.6 mL, 11 mmol) was added. The reaction mixture was stirred at r.t. for 12 h. After the completion of the reaction (judged by TLC) aq NH_4Cl solution (25 mL) was added to the reaction mixture and this was washed with H_2O (2 × 20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, evaporated and the residue was trituated with Et_2O. The crystallized product was collected to yield a white powder, which could be recrystallized from EtOH to give **6a**–**j**. The reaction times and yields (based on the dipolarophiles) are summarized in Table 2. Selected data for representative examples:

Ethyl 3-(4-chlorophenyl)-3a-nitro-4-phenyl-benzopirano[3,4-*c*]-pyrrolidine-1-carboxylate (6a): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.51 (d, 1 H, *J* = 7.6 Hz, H-9), 7.35 (2 H, d, *J* = 8.7 Hz, Ar^3-3′ and 5′H), 7.27 (2 H, d, *J* = 8.7 Hz, Ar^3-2′ and 6′H), 7.12 (7 H, m, Ar-H), 6.77 (d, 1 H, *J* = 7.5 Hz, H-6), 5.48 (1 H, s, H-4), 4.88 (1 H, br m, H-3), 4.74 (1 H, d, *J* = 3.6 Hz, H-9*b*), 4.43 (2 H, q, *J* = 7.1 Hz, *O*CH_2), 4.05 (1 H, br s, H-1), 2.99 (1 H, br s, H-2), 1.41 (3 H, t, *J* = 7.1 Hz, CH_2CH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 171.8 (q, C=O), 149.7 (q, C-5*a*), 135.4 (q, Ar^3-4′C), 134.7 (q, Ar^3-1′C), 129.1 (2 × CH, Ar^3-2′ and 6′C), 129.0 (CH, C-7), 128.9 (CH, C-9), 128.8 (CH, Ar^4-1′C), 128.5 (2 × CH, Ar^3-3′ and 5′C), 128.4 (q, C-9*a*), 128.3 (2 × CH, Ar^4-2′ and 6′C), 128.2 (2 × CH, Ar^4-3′ and 5′C), 124.8 (CH, Ar^4-4′C), 123.2 (CH, C-8), 118.2 (CH, C-6), 96.4 (q, C-3*a*), 75.5 (CH, C-4), 69.4 (CH, C-3), 68.3 (CH, C-1), 62.2 (CH_2), 45.6 (CH, H-9*b*), 14.3 (CH_3). IR (KBr): 3334, 2979, 1733, 1586, 1540, 1487, 1453, 1368, 1298, 1228, 1212, 1114, 1094, 1015 cm^{-1}.

Methyl 1-benzyl-3,4-*bis*-(4-chlorophenyl)-3a-nitro-benzopirano[3,4-*c*]-pyrrolidine-1-carboxylate (6f): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.76 (1 H, dd, *J* = 1.7 and 7.8 Hz, H-9), 7.35 (2 H, d, *J* = 8.6 Hz, Ar^3-3′ and 5′H), 7.27 (2 H, d, *J* = 8.6 Hz, Ar^3-2′ and 6′H), 7.15 (4 H, m, Bn-H and H-7), 7.14 (2 H, d, *J* = 8.5 Hz, Ar^4-3′ and 5′H), 7.10 (1 H, dt, *J* = 1.7 and 7.8 Hz, H-8), 7.05 (2 H, d, *J* = 8.5 Hz, Ar^4-2′ and 6′H), 6.96 (2 H, m, Bn-H), 6.76 (1 H, dd, *J* = 1.7 and 7.8 Hz, H-6), 5.55 (1 H, s, H-4), 5.10 (1 H, s, H-9*b*), 5.09 (1 H, d, *J* = 7.8 Hz, H-3), 3.78 (3 H, s, *O*Me), 2.94 (1 H, br d, *J* = 7.8 Hz, H-2), 2.81 (1 H, d, *J* = 13.7 Hz, α-CH_2), 2.37 (1 H, d, *J* = 13.7 Hz, β-CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.4 (q, C=O), 152.1 (q, C-5*a*), 136.0 (q, Bn-1′C), 135.4 (q, Ar^3-4′C), 134.9 (q, Ar^4-4′C), 133.3 (q, Ar^3-1′C), 132.9 (q, Ar^4-1′C), 130.6 (CH, C-9), 129.9 (2 × CH, Bn-2′ and 6′C), 129.6 (2 × CH, Ar^4-2′ and 6′C), 129.3 (CH, C-7), 129.2 (2 × CH, Ar^3-3′ and 5′C), 128.5 (2 × CH, Bn-3′ and 5′C), 128.3 (2 × CH, Ar^4-3′ and 5′C), 128.1 (2 × CH, Ar^3-2′ and 6′C), 127.0 (CH, Bn-4′C), 123.1 (CH, C-8), 122.2 (q, C-9*a*), 118.7 (CH, C-6), 98.5 (q, C-3*a*), 77.0 (CH, C-4), 72.2 (q, C-1), 67.4 (CH, C-3), 52.7 (*O*CH_3), 49.8 (CH, C-9*b*), 42.2 (CH_2). IR (KBr): 3341, 3031, 1751, 1601, 1542, 1491, 1456, 1436, 1239, 1208, 1130, 1111, 1096, 1079, 1042, 1014, 1006 cm^{-1}.

(16) (a) Bende, Z.; Simon, K.; Tóth, G.; Tőke, L.; Weber, L. *Liebigs Ann. Chem.* **1982**, 924. (b) Bende, Z.; Bitter, I.; Tőke, L.; Weber, L.; Tóth, G.; Janke, F. *Liebigs Ann. Chem.* **1982**, 2146. (c) Bende, Z.; Tőke, L.; Weber, L.; Tóth, G.; Janke, F.; Csonka, G. *Tetrahedron* **1983**, *40*, 369. (d) Tóth, G.; Tischer, T.; Bende, Z.; Szejtli, G.; Tőke, L. *Monatsh. Chem.* **1990**, *121*, 529. (e) Janke, F.; Himmelreich, U.; Tóth, G.; Tischer, T.; Bende, Z.; Tőke, L. *J. Heterocycl. Chem.* **1991**, *28*, 867. (f) Fejes, I.; Nyerges, M.; Tőke, L.; Pak, C. S. *Tetrahedron* **2000**, *56*, 639.

(17) **General Procedure for the Preparation of Compounds 8:** The corresponding 3-nitrochromene (**3**, 0.80 mmol) and 6,7-dimethoxy-(2-methoxycarbonylmethyl)-3,4-dihydro-isoquinolinium bromide (0.29 g, 0.85 mmol) was dissolved in dry MeOH (10 mL) and Et_3N (0.14 mL, 0.10 g, 1.00 mmol) was added under argon atmosphere. The reaction mixture was stirred at r.t. for 24 h. The solvent was removed in vacuo, the residue was suspended in Et_2O (20 mL). The ethereal solution was washed with H_2O (10 mL) and brine (5 mL), dried over $MgSO_4$ and evaporated in vacuo to yield a white solid, which was recrystallized from EtOH to give **8a**,**b**,d. The reaction times and yields are summarized in Table 4. Selected data for representative example:

Methyl 8,9-dimethoxy-6a-nitro-6-(4-methoxyphenyl)-6a,6b,11,12,14,14a-hexahydro-6*H*-chromeno[3′,*4*′:3,4]pyrrolidino[2,1-*a*]isoquinoline-14-carboxylate (8b): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.18 (1 H, t, *J* = 7.5 Hz, H-3), 7.06 (1 H, d, *J* = 7.5 Hz, H-1), 6.93 (1 H, d, *J* = 7.5 Hz, H-4), 6.90 (1 H, t, *J* = 7.5 Hz, H-2), 6.85 (2 H, d, *J* = 8.2 Hz, Ar^6-2′ and 6′H), 6.51 (1 H, s, H-10), 6.46 (2 H, d, *J* = 8.2 Hz, Ar^6-3′ and 5′H), 6.10 (1 H, s, H-7), 5.77 (1 H, s, H-6), 4.86 (1 H, s, H-6*b*), 4.12 (1 H, d, *J* = 11.3 Hz, H-14*a*), 4.11 (1 H, d, *J* = 11.3 Hz, H-14), 3.83 (3 H, s, *O*Me), 3.70 (3 H, s, *O*Me), 3.36 (3 H, s, *O*Me), 3.32 (3 H, s, *O*Me), 3.18 (1 H, m, H-11), 3.01 (1 H, m, H-12), 2.70 (1 H, m, H-12), 2.62 (1 H, m, H-11). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.4 (q, C=O), 159.6 (q, Ar^6-4′C), 153.6 (q, C-4*a*), 147.8 (q, C-9), 146.7 (q, C-8), 129.9 (2 × CH, Ar^6-2′ and 6′C), 129.4 (CH, C-1), 128.8 (CH, C-3), 128.0 (q, Ar^6-1′C), 127.5 (q, C-10*a*), 127.4 (C-14*b*), 123.4 (C-6*c*), 120.5 (CH, C-2), 116.2 (CH, C-4), 113.2 (C-10), 112.9 (2 × CH, Ar^6-3′ and 5′C), 109.8 (CH, C-7), 90.4 (q, C-6*a*), 75.8 (CH, C-6), 67.7 (CH, C-14), 65.7 (C-6*b*), 55.8 (*O*Me), 55.2 (*O*Me), 54.6 (*O*Me), 51.7 (*O*Me), 47.2 (CH, C-14*a*), 46.8 (C-12), 29.7 (C-11). IR (KBr): 2990, 2945, 2913, 2835, 1749, 1612, 1585, 1552, 1519, 1490, 1459, 1437, 1353, 1249, 1212, 1193, 1150, 1117, 1076, 1042, 1021 cm^{-1}.