Synthesis of azoxabicyclo[3.3.1]nonanones based on diastereoselective reactions of 1,1-bis(trimethylsilyloxy)ketene acetals with isoquinolines and quinolines†

Andreas Schmidt,[a] Dirk Michalik,*[b] Sven Rotzoll,[a,b] Ehsan Ullah,[a,b] Christine Fischer,[b] Helmut Reinke,[a] Helmar Görls[c] and Peter Langer*[a,b]

Received 10th March 2008, Accepted 9th May 2008
First published as an Advance Article on the web 12th June 2008
DOI: 10.1039/b804139c

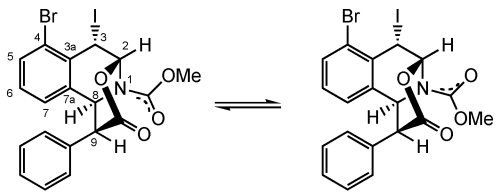
Densely functionalized azoxabicyclo[3.3.1]nonanones were prepared by regio- and diastereoselective condensation of 1,1-bis(silyloxy)ketene acetals with isoquinolinium and quinolinium salts and subsequent regioselective and stereospecific iodolactonization.

Introduction

1,1-Bis(trimethylsilyloxy)ketene acetals can be regarded as masked carboxylic acid dianions and represent useful 1,3-dinucleophilic building blocks in cyclization reactions.[1–3] Rudler *et al.* have reported the synthesis of lactones based on reactions of 1,1-bis(trimethylsilyloxy)ketene acetals with chromium(0) complexes,[4] allyl acetates,[5] and tropylium ions.[6] We have reported the cyclocondensation of 1,1-bis(trimethylsiloxy)ketene acetals with oxalyl chloride[7] and 3-(siloxy)alk-2-en-1-ones, respectively.[8] Iminium salts represent important synthetic building blocks.[9,10] The cyclization of iminium salts with bis(silyl enol ethers) has been recently reviewed.[11] Rudler *et al.* have reported the reaction of 1,1-bis(trimethylsiloxy)ketene acetals with pyridine[12a] and related N-heterocycles.[12b] Cyclizations of 1,1-bis(trimethylsiloxy)ketene acetals with pyrazine and quinoxaline were reported by Rudler[12b] and by us.[13] The cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-dienes (masked 1,3-dicarbonyl dianions)[14] with isoquinoline,[15] quinoxaline,[16] and quinazoline[17] provide a convenient approach to various bridged N-heterocycles. Recently, we reported the synthesis of 7,8-benzo-9-aza-4-oxabicyclo[3.3.1]nonan-3-ones based on the cyclocondensation of isoquinolinium salts with 1,1-bis(trimethylsiloxy)ketene acetals.[18] Herein, we report full details of these studies and address questions related to the stereochemistry of the reactions. In addition, the reaction of 1,1-bis(trimethylsiloxy)ketene acetals with quinoline activated by methyl chloroformate is reported.

Results and discussion

1,1-Bis(trimethylsilyloxy)ketene acetals **2** were prepared in two steps from the corresponding carboxylic acids in analogy to known procedures.[7,19] The reaction of alkyl-substituted 1,1-bis(trimethylsilyloxy)ketene acetals **2a–d** with isoquinoline (**1a**) in the presence of methyl chloroformate afforded the condensation products **3a–d** (Scheme 1, Table 1). Treatment of **3a–d** with iodine in the presence of sodium bicarbonate (iodolactonization) afforded the 7,8-benzo-9-aza-4-oxabicyclo[3.3.1]nonan-3-ones **4a–d**. The reaction of **1a** with aryl-substituted 1,1-bis(trimethylsilyloxy)ketene acetals **2e–h** gave the condensation products **3e–h** which were transformed into **4e–g**. The transformation of **3h** into **4h** (R^1 = 4-(MeO)C_6H_4) was unexpectedly not successful. 7,8-Benzo-9-aza-4-oxabicyclo[3.3.1]nonan-3-ones **4i–k** were prepared from 5-bromoisoquinoline (**1b**). Notably, the formation of all condensation products **3a–k** proceeded with very good diastereoselectivity. In most cases, the *syn*-configured diastereomer was formed. The *anti*-diastereomer was formed in the case of **4c** and **4e**. Although the reason for the different diastereoselectivity remains unclear at present, the results show that stereochemical issues of the reactions reported herein have to be treated with great care. In fact, different diastereoselectivities were observed for similar types of substituents and substrates. Minor changes of the reaction conditions may also play a role. It is noteworthy that the iodolactonization of (diastereomerically pure) acids **3a–k** proceeded, as expected, with excellent *trans*-stereospecificity and afforded products **4a–k** as diastereomerically pure racemic material.



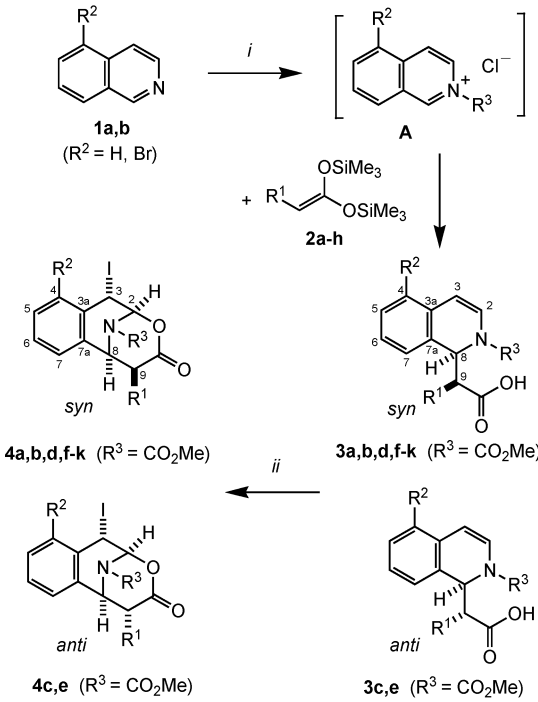
Scheme 1 Rotamers of compound **4k**.

The structure of all products was established by spectroscopic methods. The ^{1}H and ^{13}C NMR spectra of compounds **3** and **4** are largely dominated by the hindered rotation about the N–CO bond of the carbamate moiety which gives rise to the existence of two rotamers: I (major) and II (minor) (Scheme 1). Hence,

[a]*Institut für Chemie, Universität Rostock, Albert-Einstein-Str., 3a, 18059, Rostock, Germany. E-mail: peter.langer@uni-rostock.de; Fax: +49 381 49864112; Tel: +49 381 4986410*
[b]*Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Str., 29a, 18059, Rostock, Germany*
[c]*Institut für Anorganische und Analytische Chemie, Universität Jena, August-Bebel-Str. 2, 07740, Jena, Germany*

† Electronic supplementary information (ESI) available: For crystallographic data in CIF or other electronic format. See DOI: 10.1039/b804139c

Table 1 Synthesis of **4a–k**

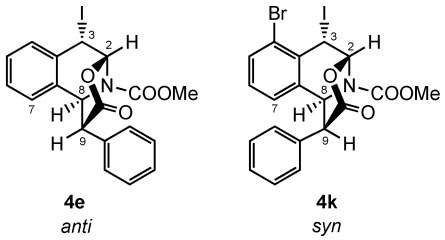


1	2	3,4	R^1	R^2	3 (%)[a]	4 (%)[a]
a	**a**	**a**	Me	H	56	46
a	**b**	**b**	Et	H	62	61
a	**c**	**c**	*n*Bu	H	65	70
a	**d**	**d**	*n*Oct	H	60	67
a	**e**	**e**	Ph	H	47	65
a	**f**	**f**	4-MeC_6H_4	H	54	64
a	**g**	**g**	4-ClC_6H_4	H	83	72
a	**h**	**h**	4-$(MeO)C_6H_4$	H	75	0
b	**c**	**i**	*n*Bu	Br	36	73
b	**d**	**j**	*n*Oct	Br	54	67
b	**e**	**k**	Ph	Br	36	53

[a] Yields of isolated products.

some signals appear at room temperature as broadened or doubled signals. Fig. 1 shows the influence of the temperature on the ^{1}H NMR spectrum of compound **4k**. At 243 K two sets of signals and at 300 K only one set of signals are observed. The NMR signals of **3** and **4** were assigned by DEPT and two-dimensional ^{1}H,^{1}H COSY, ^{1}H,^{1}H NOESY and ^{1}H,^{13}C correlation spectra (HSQC, HETCOR, HMBC). For example, in the HMBC spectrum of **4c** cross-peaks are observed between C-3 and H-4, between C-8 and H-7, and between C–CO_2Me and H-2, H-8, H-9 and H-10, which confirm the assignment of the signals and the given structures.

The stereochemistry of compounds **4** was established based on the analysis of anisotropic effects and coupling constants of the ^{1}H NMR spectra and based on the results of ^{1}H,^{1}H NOESY measurements. From the NMR data of **4c** and **4e** it can be concluded that the butyl and the phenyl group (located at carbon C-9), respectively, are in the spatial vicinity of the N–CO_2Me moiety (*anti* position). In contrast, the alkyl or aryl substituent of derivatives **4a,b,d,f–k** is spatially close to the aromatic proton H-7, which leads to the assumption that a *syn* configuration is present (Scheme 2).



Scheme 2 The *anti* and *syn* structures of compounds **4e** and **4k**.

The ^{1}H and ^{13}C NMR spectra of **4c** and **4e** are very similar. For example, a signal splitting is observed at ambient temperature, while in the spectra of the other derivatives **4** only a broadening of the respective signals is observed. The *anti* configuration of **4c** was also proved by NOE correlations between MeO and $Me_{(13)}$ of rotamer II. For the MeO group of compound **4e**, high-field proton chemical shifts and a relatively large difference between the respective signals of rotamers I and II ($\Delta\delta$ = 0.50 ppm) is observed compared to the MeO signals of compound **4k** ($\Delta\delta$ = 0.04 ppm). This finding can be explained by the anisotropic effect of the phenyl group which is located in the spatial vicinity of the N–CO_2Me moiety of **4e**. In addition, the coupling constants of the vicinal coupling of protons H-8 and H-9, which could be determined for compounds **4c**, **4e** ($^3J_{8,9}$ = 1.0 Hz) and **4k** ($^3J_{8,9}$ = 5.7 Hz), indicate a different configuration at carbon atom C-9 of these compounds.

In contrast to **4c** and **4e**, the alkyl and aryl groups of all other compounds **4** are spatially located close to the aromatic proton H-7 (*syn* configuration). In the case of the aryl-substituted compounds **4f**, **4g** and **4k**, the vicinity of the aryl group and proton H-7 is also supported by a characteristic high-field shift of proton H-7, which can be explained by its location in the anisotropic cone of the phenyl ring. Thus, no or only small shift differences are observed for the MeO signals of the two rotamers, due to the absence of the anisotropic effect of the phenyl ring. The configuration at C-3 could be also confirmed by inspection of the NOESY spectra. For **4c** and **4e**, correlations were observed for H-3 and H-4, which proves that the iodine atom is located *cis* to the nitrogen. It should be noted that in the phase-sensitive NOESY spectra, besides the NOE correlations, EXSY signals are also displayed. For example, in the case of **4c** and **4e**, EXSY signals for protons H-$2_{(I)}$ and H-$2_{(II)}$, H-$8_{(I)}$ and H-$8_{(II)}$, and $MeO_{(I)}$ and $MeO_{(II)}$ (**4e**) independently support the dynamic process operating in these compounds as already mentioned above for **4k** (Fig. 1).

Quinolines

The methyl chloroformate-mediated reaction of quinoline (**5**) with 1,1-bis(trimethylsilyloxy)ketene acetals **2i** (R^1 = *n*Pr) afforded the condensation product **7a** as a 1 : 1 mixture of diastereomers (Scheme 3, Table 2). Notably, **7a** was formed with very good regioselectivity (by attack of **2i** onto carbon atom C-2 of the quinolinium salt). A diastereomerically pure sample of *syn*-**7a** could be separated by crystallization and characterized by X-ray crystal structure analysis (Fig. 2). The reaction of **7a** with iodine and sodium bicarbonate afforded **8a** by iodolactonization (dr = 1 : 1). The reaction of **5** with **2d** (R^1 = *n*Oct) afforded diastereomerically pure *anti*-**7b** and *syn*-**7b** in 46 and 17% yields, respectively (Scheme 3, Table 2). The iodolactonization of *anti*-**7b**

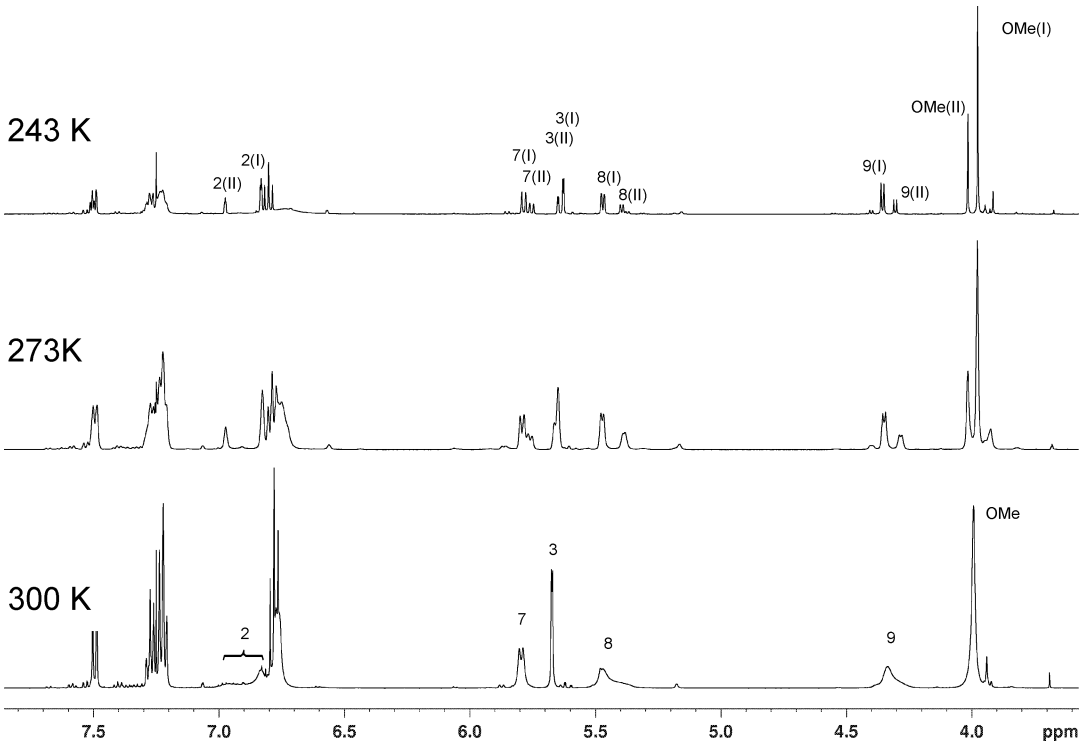
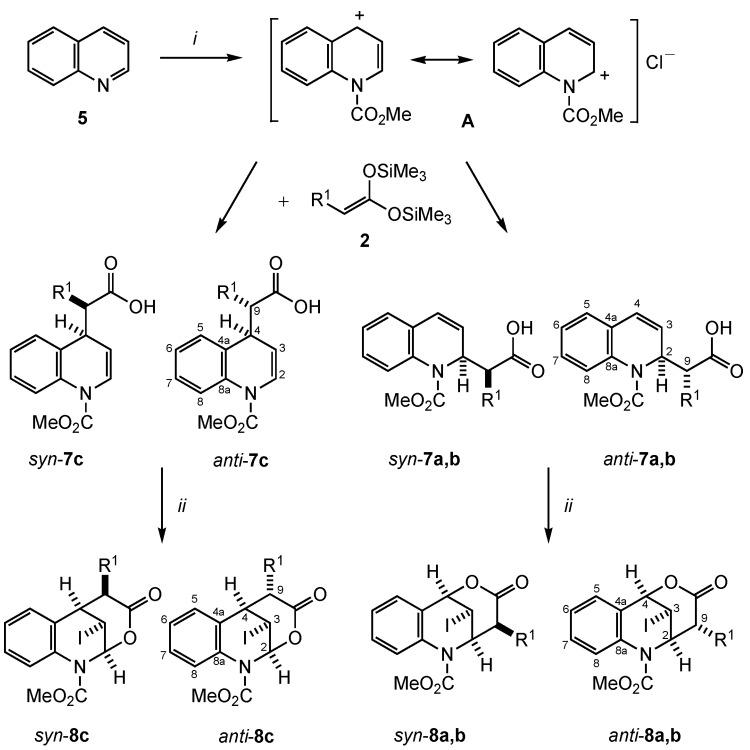


Fig. 1 ^{1}H NMR spectra of **4k** recorded at 300 K, 273 K and 243 K ($CDCl_3$, 500 MHz).



Scheme 3 Cyclization of 1,1-bis(trimethylsilyloxy)ketene acetals **2d,e,I** with **5**. *Reagents and conditions*: *i*, **5** (1.0 equiv.), **2** (2.0 equiv.), $ClCO_2Me$ (1.2 equiv.), CH_2Cl_2, 0 °C, 2 h, 20 °C, 12 h; *ii*, I_2 (2.0 equiv.), CH_2Cl_2, $NaHCO_3$, H_2O, 20 °C, 12 h (the atom numbers refer to the NMR assignments; see Experimental section).

Table 2 Synthesis of **8a–c**

Entry	R^1	**7** (%)[a]	*syn*/*anti*	**8** (%)[a]	*syn*/*anti*
a	*n*Pr	38	1 : 1[b]	86	1 : 1
b	*n*Oct	46	2 : 98	52	2 : 98
		17	98 : 2	—[c]	—
c	Ph	56	1 : 1.2[d]	50	1 : 1[e]

[a] Yields of isolated products. [b] A sample of diastereomerically pure *syn*-**7a** could be separated. [c] Experiment was not carried out. [d] Assignment arbitrary. [e] A sample of diastereomerically pure *anti*-**8c** could be separated.

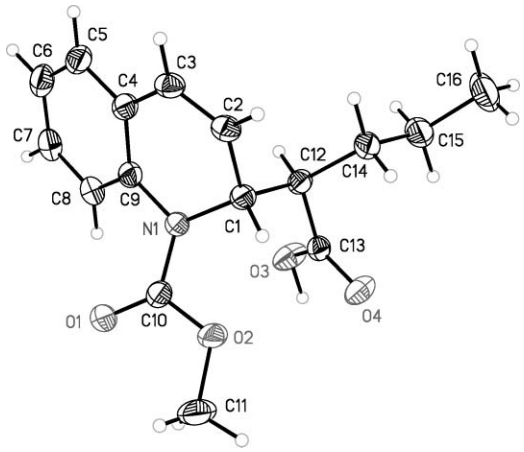


Fig. 2 Ortep plot of *syn*-**7a** (CCDC 680062).†

afforded diastereomerically pure *anti*-**8b**. The reaction of **5** with **2e** (R^1 = Ph) gave **7c** as a mixture of diastereomers. Product **7c** was again formed with very good regioselectivity. However, the attack of **2c** onto the quinoline moiety occurred at carbon C-4 rather than C-2. The iodolactonization of **7c** afforded **8c** as a mixture of diastereomers. A diastereomerically pure sample of *anti*-**8c** could be separated by repeated chromatography.

The *syn*/*anti* assignment of compounds **7** and **8** is based on NMR results and on the X-ray crystal structure analysis of *syn*-**7a** (Fig. 2 and 3).† Isomers *syn*-**7b** and *anti*-**7b** could not be unambiguously assigned by simple comparison of the NMR data with those of **7a**. However, an assignment proved to be possible by transformation of *anti*-**7b** into *anti*-**8b** as the stereochemistry of the latter could be unambiguously established by NMR. In the NOESY spectrum of **8b** correlations are found between proton H-3 and protons H-2, H-4 and H-10b, but not between H-3 and H-9. Likewise, the *anti* configuration of **8c** was established: in the NOESY spectrum of **8c** correlations were observed between proton H-3 and protons H-2, H-4 and H-*ortho*, but not between H-3 and H-9. In the case of compounds **7c** and **8a**, the diastereomers could not be unambiguously assigned.

Rudler and coworkers have previously reported the reaction of quinoline with 2,2-dimethyl-1,1-bis(trimethylsilyloxy)ethene.[12b] The attack of the nucleophile occurred at carbon atom C-4 of quinoline activated by methyl chloroformate. Due to the use of a symmetrical bis(silyloxy)ketene acetal, no issue of diastereoselectivity arose.

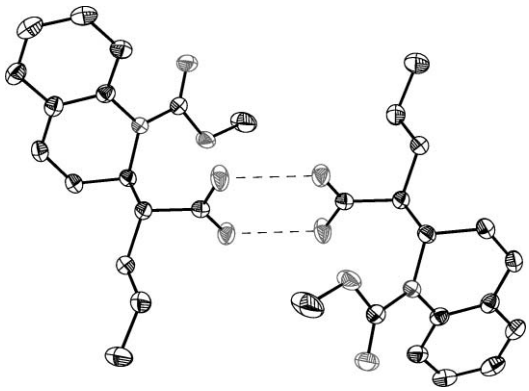


Fig. 3 Dimeric structure of *syn*-**7a**.

Conclusions

In conclusion, a number of densely functionalized azoxabicyclo[3.3.1]nonanones were prepared by condensation of 1,1-bis(silyloxy)ketene acetals with isoquinolinium and quinolinium salts and subsequent iodolactonization. The structures of the complex products, which show a dynamic behaviour, were thoroughly elucidated by NMR spectroscopy. The diastereoselectivity of the reaction of isoquinoline with 1,1-bis(silyloxy)ketene acetals depends on the substituents of the latter. However, a clear trend was not observed. The regioselectivity of the attack of 1,1-bis(silyloxy)ketene acetals onto quinoline again depends on the substituents. C-4 regioselectivity was observed for aryl-substituted and 2,2-disubstituted 1,1-bis(silyloxy)ketene acetals. In contrast, the reaction of alkyl-substituted 1,1-bis(silyloxy)ketene acetals with quinoline occurs at carbon atom C-2 of the latter.

Experimental

General

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^{1}H and ^{13}C NMR, the deuterated solvents indicated were used. The ^{1}H NMR (250.13 and 300.13 MHz) and ^{13}C NMR (62.9 and 75.5 MHz) were recorded on Bruker spectrometers AC 250 and ARX 300, respectively, at 300 K. In addition to the routine measurements, selected NMR spectra were recorded on a Bruker spectrometer AVANCE 500 (^{1}H: 500.13 MHz and ^{13}C: 125.8 MHz) at 300 K (**4k** also at lower temperatures), which is indicated in the NMR data. Calibration of spectra was carried out using the solvent signals ($CDCl_3$: δ ^{1}H = 7.25, δ ^{13}C = 77.0; DMSO-d_6: δ ^{1}H = 2.50, δ ^{13}C = 39.7). The NMR signals were assigned by DEPT and two-dimensional ^{1}H,^{1}H COSY, ^{1}H,^{1}H NOESY and ^{1}H,^{13}C correlation spectra (HSQC, HETCOR, HMBC). For assignment of NMR signals the atoms are numbered according to Schemes 1 and 3. The numbering of atoms of the aliphatic residues R^1 follows the carbon chain starting from 10. Atoms of R^1 = aryl are given corresponding to *i*-, *o*-, *m*-, *p*-nomenclature. Mass spectrometry (MS) data were obtained by using the electron ionization (70 eV), chemical ionization (CI, H_2O), or electrospray (ESI) techniques. For preparative scale chromatography, silica gel (60–200 mesh) was used.

Typical procedure for the synthesis of 1*H*-isoquinoline-2-carboxylic acids 3

To a CH_2Cl_2 solution (20 mL) of isoquinoline (0.250 g, 1.90 mmol) was added 1,1-bis(trimethylsilyloxy)hex-1-ene (1.00 g, 3.80 mmol) and methyl chloroformate (0.218 g, 2.30 mmol) at 0 °C. The solution was stirred for 2 h at 0 °C and for 12 h at 20 °C. A saturated aqueous solution of ammonium chloride (20 mL) was added and the organic and the aqueous layers were separated. The latter was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography (silica gel, hexane → hexane–EtOAc = 2 : 1) to give **3c** as a slightly brownish solid (0.384 g, 65%). Due to the restricted rotation of the carbamate moiety, many compounds **3** exist as racemic mixtures of two rotamers (doubled or broadened signals).

Methyl 1-(1-carboxyethyl)-1*H*-isoquinoline-2-carboxylate (3a). Starting with isoquinoline (**1a**) (0.250 g, 1.93 mmol), **2a** (0.632 g, 2.90 mmol) and methyl chloroformate (0.363 g, 3.87 mmol), **3a** (0.283 g, 56%) was isolated as a colourless solid; mp. 126 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.26–7.06 (m, 4H, ArH); 6.96, 6.80 (2 'd', 1H, $^3J_{2,3}$ = 7.6 Hz, H-2); 5.98, 5.89 (2 d, 1H, $^3J_{2,3}$ = 7.6 Hz, H-3); 5.71, 5.58 (2 'd', 1H, $^3J_{8,9}$ = 8.2 Hz, H-8); 3.79 (s, 3H, OMe); 2.83 (m, 1H, H-9); 1.19, 1.16 (2 d, 3H, ^3J = 6.0 Hz, Me). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 179.5, 179.3 (COOH); 154.1, 154.0 (NCO); 130.6, 130.5, 130.4, 130.3 (C-Ar); 128.2, 128.1, 127.1, 127.0, 126.8, 126.5, 125.2, 124.9, 124.8, 124.5 (CH-Ar, C-2); 110.4, 110.1 (C-3); 57.0, 56.6 (C-8); 53.6, 53.1 (OMe); 45.3, 44.9 (C-9); 13.7, 13.5 (Me). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3414 (s), 2959 (s), 1712 (s), 1686 (m), 1603 (w), 1453 (s), 1340 (m), 775 (m). MS (EI; 70 eV) *m*/*z* (%) = 262.4 ([M + 1]$^+$, 12), 203 (40), 188 (58), 129 (100), 102 (61), 75 (13). HRMS (EI): calcd for $C_{14}H_{16}NO_4$ ([M + 1]$^+$): 262.1074; found: 262.1094.

Methyl 1-(1-carboxypropyl)-1*H*-isoquinoline-2-carboxylate (3b). Starting with isoquinoline (**1a**) (0.250 g, 1.93 mmol), **2b** (0.903 g, 3.87 mmol) and methyl chloroformate (0.363 g, 3.87 mmol), **3b** (0.330 g, 62%) was isolated as a slightly brownish solid; mp. 102–103 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.23–7.05 (m, 4H, ArH); 6.94, 6.78 (2 dd, 1H, $^3J_{2,3}$ = 7.6 Hz, $^4J_{2,8}$ = 1.0 Hz, H-2); 6.01, 5.90 (2 d, 1H, $^3J_{2,3}$ = 7.6 Hz, H-3); 5.67, 5.53 (2 dd, 1H, $^3J_{8,9}$ = 8.5 Hz, $^4J_{2,8}$ = 1.0 Hz, H-8); 3.80 (s, 3H, OMe); 2.70 (m, 1H, H-9); 1.85–1.45 (m, 2H, CH_2); 0.87 (t, 3H, ^3J = 7.4 Hz, Me). ^{13}C NMR (76 MHz, $CDCl_3$): δ = 179.1, 179.0 (COOH); 154.2, 153.9 (NCO); 130.5, 130.4, 130.3, 130.2 (C-Ar); 128.2, 128.1, 127.1, 127.0, 126.6, 126.3, 125.0 (2), 124.8, 124.4 (CH-Ar, C-2); 110.7, 110.4 (C-3); 56.9, 56.3 (C-8); 53.5, 53.2 (OMe); 52.4, 52.2 (C-9); 21.7, 21.6 (CH_2); 11.8 (2) (Me). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3443 (m), 3282 (m), 2964 (m), 1728 (s), 1684 (s), 1636 (m), 1458 (s), 1363 (s), 779 (s). MS (EI; 70 eV) *m*/*z* (%) = 275.0 (M$^+$, 2), 188 (100), 129 (98), 115 (60), 102 (85), 59 (60). HRMS (EI): calcd for $C_{15}H_{17}NO_4$ ([M]$^+$): 275.1152; found: 275.1153.

Methyl 1-(1-carboxypentyl)-1*H*-isoquinoline-2-carboxylate (3c). Starting with isoquinoline (**1a**) (0.250 g, 1.93 mmol), **2c** (1.00 g, 3.87 mmol) and methyl chloroformate (0.218 g, 2.32 mmol), **3c** (0.380 g, 65%) was isolated as a slightly brownish solid; mp. 82–83 °C (major rotamer (I) 55%, minor rotamer (II) 45%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.40 (br s, 1H, $OH_{(II)}$); 8.50 (br s, 1H, $OH_{(I)}$); 7.24–7.04 (m, 4$H_{(I)}$, 4$H_{(II)}$, H-4,5,6,7$_{(I)}$,4,5,6,7$_{(II)}$); 6.94 (dd, 1H, $^3J_{2,3}$ = 7.5 Hz, $^4J_{2,8}$ = 1.0 Hz, H-2$_{(II)}$); 6.78 (dd, 1H, $^3J_{2,3}$ = 7.5 Hz, $^4J_{2,8}$ = 1.0 Hz, H-2$_{(I)}$); 6.01 (d, 1H, $^3J_{2,3}$ = 7.5 Hz, H-3$_{(II)}$); 5.90 (d, 1H, $^3J_{2,3}$ = 7.5 Hz, H-3$_{(I)}$); 5.67 (dd, 1H, $^3J_{8,9}$ = 8.5 Hz, $^4J_{2,8}$ = 1.0 Hz, H-8$_{(I)}$); 5.52 (dd, 1H, $^3J_{8,9}$ = 9.0 Hz, $^4J_{2,8}$ = 1.0 Hz, H-8$_{(II)}$); 3.81 (s, 3H, $OMe_{(II)}$); 3.80 (s, 3H, $OMe_{(I)}$); 2.79–2.73 (m, 1$H_{(I)}$, 1$H_{(II)}$, H-9$_{(I)}$,9$_{(II)}$); 1.78–1.65 (m, 1H, H-10$_{(II)}$); 1.49–1.39 (m, 1H, H-10$_{(I)}$); 1.32–1.13 (m, 2$H_{(I)}$, 2$H_{(II)}$, H-11,12$_{(I)}$,11,12$_{(II)}$); 0.84 (t, 3$H_{(I)}$, 3$H_{(II)}$, ^3J = 7.2 Hz, $OMe_{(I),(II)}$). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 178.8 ($COOH_{(II)}$); 178.7 ($COOH_{(I)}$); 154.2 ($NCO_{(II)}$); 153.9 ($NCO_{(I)}$); 130.6, 130.4 (C-3a$_{(II)}$,7a$_{(II)}$); 130.4, 130.2 (C-3a$_{(I)}$,7a$_{(I)}$); 128.2, 126.9, 126.3, 125.0 (C-4,5,6,7$_{(II)}$); 128.1, 127.1, 126.7, 124.8 (C-4,5,6,7$_{(I)}$); 125.0 (C-2$_{(II)}$); 124.4 (C-2$_{(I)}$); 110.8 (C-3$_{(II)}$); 110.4 (C-3$_{(I)}$); 57.0 (C-8$_{(II)}$); 56.4 (C-8$_{(I)}$); 53.5 ($OMe_{(I)}$); 53.2 ($OMe_{(II)}$); 50.5 (C-9$_{(II)}$); 50.4 (C-9$_{(I)}$); 29.5 (C-11$_{(I)}$); 29.4 (C-11$_{(II)}$); 28.1 (C-10$_{(I)}$); 28.0 (C-10$_{(II)}$); 22.4, 22.4 (C-12$_{(I),(II)}$); 13.8, 13.8 ($Me_{(I),(II)}$); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3437 (m), 2956 (m), 1710 (s), 1693 (s), 1632 (m), 1456 (s), 1356 (s), 765 (m). MS (CI; pos.) *m*/*z* (%) = 304.0 ([M + 1]$^+$). HRMS (EI): calcd for $C_{17}H_{21}NO_4$ ([M]$^+$): 303.1465 found: 303.1472.

Methyl 1-(1-carboxynonyl)-1*H*-isoquinoline-2-carboxylate (3d). Starting with isoquinoline (**1a**) (0.250 g, 1.93 mmol), **2d** (0.914 g, 2.90 mmol) and methyl chloroformate (0.363 g, 3.87 mmol), **3d** (0.420 g, 60%) was isolated as a colourless solid; mp. 120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23–7.06 (m, 4H, ArH); 6.93, 6.79 (2 d, 1H, $^3J_{2,3}$ = 7.6 Hz, H-2); 6.03, 5.91 (2 d, 1H, $^3J_{2,3}$ = 7.6 Hz, H-3); 5.66, 5.52 (2 d, 1H, $^3J_{8,9}$ = 8.8 Hz, H-8); 3.81, 3.81 (2 s, 3H, OMe); 2.75 (m, 1H, H-9); 1.80–1.65 (m, 1H, H-10a); 1.50–1.35 (m, 1H, H-10b); 1.22 (br 's', 12H, 6 CH_2); 0.87 (t, 3H, ^3J = 7.0 Hz, Me). ^{13}C NMR (76 MHz, $CDCl_3$): δ = 178.3, 178.0 (COOH); 153.9, 153.7 (NCO); 130.5, 130.3 (2), 130.1 (C-Ar); 128.6, 128.5, 127.5, 127.0, 126.7, 126.3, 125.4, 125.0, 124.8, 124.4 (CH-Ar, C-2); 110.8, 110.6 (C-3); 57.0, 56.8 (C-8); 53.5, 53.2 (OMe); 50.3 (C-9); 31.8 (2), 29.4, 29.3, 29.2 (2), 28.4, 27.3 (2), 22.6 (2) (CH_2); 14.1 (Me). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3444 (br), 3288 (m), 2919 (m), 1727 (s), 1683 (s), 1635 (m), 1460 (s), 1360 (s), 778 (s). MS (EI, 70 eV) *m*/*z* (%) = 358.8 (M$^+$, 2), 301 (4), 188 (100), 144 (90), 129 (84), 103 (44), 43 (49). HRMS (EI): calcd for $C_{21}H_{29}NO_4$ ([M]$^+$): 359.2091; found: 359.2074.

Methyl 1-(1-carboxyphenylmethyl)-1*H*-isoquinoline-2-carboxylate (3e). Starting with isoquinoline (**1a**) (0.250 g, 1.93 mmol), **2e** (1.08 g, 3.87 mmol) and methyl chloroformate (0. 218 g, 2.32 mmol), **3e** (0.290 g, 47%) was isolated as a colourless solid; mp. 178 °C (major rotamer (I) 57%, minor rotamer (II) 43%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22–7.00 (m, 7H, H-4,5, Ph); 6.97 (d, 1H, $^3J_{2,3}$ = 7.5 Hz, H-2$_{(II)}$); 6.81–6.77 (m, 2$H_{(I)}$, 1$H_{(II)}$, H-2$_{(I)}$,6$_{(I)}$,6$_{(II)}$); 6.39 (d, 1H, $^3J_{6,7}$ = 8.0 Hz, H-7$_{(I)}$); 6.34 (d, 1H, $^3J_{6,7}$ = 8.0 Hz, H-7$_{(II)}$); 6.03 (d, 1H, $^3J_{2,3}$ = 7.5 Hz, H-3$_{(II)}$); 6.01 (d, 1H, $^3J_{8,9}$ = 9.5 Hz, H-8$_{(I)}$); 5.93 (d, 1H, $^3J_{2,3}$ = 7.5 Hz, H-3$_{(I)}$); 5.83 (d, 1H, $^3J_{8,9}$ = 9.5 Hz, H-8$_{(II)}$); 3.99 (d, 1H, $^3J_{8,9}$ = 9.5 Hz, H-9$_{(II)}$); 3.97 (d, 1H, $^3J_{8,9}$ = 9.5 Hz, H-9$_{(I)}$); 3.82 (s, 3H, $OMe_{(II)}$); 3.75 (s, 3H, $OMe_{(I)}$). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.6 ($COOH_{(II)}$); 176.3 ($COOH_{(I)}$); 154.0 ($NCO_{(II)}$); 153.6 ($NCO_{(I)}$); 134.1, 134.1 (*i*-Ph$_{(I),(II)}$); 130.4, 128.7 (C-3a$_{(II)}$,7a$_{(II)}$); 130.1, 128.9 (C-3a$_{(I)}$,7a$_{(I)}$); 129.7 (*o*-Ph$_{(I)}$); 129.5 (*o*-Ph$_{(II)}$); 128.1 (2) (*m*-Ph$_{(I),(II)}$); 128.0 (C-5$_{(II)}$); 127.9 (C-5$_{(I)}$); 127.7 (2) (*p*-Ph$_{(I),(II)}$); 127.4 (C-7$_{(I)}$); 127.2 (C-7$_{(II)}$); 126.3 (C-6$_{(I)}$); 126.0 (C-6$_{(II)}$); 125.1 (C-2$_{(II)}$); 124.6 (C-4$_{(II)}$); 124.5 (C-4$_{(I)}$); 124.4 (C-2$_{(I)}$); 110.5 (C-3$_{(II)}$); 110.3 (C-3$_{(I)}$); 58.6 (C-8$_{(II)}$);

57.9 (C-$8_{(I)}$); 54.0 (2) (C-$9_{(I),(II)}$); 53.5 ($OMe_{(I)}$); 53.3 ($OMe_{(II)}$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3429 (br), 2956 (m), 1716 (s), 1698 (s), 1630 (m), 1444 (s), 1353 (s), 766 (s). MS (CI; neg.) m/z (%) = 322.0 ([M − H]$^-$). Anal. Calcd for $C_{19}H_{17}NO_4$ (323.00): C 70.58, H 5.26, N 4.33; found: C 70.85, H 5.01, N 3.41.

Methyl 1-(1-carboxy-(4-tolyl)methyl)-1*H*-isoquinoline-2-carboxylate (3f). Starting with isoquinoline (**1a**) (0.250 g, 1.93 mmol), **2f** (0.850 g, 2.90 mmol) and methyl chloroformate (0.365 g, 3.87 mmol), **3f** (0.350 g, 54%) was isolated as a colourless solid; mp. 208 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 12.60 (s, 1H, OH); 7.33–7.08 (m, 8H, ArH); 6.78, 6.67 (2 dd, 1H, $^3J_{2,3}$ = 7.5 Hz, $^4J_{2,8}$ = 1.2 Hz, H-2); 6.24, 6.19 (2 d, 1H, $^3J_{2,3}$ = 7.5 Hz, H-3); 5.89, 5.73 (2 dd, 1H, $^3J_{8,9}$ = 10.6 Hz, $^4J_{2,8}$ = 1.2 Hz, H-8); 3.72, 3.67 (2 d, 1H, $^3J_{8,9}$ = 10.6 Hz, H-9); 3.37, 3.25 (2 s, 3H, OMe); 2.28, 2.27 (2 s, 3H, Me). ^{13}C NMR (76 MHz, DMSO-d_6): δ = 172.5, 172.4 (COOH); 153.0, 152.7 (NCO); 137.1, 136.9 (*p*-C_6H_4); 132.2, 132.0, 131.1, 130.8, 130.4, 130.2 (C-Ar, *i*-C_6H_4); 128.7 (*o*-, *m*-C_6H_4); 128.4, 128.3, 127.1, 127.0 (2), 126.9, 125.1 (2) (CH-Ar); 125.3, 124.9 (C-2); 110.6, 110.3 (C-3); 57.3, 56.0 (C-8); 54.5, 54.2 (C-9); 53.2, 52.6 (OMe); 20.8 (Me). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3410 (br), 2940 (s), 1709 (m), 1692 (m), 1349 (m), 1245 (w), 778 (w). MS (CI; pos.) m/z (%) = 338.2 ([M + 1]$^+$). HRMS (CI, neg.): calcd for $C_{20}H_{18}NO_4$ ([M]$^-$): 336.1230; found: 336.1224.

Methyl 1-[carboxy-(4-chlorophenyl)methyl]-1*H*-isoquinoline-2-carboxylate (3g). Starting with isoquinoline (**1a**) (0.250 g, 1.93 mmol), **2g** (0.916 g, 2.90 mmol) and methyl chloroformate (3.86 g, 3.87 mmol), **3g** (0.583 g, 83%) was isolated as a colourless solid; mp. 181 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 12.60 (s, 1H, OH); 7.42–7.20 (m, 8H, ArH); 6.79, 6.68 (2 dd, 1H, $^3J_{2,3}$ = 7.5 Hz, $^4J_{2,8}$ = 1.0 Hz, H-2); 6.25, 6.20 (2 d, 1H, $^3J_{2,3}$ = 7.5 Hz, H-3); 5.89, 5.75 (2 dd, 1H, $^3J_{8,9}$ = 10.5 Hz, $^4J_{2,8}$ = 1.0 Hz, H-8); 3.79, 3.75 (2 d, 1H, $^3J_{8,9}$ = 10.5 Hz, H-9); 3.40, 3.30 (2 s, 3H, OMe). ^{13}C NMR (63 MHz, DMSO-d_6): δ = 172.5, 172.1 (COOH); 152.9, 152.7 (NCO); 134.2, 134.0 (*p*-C_6H_4); 132.7, 132.5 (*i*-C_6H_4); 130.7 (*o*-C_6H_4); 130.6, 130.4 (2), 130.1 (C-Ar); 128.5, 128.4, 127.2, 127.0 (2), 126.9, 125.1 (2) (CH-Ar); 125.1, 124.6 (C-2); 110.7, 110.6 (C-3); 57.3, 56.1 (C-8); 54.2, 54.0 (C-9); 53.3, 52.6 (OMe). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3430 (br), 3028 (m), 1732 (s), 1706 (s), 1491 (s), 1334 (s), 1253 (s), 705 (s). MS (CI; pos.) m/z (%) = 358.0 ([M + 1]$^+$).

Methyl 1-[carboxy-(4-methoxyphenyl)methyl]-1*H*-isoquinoline-2-carboxylate (3h). Starting with isoquinoline (**1a**) (0.258 g, 2.00 mmol), **2h** (0.846 g, 3.00 mmol) and methyl chloroformate (0.376 g, 4.00 mmol), **3h** (0.263 g, 75%) was isolated as a colourless solid; mp. 213 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 12.45 (s, 1H, OH); 7.31–7.15 (m, 6H, ArH, *m*-C_6H_4); 6.91–6.84 (m, 2H, *o*-C_6H_4); 6.78, 6.68 (2 dd, 1H, $^3J_{2,3}$ = 7.6 Hz, $^4J_{2,8}$ = 1.0 Hz, H-2); 6.23, 6.18 (2 d, 1H, $^3J_{2,3}$ = 7.6 Hz, H-3); 5.86, 5.72 (2 dd, 1H, $^3J_{8,9}$ = 10.7 Hz, $^4J_{2,8}$ = 1.0 Hz, H-8); 3.73, 3.73 (2 s, 3H, OMe); 3.70, 3.66 (2 d, 1H, $^3J_{8,9}$ = 10.7 Hz, H-9); 3.39, 3.30 (2 s, 3H, OMe). ^{13}C NMR (76 MHz, DMSO-d_6): δ = 173.2, 172.6 (COOH); 159.0, 158.9 (*p*-C_6H_4); 153.0, 152.7 (NCO); 131.2, 130.9, 130.5, 130.4 (C-Ar); 130.0 (*o*-C_6H_4); 128.4, 128.3, 127.1, 126.9, 125.3, 125.1, 124.8 (CH-Ar, C-2); 113.6 (2) (*m*-C_6H_4); 110.5, 110.3 (C-3); 57.4, 56.1 (C-8); 55.3 (2) (*Me*OC_6H_4); 54.1, 53.9 (C-9); 53.2, 52.7 (OMe). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3443 (br), 3214 (s), 1725 (s), 1679 (s), 1458 (s), 1364 (s), 1248 (s), 779 (s). MS (EI; 70 eV) m/z (%) = 354.0 (M$^+$, 2), 188 (100), 148 (26), 129 (23), 91 (5), 85 (30), 69 (72). Anal. Calcd for $C_{20}H_{19}NO_5$ (353.36): C 67.98, H 5.42, N 3.96; found: C 67.87, H 5.43, N 3.73.

Methyl 5-bromo-1-(carboxybutyl)-1*H*-isoquinoline-2-carboxylate (3i). Starting from 5-bromoisoquinoline (0.416 g, 2.0 mmol), 1,1-bis(trimethylsilyloxy)pent-1-ene (1.042 g, 4.0 mmol) and methyl chloroformate (0.230 g, 2.4 mmol), **3i** (0.271 g, 36%) was isolated as a colourless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.45 ('d', 1H, ^3J = 8.0 Hz, ArH); 7.08–6.94 [m (2H, ArH) (1$H_{(II)}$, H-$2_{(II)}$)]; 6.88 ('d', 1$H_{(I)}$, $^3J_{2,3}$ = 8.0 Hz, H-$2_{(I)}$); 6.37, 6.27 (2 d, 1H, $^3J_{2,3}$ = 8.0 Hz, H-3); 5.63, 5.49 (2 'd', 1H, $^3J_{8,9}$ = 9.0 Hz, H-8); 3.82 (s, 3H, OMe); 2.76 (m, 1H, H-9); 1.75–1.14 (m, 6H, CH_2); 0.85 (t, 3H, ^3J = 7.0 Hz, Me). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 178.7 (COOH); 153.9, 153.7 (NCO); 132.4, 132.3, 127.9, 127.7, 126.7, 126.1, 125.9, 125.6 (CH-Ar, C-2); 132.1, 131.9, 130.2, 130.0, 120.7, 120.5 (C-Ar); 109.4, 109.0 (C-3); 57.0, 56.5 (C-8); 53.7, 53.4 (OMe); 50.0 (C-9); 29.4, 29.3, 28.1, 22.4 (CH_2); 13.8 (Me). MS (CI; pos.): m/z (%) = 384 ([M + 1]$^+$, ^{81}Br), 382 ([M + 1]$^+$, ^{79}Br). HRMS (CI; neg.): calcd for $C_{17}H_{20}BrNO_4$ ([M]$^-$, ^{79}Br) 381.0576, found 381.0559; calcd for $C_{17}H_{20}BrNO_4$ ([M]$^-$, ^{81}Br) 383.0556, found 383.0536.

Methyl 5-bromo-1-(carboxyoctyl)-1*H*-isoquinoline-2-carboxylate (3j). Starting from 5-bromoisoquinoline (0.416 g, 2.0 mmol), 1,1-bis(trimethylsilyloxy)dec-1-ene (1.264 g, 4.0 mmol) and methyl chloroformate (0.230 g, 2.4 mmol), **3j** (0.472 g, 54%) was isolated as a colourless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.60 (br, 1H, OH); 7.44 (m, 1H, ArH); 7.07–6.94 [m (2H, ArH), (1$H_{(II)}$, H-$2_{(II)}$)]; 6.87 (dd, 1$H_{(I)}$, $^3J_{2,3}$ = 8.0 Hz, $^4J_{2,8}$ = 1.0 Hz, H-$2_{(I)}$); 6.37, 6.26 (2 d, 1H, $^3J_{2,3}$ = 8.0 Hz, H-3); 5.63, 5.48 (2 dd, 1H, $^3J_{8,9}$ = 8.6 Hz, $^4J_{2,8}$ = 1.0 Hz, H-8); 3.82, 3.81 (2 s, 3H, OMe); 2.75 (m, 1H, H-9); 1.76–1.07 (m, 14H, CH_2); 0.86 (t, 3H, ^3J = 7.0 Hz, Me). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 179.1, 179.0 (COOH); 153.9, 153.7 (NCO); 132.4, 132.3, 127.9, 127.7, 126.7, 126.1, 125.9, 125.6 (CH-Ar, C-2); 132.1, 131.9, 130.2, 130.0, 120.7, 120.5 (C-Ar); 109.4, 109.0 (C-3); 57.0, 56.4 (C-8); 53.7, 53.4 (OMe); 50.1 (C-9); 31.8 (2), 29.4, 29.3, 29.2 (2), 28.4, 27.3, 27.2, 22.6 (2) (CH_2); 14.1 (Me). IR (cap.): $\tilde{\nu}$ = 3072 (br, w), 2954 (s), 2925 (s), 2855 (s), 2671 (br, w), 1728 (s), 1707 (s), 1628 (m), 1555 (w), 1447 (s), 1410 (m), 1352 (s), 1276 (s), 1231 (m), 1195 (m), 1111 (m), 941 (m), 767 (m) cm^{-1}. MS (CI; pos.): m/z (%) = 440 ([M + 1]$^+$, ^{81}Br), 438 ([M + 1]$^+$, ^{79}Br). HRMS (CI; neg.): calcd for $C_{21}H_{27}BrNO_4$ ([M − H]$^-$, ^{81}Br) 436.1129, found 436.1120; calcd for $C_{21}H_{27}BrNO_4$ ([M − H]$^-$, ^{79}Br) 438.1109, found 438.1100.

Methyl 5-bromo-1-(carboxyphenyl)-1*H*-isoquinoline-2-carboxylate (3k). Starting from 5-bromoisoquinoline (0.416 g, 2.0 mmol), 2-phenyl-1,1-bis(trimethylsilyloxy)ethene (1.122 g, 4.0 mmol) and methyl chloroformate (0.230 g, 2.4 mmol), **3k** (0.292 g, 36%) was isolated as a colourless solid; mp. 202–203 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.17 (m, 7H), 6.95–6.88 (m, 1H, ArH, Ph); 6.96, 6.74 (2 dd, 1H, $^3J_{2,3}$ = 7.8 Hz, $^4J_{2,8}$ = 1.2 Hz, H-2); 6.47, 6.38 (2 d, 1H, $^3J_{2,3}$ = 7.8 Hz, H-3); 6.04, 5.79 (2 dd, 1H, $^3J_{8,9}$ = 10.5 Hz, $^4J_{2,8}$ = 1.2 Hz, H-8); 4.01, 3.96 (2 d, 1H, $^3J_{8,9}$ = 10.5 Hz, H-9); 3.44, 3.30 (2 s, 3H, OMe). ^{13}C NMR (76 MHz, $CDCl_3$): δ = 176.5, 176.4 (COOH); 153.2, 152.9 (NCO); 133.8, 133.5 (*i*-Ph); 132.5, 132.4, 129.1, 128.9, 128.4, 128.3 (2), 128.2, 128.0, 127.8, 126.9, 126.3 (CH-Ar, *o*-, *m*-, *p*-Ph, C-2); 132.2, 131.7, 130.2, 129.8, 120.6, 120.5 (C-Ar); 109.1, 109.0 (C-3); 57.8, 56.4 (C-8); 54.2, 53.7 (C-9); 53.3, 52.7 (OMe). IR (KBr):

$\tilde{\nu}$ = 3440 (w), 3089 (br, m), 1730 (s), 1671 (s), 1465 (s), 1449 (s), 1413 (m), 1366 (s), 1323 (m), 1257 (s), 1202 (w), 1166 (m), 1120 (w) cm^{-1}. MS (CI; pos.): *m/z* (%) = 404 ($[M + 1]^+$, ^{81}Br), 402 ($[M + 1]^+$, ^{79}Br). Anal. Calcd for $C_{19}H_{16}BrNO_4$ (402.24): C 56.73, H 4.01, N 3.48. Found: C 56.54, H 4.14, N 3.19.

Typical procedure for the preparation of 7,8-benzo-9-aza-4-oxabicyclo[3.3.1]nonan-3-ones (4)

To a CH_2Cl_2 solution (6 mL) of **3c** (0.100 g, 0.35 mmol) and iodine (0.17 g 0.70 mmol) was added a saturated aqueous solution of $NaHCO_3$ (3.5 mL) and the solution was stirred for 12 h at 20 °C. The excess of iodine was removed by addition of a saturated aqueous solution of sodium sulfite (20 mL). The organic and the aqueous layers were separated. The latter was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography (silica gel, hexane → hexane–EtOAc = 2 : 1) to give **4c** as a yellow oil (0.10 g, 70%). Due to the restricted rotation of the urethane moiety, compounds **4** exist as racemic mixtures of two rotamers (doubled or broadened signals).

Methyl 8-iodo-12-methyl-11-oxo-10-oxa-13-azatricyclo[7.3.1.0^{2,7}]-trideca-2,4,6-triene-13-carboxylate (4a). Starting with **3a** (0.080 g, 0.30 mmol), iodine (0.084 g, 0.34 mmol) and a saturated aqueous $NaHCO_3$ solution (3.5 mL) in CH_2Cl_2 (6.0 mL), **4a** (0.054 g, 46%) was isolated as a brownish solid; mp. 53 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (dd, 1H, $^3J_{4,5}$ = 7.8 Hz, $^4J_{4,6}$ = 2.0 Hz, H-4); 7.35–7.27 (m, 2H, H-5,6); 7.00 (dd, 1H, $^3J_{6,7}$ = 7.4 Hz, $^4J_{5,7}$ = 1.3 Hz, H-7); 6.80–6.68 (br, 1H, H-2); 5.75 (d, 1H, $^3J_{2,3}$ = 1.8 Hz, H-3); 5.35–5.21 (br, 1H, H-8); 3.91 (s, 3H, OMe); 3.00 (br 's', 1H, H-9); 1.15 (d, 3H, ^3J = 7.2 Hz, Me). ^{13}C NMR (76 MHz, $CDCl_3$): δ = 169.8 (COO); 154.5, 154.1 (NCO); 132.6–132.2 (br, C-Ar); 131.9, 131.2, 129.3, 128.4, 128.1 (CH-Ar); 86.6, 86.2 (br) (C-2); 54.0 (OMe); 52.8 (br), 52.7 (br) (C-8); 43.0 (br), 42.7 (C-9); 24.0, 23.6 (br) (C-3); 13.1, 12.9 (Me). IR (KBr, cm^{-1}): $\tilde{\nu}$= 3428 (br), 2956 (w), 1708 (s), 1635 (s), 1454 (m), 1333 (m), 1254 (m), 1250 (m), 766 (m). MS (EI, 70 eV): *m/z* (%) = 389.0 ($[M + 2]^+$, 10), 331 (39), 271 (19), 204 (39), 188 (100), 142 (9).

Methyl 12-ethyl-8-iodo-11-oxo-10-oxa-13-azatricyclo[7.3.1.0^{2,7}]-trideca-2,4,6-triene-13-carboxylate (4b). Starting with **3b** (0.120 g, 0.43 mmol), iodine (0.120 g, 0.48 mmol) and a saturated aqueous $NaHCO_3$ solution (4.36 mL) in CH_2Cl_2 (7.0 mL), **4b** (0.107 g, 61%) was isolated as a slightly yellow solid; mp. 63 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (m, 1H, H-4); 7.33–7.23 (m, 2H, H-5,6); 7.02 (br d, 1H, H-7); 6.80–6.65 (br, 1H, H-2); 5.74 (d, 1H, $^3J_{2,3}$ = 1.8 Hz, H-3); 5.47–5.34 (br, 1H, H-8); 3.91 (s, 3H, OMe); 2.69 (br 's', 1H, H-9); 1.89 (m, 1H, CH_2(a)); 1.30 (m, 1H, CH_2(b)); 1.17 (t, 3H, ^3J = 7.4 Hz, Me). ^{13}C NMR (76 MHz, $CDCl_3$): δ = 169.3 (br, COO); 154.0 (NCO); 132.7–132.3 (br, C-Ar); 131.9, 131.4, 129.3, 128.6, 128.3, 127.6 (CH-Ar); 86.2, 85.7 (br) (C-2); 54.0 (OMe); 51.4 (br), 50.7, 50.0 (C-8,9); 24.1, 23.7 (br) (C-3); 20.0 (CH_2); 12.2 (Me). IR (KBr, cm^{-1}): $\tilde{\nu}$= 3439 (br), 2961 (s), 1743 (s), 1730 (s), 1442 (m), 1318 (m), 1250 (m), 1097 (m), 765 (m). MS (EI, 70 eV): *m/z* (%) = 401.0 (M^+, 2), 314 (8), 204 (100), 188 (90), 144 (30), 129 (60). HRMS (EI): calcd for $C_{15}H_{16}INO_4$ ($[M]^+$): 401.0119; found: 401.0112.

Methyl 12-butyl-8-iodo-11-oxo-10-oxa-13-azatricyclo[7.3.1.0^{2,7}]-trideca-2,4,6-triene-13-carboxylate (4c). Starting with **3c** (0.100 g, 0.35 mmol), iodine (0.177 g, 0.70 mmol) and a saturated aqueous $NaHCO_3$ solution (2.0 mL) in CH_2Cl_2 (6.0 mL), (**4c**) (0.105 g, 70%) was isolated as a yellow oil (major rotamer (I) 55%, minor rotamer (II) 45%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.35 (m, $1H_{(I)}$, $1H_{(II)}$, H-$4_{(I)}$,$4_{(II)}$); 7.30–7.24 (m, $2H_{(I)}$, $2H_{(II)}$, H-5,$6_{(I)}$,5,$6_{(II)}$); 7.02–6.97 (m, $1H_{(I)}$, $1H_{(II)}$, H-$7_{(I)}$,$7_{(II)}$); 6.82 ('t', H, $^3J_{2,3}$ = 1.8 Hz, $^4J_{2,8}$ = 1.5 Hz, H-$2_{(II)}$); 6.68 ('t', 1H, $^3J_{2,3}$ = 1.8 Hz, $^4J_{2,8}$ = 1.5 Hz, H-$2_{(I)}$); 5.69 (d, 1H, $^3J_{2,3}$ = 1.8 Hz, H-$3_{(II)}$); 5.68 (d, 1H, $^3J_{2,3}$ = 1.8 Hz, H-$3_{(I)}$); 5.50 (br 's', 1H, $^4J_{2,8}$ = 1.5 Hz, $^3J_{8,9}$ = 1.0 Hz, H-$8_{(I)}$); 5.36 (br 's', 1H, $^4J_{2,8}$ = 1.5 Hz, $^3J_{8,9}$ = 1.0 Hz, H-$8_{(II)}$); 3.89 (s, 3H, $OMe_{(I)}$); 3.88 (s, 3H, $OMe_{(II)}$); 2.56–2.50 (m, $1H_{(I)}$, $1H_{(II)}$, H-$9_{(I)}$,$9_{(II)}$); 1.75–1.35 (m, $6H_{(I)}$, $6H_{(II)}$, H-10,11,12(a,b)$_{(I)}$, 10,11,12(a,b)$_{(II)}$); 0.944 (t, 3H, ^3J = 7.2 Hz, $Me_{(II)}$); 0.936 (t, 3H,^3J = 7.2 Hz, $Me_{(I)}$). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.3 ($COO_{(I)}$); 169.0 ($COO_{(II)}$); 154.3 ($NCO_{(II)}$); 153.8 ($NCO_{(I)}$); 132.2, 132.2 (C-3a$_{(II)}$,7a$_{(II)}$); 132.2, 131.9 (C-3a$_{(I)}$,7a$_{(I)}$); 131.6 (C-$4_{(II)}$); 131.5 (C-$4_{(I)}$); 129.5, 128.9 (C-$5_{(I)}$,$6_{(I)}$); 129.4, 129.1 (C-$5_{(II)}$,$6_{(II)}$); 126.6 (C-$7_{(I)}$); 126.4 (C-$7_{(II)}$); 85.4 (C-$2_{(I)}$); 84.8 (C-$2_{(II)}$); 53.8 ($OMe_{(I)}$); 53.6 ($OMe_{(II)}$); 52.2 (C-$9_{(I)}$); 51.9 (C-$9_{(II)}$); 51.8 (C-$8_{(II)}$); 50.6 (C-$8_{(I)}$); 30.7 (C-$10_{(I)}$); 30.5 (C-$10_{(II)}$); 29.4 (C-$11_{(I)}$); 29.3 (C-$11_{(II)}$); 23.5 (C-$3_{(I)}$); 23.0 (C-$3_{(II)}$); 22.3 (C-$12_{(II)}$); 22.2 (C-$12_{(I)}$); 13.8, 13.8 ($Me_{(I),(II)}$). IR (KBr, cm^{-1}): $\tilde{\nu}$= 3467 (br), 2956 (s), 1760 (s), 1716 (s), 1456 (m), 1333 (m), 1254 (m), 1002 (m), 763 (m). MS (EI, 70 eV): *m/z* (%) = 429 (M^+, 2), 302 (7), 204 (19), 188 (100), 144 (25), 129 (36). HRMS (EI): calcd for $C_{17}H_{20}INO_4$ ($[M]^+$): 429.0432; found: 429.0426.

Methyl 8-iodo-12-octyl-11-oxo-10-oxa-13-azatricyclo[7.3.1.0^{2,7}]-trideca-2,4,6-triene-13-carboxylate (4d). Starting with **3d** (0.100 g, 0.27 mmol), iodine (0.077 g, 0.30 mmol) and a saturated aqueous solution of $NaHCO_3$ (2.0 mL) in CH_2Cl_2 (5.0 mL), **4d** (0.088 g, 67%) was isolated as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.43 (dd, 1H, $^3J_{4,5}$ = 7.5 Hz, $^4J_{4,6}$ = 2.0 Hz, H-4); 7.34–7.23 (m, 2H, H-5,6); 7.00 (dd, 1H, $^3J_{6,7}$ = 7.0 Hz, $^4J_{5,7}$ = 1.3 Hz, H-7); 6.80–6.65 (br, 1H, H-2); 5.75 (d, 1H,$^3J_{2,3}$ = 1.8 Hz, H-3); 5.45–5.34 (br, 1H, H-8); 3.91 (s, 3H, OMe); 2.76 (br 's', 1H, H-9); 1.83 (m, 1H, H-10(a)); 1.56 (m, 2H, H-10(b),11(a)); 1.34–1.25 (m, 11H, H-11(b), 5 CH_2); 0.88 (t, 3H, ^3J = 7.2 Hz, Me). ^{13}C NMR (76 MHz, $CDCl_3$): δ = 169.5 (COO); 154.0 (NCO); 132.7 (br), 132.5 (br) (C-Ar); 132.0, 129.3, 128.6, 128.3, 127.7 (CH-Ar); 86.2, 85.7 (br) (C-2); 54.0 (OMe); 51.6 (br), 50.9, 48.9 (br), 48.4 (C-8,9); 31.8 (C-10); 29.4, 29.3, 29.2, 27.3, 26.6, 22.6 (CH_2); 24.2 (br), 23.7 (br) (C-3); 14.1 (Me). MS (CI; pos.): *m/z* (%) = 486.1 ($[M + 2]^+$). HRMS (CI; neg.): calcd for $C_{21}H_{27}INO_4$ ($[M]^-$): 484.0979; found: 484.0984.

Methyl 8-iodo-11-oxo-12-phenyl-10-oxa-13-azatricyclo[7.3.1.0^{2,7}]-trideca-2,4,6-triene-13-carboxylate (4e). Starting with **3e** (0.100 g, 0.30 mmol), iodine (0.152 g, 0.60 mmol) and a saturated aqueous $NaHCO_3$ solution (2.5 mL) in CH_2Cl_2 (5.0 mL), **4e** (0.088 g, 65%) was isolated as a yellow oil (major rotamer (I) 70%, minor rotamer (II) 30%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.21 (m, 9H, H-4,5,6,7, Ph); 7.01 ('t', 1H, $^3J_{2,3}$ = 1.8 Hz, $^4J_{2,8}$ = 1.5 Hz, H-$2_{(I)}$); 6.85 ('t', 1H, $^3J_{2,3}$ = 1.8 Hz, $^4J_{2,8}$ = 1.5 Hz, H-$2_{(II)}$); 5.78 (d, 1H, $^3J_{2,3}$ = 1.8 Hz, H-$3_{(I)}$); 5.76 (d, 1H, $^3J_{2,3}$ = 1.8 Hz, H-$3_{(II)}$); 5.61 (br 's', 1H, $^4J_{2,8}$ = 1.5 Hz, $^3J_{8,9}$ = 1.0 Hz, H-$8_{(II)}$); 5.45 (br 's', 1H, $^4J_{2,8}$ = 1.5 Hz, $^3J_{8,9}$ = 1.0 Hz, H-$8_{(I)}$); 3.96 (br 's', $1H_{(II)}$, H-$9_{(II)}$); 3.95 (br 's', $1H_{(I)}$, H-$9_{(I)}$); 3.68

(s, 3H, $OMe_{(II)}$); 3.18 (s, 3H, $OMe_{(I)}$). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.8 ($COO_{(I)}$); 167.0 ($COO_{(II)}$); 154.5 ($NCO_{(I)}$); 153.2 ($NCO_{(II)}$); 136.2 (*i*-$Ph_{(I)}$); 135.9 (*i*-$Ph_{(II)}$); 132.4, 131.5 (C-$3a_{(I)}$,$7a_{(I)}$); 132.1, 131.8 (C-$3a_{(II)}$,$7a_{(II)}$); 131.7 (C-$4_{(I)}$); 131.6 (C-$4_{(II)}$); 129.7, 129.3 (C-$5_{(II)}$,$6_{(II)}$); 129.6, 129.5 (C-$5_{(I)}$,$6_{(I)}$); 129.1 (*m*-$Ph_{(I)}$); 129.0 (*m*-$Ph_{(II)}$); 128.3 (*p*-$Ph_{(II)}$); 128.0 (*p*-$Ph_{(I)}$); 127.7 (*o*-$Ph_{(I)}$); 127.5 (*o*-$Ph_{(II)}$); 126.9 (C-$7_{(II)}$); 126.7 (C-$7_{(I)}$); 86.1 (C-$2_{(II)}$); 85.7 (C-$2_{(I)}$); 57.5 (C-$8_{(II)}$); 57.4 (C-$9_{(I)}$); 56.4 (C-$8_{(I)}$); 54.9 (C-$9_{(II)}$); 53.7 ($OMe_{(II)}$); 53.0 ($OMe_{(I)}$); 23.4 (C-$3_{(II)}$); 22.8 (C-$3_{(I)}$). IR (KBr, cm^{-1}): $\tilde{\nu}$= 3429 (br), 2953 (w), 1745 (s), 1721 (s), 1444 (m), 1322 (m), 1238 (m), 1002 (m), 726 (w). MS (EI; 70 eV) *m*/*z* (%) = 449.0 (M^+, 2), 355(3), 279 (30), 225 (15), 118 (100), 167 (63), 77 (50). HRMS (EI): calcd for $C_{19}H_{16}INO_4$ (449.0): 449.0119; found: 449.0138.

Methyl 8-iodo-11-oxo-12-*p*-tolyl-10-oxa-13-azatricyclo[7.3.1.0^{2,7}]-trideca-2,4,6-triene-13-carboxylate (4f). Starting with **3f** (0.090 g, 0.26 mmol), iodine (0.073 g, 0.30 mmol) and a saturated $NaHCO_3$ solution (2.5 mL) in CH_2Cl_2 (5 mL), **4f** (0.077 g, 64%) was isolated as a brownish solid; mp. 82 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.43 ('d', 1H, H-4); 7.25 ('t', 1H, H-5); 7.03 ('d', 2H, *m*-C_6H_4); 6.88–6.75 (br, 1H, H-2); 6.64 (br 'd', 2H, *o*-C_6H_4); 5.87 ('d', 1H, $^3J_{6,7}$ = 7.8 Hz, H-7); 5.84 (d, 1H, $^3J_{2,3}$ = 1.8 Hz, H-3); 5.45–5.33 (br, 1H, H-8); 4.27 (br, 1H, H-9); 3.97 (s, 3H, OMe); 2.31 (s, 3H, Me). ^{13}C NMR (76 MHz, $CDCl_3$): δ = 167.7 (COO); 154.2 (NCO); 137.8 (*p*-C_6H_4); 132.2, 131.3, 130.2 (C-Ar, *i*-C_6H_4); 130.1 (*o*-C_6H_4); 131.3, 129.5, 129.3, 127.3 (CH-Ar); 128.9 (*m*-C_6H_4); 86.7 (br, C-2); 54.5 (br), 54.2 (br), 54.1 (C-8,9, OMe); 23.9 (br, C-3); 21.1 (Me). IR (KBr, cm^{-1}): $\tilde{\nu}$= 3433 (br), 2955 (w), 1758 (s), 1718 (s), 1443 (s), 1316 (s), 1251 (m), 1044 (m), 767 (w). MS (EI; 70 eV) *m*/*z* (%) = 463.0 (M^+, 10), 313 (18), 253 (53), 204 (25), 188 (100), 132 (87), 44 (48). HRMS (EI): calcd for $C_{20}H_{18}INO_4$ ($[M]^+$): 463.0275; found: 463.0270.

Methyl 12-(4-chlorophenyl)-8-iodo-11-oxo-10-oxa-13-azatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-13-carboxylate (4g). Starting with **3g** (0.200 g, 0.56 mmol), iodine (0.156 g, 0.61 mmol) and a saturated aqueous $NaHCO_3$ solution (5.6 mL) in CH_2Cl_2 (9.0 mL), **4g** (0.195 g, 72%) was isolated as a colourless solid; mp. 93 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.44 ('d', 1H, $^3J_{4,5}$ = 7.9 Hz, H-4); 7.27 (d't', 1H, $^3J_{4,5}$ = 7.9 Hz, $^3J_{5,6}$ = 7.6 Hz, $^4J_{5,7}$ = 1.3 Hz, H-5); 7.20 (m, 2H, *m*-C_6H_4); 6.94 (d't', 1H, $^3J_{6,7}$ = 7.9 Hz, $^3J_{5,6}$ = 7.6 Hz, $^4J_{4,6}$ = 1.3 Hz, H-6); 6.85–6.76 (br, 1H, H-2); 6.71 (br 'd', 2H, *o*-C_6H_4); 5.88 (br 'd', 1H, $^3J_{6,7}$ = 7.9 Hz, H-7); 5.83 (d, 1H, $^3J_{2,3}$ = 2.0 Hz, H-3); 5.41 (br, 1H, H-8); 4.27 (br, 1H, H-9); 3.97 (s, 3H, OMe). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.2 (COO); 154.1 (NCO); 134.1 (*p*-C_6H_4); 132.3 (br), 131.9, 127.2 (C-3a,7a, *i*-C_6H_4); 131.6 (*o*-C_6H_4); 131.5 (C-4); 129.6 (C-5); 129.2 (C-7); 128.5 (*m*-C_6H_4); 127.4 (C-6); 86.9 (br), 86.5 (br) (C-2); 54.3 (br), 54.2, 54.0 (br) (C-8,9, OMe); 23.4 (br), 23.1 (br) (C-3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3433 (br), 2925 (w), 1727 (s), 1717 (s), 1445 (s), 1360 (m), 1249 (m), 1092 (m), 764 (w). MS (CI; 70eV) *m*/*z* (%) = 484.2 ($[M + 2]^+$). HRMS (CI; neg.): calcd for $C_{19}H_{15}INO_4Cl$ ($[M]^-$): 482.9729; found: 482.9716.

Methyl 6-bromo-8-iodo-11-oxo-12-butyl-10-oxa-13-azatricyclo-[7.3.1.0^{2,7}]trideca-2,4,6-triene-13-carboxylate (4i). Starting with **3i** (0.237 g, 0.62 mmol), iodine (0.236 g, 0.93 mmol) and a saturated aqueous $NaHCO_3$ solution (5.6 mL) in CH_2Cl_2 (9.0 mL), **4i** (0.229 g, 73%) was isolated as a colourless solid; mp. 123–124 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.55 (dd, 1H, $^3J_{5,6}$ = 8.0 Hz, $^4J_{5,7}$ = 1.1 Hz, H-5); 7.19 ('t', 1H, $^3J_{5,6}$ = 8.0 Hz, $^3J_{6,7}$ = 7.5 Hz, H-6); 7.01 (br 'd', 1H, $^3J_{6,7}$ = 7.5 Hz, H-7); 6.86–6.68 (br, 1H, H-2); 5.56 (d, 1H, $^3J_{2,3}$ = 2.1 Hz, H-3); 5.47–5.34 (br, 1H, H-8); 3.92 (s, 3H, OMe); 2.77 (br 's', 1H, H-9); 1.80 (m, 1H), 1.55 (m, 2H), 1.38 (m, 2H), 1.21 (m, 1H) (CH_2); 0.95 (t, 3H, ^3J = 7.3 Hz, Me). ^{13}C NMR (76 MHz, $CDCl_3$): δ = 169.1 (COO); 153.8 (NCO); 134.1, 129.4, 127.1 (CH-Ar); 131.8 (br), 130.9 (br), 127.0 (C-Ar); 85.8, 85.2 (C-2); 54.0 (OMe); 51.6, 50.9, 49.4, 48.7 (C-8,9); 29.4, 26.2, 22.4 (CH_2); 26.1 (br, C-3); 13.8 (Me). IR (KBr): $\tilde{\nu}$ = 3433 (br, m), 2956 (m), 2928 (m), 2863 (w), 1756 (s), 1718 (s), 1561 (w), 1445 (s), 1416 (m), 1345 (s), 1300 (m), 1105 (m), 959 (s) cm^{-1}. MS (ESI): *m*/*z* = 509.96 ($[M + 1]^+$, ^{81}Br), 507.96 ($[M + 1]^+$, ^{79}Br). Anal. Calcd for $C_{17}H_{19}BrINO_4$ (508.15): C, 40.18; H, 3.77; N, 2.76. Found: C, 40.54; H, 3.73; N, 2.67.

Methyl 6-bromo-8-iodo-11-oxo-12-octyl-10-oxa-13-azatricyclo-[7.3.1.0^{2,7}]trideca-2,4,6-triene-13-carboxylate (4j). Starting with **3j** (0.365 g, 0.83 mmol), iodine (0.316 g, 1.245 mmol) and a saturated aqueous $NaHCO_3$ solution (5.6 mL) in CH_2Cl_2 (9.0 mL), **4j** (0.324 g, 67%) was isolated as a colourless solid; mp. 113–115 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.57 (dd, 1H, $^3J_{5,6}$ = 8.0 Hz, $^4J_{5,7}$ = 1.1 Hz, H-5); 7.21 ('t', $^3J_{5,6}$ = 8.0 Hz, $^3J_{6,7}$ = 7.5 Hz, 1H, H-6); 7.03 (br d, 1H, $^3J_{6,7}$ = 7.5 Hz, H-7); 6.87–6.70 (br, 1H, H-2); 5.57 (d, 1H, $^3J_{2,3}$ = 2.1 Hz, H-3); 5.49–5.36 (br, 1H, H-8); 3.94 (s, 3H, OMe); 2.80 (br 's', 1H, H-9); 1.93 (m, 1H), 1.58 (m, 2H), 1.39–1.23 (m, 11H) (7 CH_2); 0.89 (t, 3H, ^3J = 7.1 Hz, Me). ^{13}C NMR (76 MHz, $CDCl_3$): δ = 169.2 (br), 168.9 (COO); 153.8 (NCO); 134.1, 129.5, 127.1 (CH-Ar); 131.9 (br), 131.0 (br), 127.0 (C-Ar); 85.8, 85.2 (C-2); 54.0 (OMe); 51.6 (br), 50.9, 49.3 (br), 48.8 (C-8,9); 31.8, 29.3 (2), 29.2, 27.3, 26.5, 22.6 (CH_2); 26.2 (br), 25.9 (br) (C-3); 14.1 (Me). IR (KBr): $\tilde{\nu}$ = 3432 (br, w), 2952 (m), 2922 (m), 2853 (m), 1754 (s), 1709 (s), 1449 (s), 1420 (w), 1355 (s), 1299 (m), 1115 (m), 959 (m), 765 (m) cm^{-1}. MS (CI pos., isobutane): *m*/*z* (%) = 566 ($[M + 1]^+$, ^{81}Br), 564 ($[M + 1]^+$, ^{79}Br). HRMS (EI): calcd for $C_{21}H_{27}BrINO_4$ (M^+, ^{79}Br) 563.0163, found 563.0149.

Methyl 6-bromo-8-iodo-11-oxo-12-phenyl-10-oxa-13-azatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-13-carboxylate (4k). Starting with **3k** (0.229 g, 0.57 mmol), iodine (0.217 g, 0.86 mmol) and a saturated aqueous $NaHCO_3$ solution (5.6 mL) in CH_2Cl_2 (9.0 mL), **4k** (0.160 g, 53%) was isolated as a slightly yellow solid; mp. 71–73 °C. ^1H NMR (500 MHz, $CDCl_3$, 300K): δ = 7.49 (dd, 1H, $^3J_{5,6}$ = 8.0 Hz, $^4J_{5,7}$ = 1.0 Hz, H-5); 7.27 (m, 1H, *p*-Ph); 7.22 (m, 2H, *m*-Ph); 6.99–6.81 (br, 1H, H-2); 6.78 ('t', 1H, $^3J_{5,6}$ = $^3J_{6,7}$ = 8.0 Hz, H-6); 6.77 (br 'd', 2H, *o*-Ph); 5.79 (br 'd', 1H, $^3J_{6,7}$ = 8.0 Hz, H-7); 5.67 (d, 1H, $^3J_{2,3}$ = 2.2 Hz, H-3); 5.50–5.36 (br, 1H, H-8); 4.34 (br, 1H, H-9); 3.99 (s, 3H, OMe). ^{13}C NMR (126 MHz, $CDCl_3$, 300K): δ = 167.2 (br, COO); 153.9 (NCO); 134.1 (C-5); 133.2 (*i*-Ph); 131.6 (br, C-3a); 130.2 (*o*-Ph); 129.9 (br, C-7a); 128.7 (br, C-7); 128.5 (C-6); 128.4 (*m*-Ph); 128.2 (*p*-Ph); 126.2 (br, C-4); 86.4 (br), 85.9 (br) (C-2); 55.3 (br), 55.0, 54.5, 54.3 (C-8,9, OMe); 25.8 (br), 25.4 (br) (C-3). ^1H NMR (500 MHz, $CDCl_3$, 243K); (major rotamer (I) 70%, minor rotamer (II) 30%): δ = 7.51 (dd, 1H, $^3J_{5,6}$ = 8.0 Hz, $^4J_{5,7}$ = 1.0 Hz, H-$5_{(II)}$); 7.50 (dd, 1H, $^3J_{5,6}$ = 8.0 Hz, $^4J_{5,7}$ = 1.0 Hz, H-$5_{(I)}$); 7.29–7.20 (m, $3H_{(I)}$, $3H_{(II)}$, *m*-$Ph_{(I),(II)}$), *p*-$Ph_{(I),(II)}$); 6.97 (dd, 1H, $^3J_{2,3}$ = 2.2 Hz, $^4J_{2,8}$ = 1.3 Hz, H-$2_{(II)}$); 6.83 (dd, 1H, $^3J_{2,3}$ = 2.2 Hz, $^4J_{2,8}$ = 1.3 Hz, H-$2_{(I)}$); 6.80 ('t', $1H_{(I)}$, $1H_{(II)}$, $^3J_{5,6}$ = $^3J_{6,7}$ = 8.0 Hz, H-$6_{(I)}$,$6_{(II)}$); 6.73 (br, $2H_{(I)}$, $2H_{(II)}$, *o*-$Ph_{(I),(II)}$); 5.79 (dd, 1H, $^3J_{6,7}$ = 8.0 Hz, $^4J_{5,7}$ = 1.0 Hz, H-$7_{(I)}$); 5.75 (dd, 1H, $^3J_{6,7}$ = 8.0 Hz, $^4J_{5,7}$ = 1.0 Hz, H-$7_{(II)}$); 5.65 (d,

1H, $^3J_{2,3}$ = 2.2 Hz, H-3$_{(II)}$); 5.63 (d, 1H, $^3J_{2,3}$ = 2.2 Hz, H-3$_{(I)}$); 5.47 (dd, 1H, $^3J_{8,9}$ = 5.7 Hz, $^4J_{2,8}$ = 1.3 Hz, H-8$_{(I)}$); 5.40 (dd, 1H, $^3J_{8,9}$ = 5.7 Hz, $^4J_{2,8}$ = 1.3 Hz, H-8$_{(II)}$); 4.36 (d, 1H, $^3J_{8,9}$ = 5.7 Hz, H-9$_{(I)}$); 4.30 (d, 1H, $^3J_{8,9}$ = 5.7 Hz, H-9$_{(II)}$); 4.02 (s, 3H, OMe$_{(II)}$); 3.98 (s, 3H, OMe$_{(I)}$). ^{13}C NMR (126 MHz, $CDCl_3$, 243K): δ = 167.8 (COO$_{(I)}$); 167.5 (COO$_{(II)}$); 153.8, 153.8 (NCO$_{(I),(II)}$); 134.1 (C-5$_{(II)}$); 134.0 (C-5$_{(I)}$); 132.7 (*i*-Ph$_{(II)}$); 132.6 (*i*-Ph$_{(I)}$); 131.2 (C-3a$_{(II)}$); 130.9 (C-3a$_{(I)}$); 130.0, 130.0 (*o*-Ph$_{(I),(II)}$); 129.4 (C-7a$_{(I)}$); 129.2 (C-7a$_{(II)}$); 128.7 (C-7$_{(I)}$); 128.6 (C-6$_{(I)}$); 128.5, 128.5 (C-6$_{(II)}$,7$_{(II)}$); 128.3, 128.3 (*m*-Ph$_{(I),(II)}$); 128.3 (*p*-Ph$_{(II)}$); 128.1 (*p*-Ph$_{(I)}$); 126.1 (C-4$_{(II)}$); 125.9 (C-4$_{(I)}$); 86.0 (C-2$_{(I)}$); 85.3 (C-2$_{(II)}$); 55.3 (C-9$_{(II)}$); 54.8 (C-8$_{(II)}$); 54.6 (C-9$_{(I)}$); 54.6 (OMe$_{(II)}$); 54.4 (OMe$_{(I)}$); 53.9 (C-8$_{(I)}$); 25.8 (C-3$_{(I)}$); 25.4 (C-3$_{(II)}$). IR (KBr): $\tilde{\nu}$ = 3449 (br, s), 1755 (m), 1725 (s), 1445 (m), 1354 (m), 1303 (m), 1264 (w), 753 (w) cm^{-1}. MS (CI; pos.): *m*/*z* (%) = 530 ([M + 1]$^+$, ^{81}Br), 528 ([M + 1]$^+$, ^{79}Br). HRMS (CI; neg., isobutane): calcd for $C_{19}H_{15}BrINO_4$ ([M − H]$^-$) 527.9307, found 527.9291.

Typical procedure for the preparation of methyl 2*H*-quinoline-1-carboxylates 7

To a CH_2Cl_2 solution (20 mL) of quinoline (0.250 g, 1.90 mmol) was added 1,1-bis(trimethylsilyloxy)pent-1-ene (0.713 g, 2.90 mmol) and methyl chloroformate (0.362 g, 3.86 mmol) at 0 °C. The solution was stirred for 2 h at 0 °C and for 12 h at 20 °C. A saturated aqueous solution of ammonium chloride (20 mL) was added and the organic and the aqueous layers were separated. The latter was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography (silica gel, hexane → hexane–EtOAc = 2 : 1) to give **7a** as colourless crystals (0.214 g, 38%), mp. 105–106 °C.

Methyl 2-(1-carboxybutyl)-2*H*-quinoline-1-carboxylate (7a). Starting with quinoline (**5**) (0.250 g, 1.93 mmol), **2a** (0.713 g, 2.90 mmol) and methyl chloroformate (0.362 g, 3.86 mmol), *syn*-**7a** (0.214 g, 38%) was isolated as a colourless solid; mp. 105–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52 (br 'd', 1H, H-8); 7.29–7.20 (m, 1H, H-7); 7.10 (m, 2H, H-5,6); 6.57 (d, 1H, $^3J_{3,4}$ = 9.5 Hz, H-4); 6.09 (dd, 1H, $^3J_{3,4}$ = 9.5 Hz, $^3J_{2,3}$ = 6.0 Hz, H-3); 5.26 (dd, 1H, $^3J_{2,9}$ = 9.5 Hz, $^3J_{2,3}$ = 6.0 Hz, H-2); 3.75 (s, 3H, OMe); 2.46 (m, 1H, H-9); 1.68 (m, 1H, H-10(a)); 1.50–1.10 (m, 3H, H-10(b), H-11); 0.84 (t, 3H, ^3J = 7.2 Hz, Me). ^{13}C NMR (76 MHz, $CDCl_3$): δ = 178.0 (COOH); 154.8 (NCO); 134.3, 127.1 (C-Ar); 127.9, 126.6, 126.5, 126.2, 125.7, 124.8 (CH-Ar); 53.5 (C-2); 53.2 (OMe); 49.0 (C-9); 30.0 (C-10); 20.7 (C-11); 14.0 (Me). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3430 (br), 2953 (m), 1697 (s), 1443 (m), 1305 (s), 753 (w). MS (CI pos.; 70 eV) *m*/*z* (%) = 290.1 ([M + 1]$^+$, 10), 330 (5), 290 (80), 188 (100). HRMS (CI; neg.): calcd for $C_{16}H_{18}NO_4$ ([M]$^-$): 288.1230; found: 288.1230.

Methyl 2-(1-carboxynonyl)-2*H*-quinoline-1-carboxylate (7b). Starting with quinoline (**5**) (0.250 g, 1.93 mmol), **2b** (0.919 g, 2.89 mmol) and methyl chloroformate (0.364 g, 3.88 mmol), *anti*-**7b** (0.320 g, 46%) was isolated as a colourless solid; mp. 77–78 °C. The second diastereomer, *syn*-**7b** (0.120 g, 17%), was isolated as a colourless oil.

7b (*anti*): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49 (br, 1H, H-8); 7.23 (m, 1H, H-7); 7.11–7.08 m, 2H, H-5,6); 6.55 (d, 1H, $^3J_{3,4}$ = 9.5 Hz, H-4); 6.09 (dd, 1H, $^3J_{3,4}$ = 9.5 Hz, $^3J_{2,3}$ = 6.0 Hz, H-3); 5.23 (br, 1H, H-2); 3.79 (s, 3H, OMe); 2.38 (d't', 1H, $^3J_{9,10(a)}$ = $^3J_{2,9}$ = 9.8 Hz, $^3J_{9,10(b)}$ = 4.0 Hz, H-9); 1.64–1.51 (m, 2H, H-10); 1.31–1.11 (m, 12H, 6 CH_2); 0.88 (t, 3H, ^3J = 7.0 Hz, Me). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 178.6 (COOH); 155.1 (NCO); 134.1 (C-8a); 127.7 (C-7); 127.4 (C-3); 127.3 (C-4a); 126.4, 126.4 (C-4,5); 125.0 (C-8); 124.8 (C-6); 53.2 (OMe); 53.0 (C-2); 48.4 (C-9); 31.8, 29.3, 29.2, 29.1, 28.5, 26.7, 22.6 (CH_2); 14.0 (Me). IR (Nujol, cm^{-1}): $\tilde{\nu}$ = 3433 (br), 2925 (w), 1727 (m), 1445 (m), 1359 (m), 1249 (w), 764 (w). MS (EI; 70 eV) *m*/*z* (%) = 359.2 (M$^+$, 1), 347(2), 204 (2), 188 (100), 144 (48), 129 (12). HRMS (EI): calcd for $C_{21}H_{29}NO_4$ ([M]$^+$): 359.2091; found: 359.2084.

7b (*syn*): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52 (br, 1H, H-8); 7.24 (m, 1H, H-7); 7.10 (m, 2H, H-5,6); 6.57 (d, 1H, $^3J_{3,4}$ = 9.5 Hz, H-4); 6.09 (dd, 1H, $^3J_{3,4}$ = 9.5 Hz, $^3J_{2,3}$ = 6.0 Hz, H-3); 5.26 (dd, 1H, $^3J_{2,9}$ = 9.5 Hz, $^3J_{2,3}$ = 6.0 Hz, H-2); 3.76 (s, 3H, OMe); 2.45 (ddd, 1H, $^3J_{2,9}$ = 9.5 Hz, $^3J_{9,10(a)}$ = 11.0 Hz, $^3J_{9,10(b)}$ = 3.6 Hz, H-9); 1.69 (m, 1H, H-10(a)); 1.46 (m, 1H, H-10(b)); 1.30–1.13 (m, 6 CH_2); 0.85 (t, 3H, ^3J = 7.0 Hz, Me). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 178.3 (COOH); 154.8 (NCO); 134.4 (C-8a); 127.8 (C-7); 127.2 (C-4a); 126.5 (br, C-3); 126.5 (C-4); 126.1 (C-5); 125.6 (br, C-8); 124.7 (C-6); 53.5 (C-2); 53.1 (OMe); 49.2 (C-9); 31.8, 29.5, 29.2, 29.1, 27.8, 27.5, 22.6 (CH_2); 14.1 (Me). IR (Nujol, cm^{-1}): $\tilde{\nu}$ = 3224 (br), 2945 (m), 1742 (s), 1671 (m), 1342 (m), 1277 (m), 1180 (m), 763 (w). MS (EI; 70 eV) *m*/*z* (%) = 359.2 (M$^+$, 1), 347 (2), 188 (100), 144 (48), 129 (12). Anal. Calcd for $C_{21}H_{29}NO_4$ (359.45): C 70.17, H 8.13, N 3.90; found: C 70.36, H 8.36, N 4.20.

Methyl 4-(carboxyphenylmethyl)-4*H*-quinoline-1-carboxylate (7c). Starting with quinoline (**5**) (0.250 g, 1.93 mmol), **2c** (0.810 g, 2.90 mmol) and methyl chloroformate (0.362 g, 3.86 mmol), **7c** (0.350 g, 56%) was isolated as a colourless solid; mp. 42–43 °C. The product was obtained as a diastereomeric mixture of enantiomers (major isomer (I) 55%, minor isomer (II) 45%, dr = 1.2 : 1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.55 (br, 1H, OH$_{(I)}$); 8.94 (br, 1H, OH$_{(II)}$); 7.90 (dd, 1H, $^3J_{7,8}$ = 8.5 Hz, $^4J_{6,8}$ = 1.2 Hz, H-8$_{(I)}$); 7.84 (dd, 1H, $^3J_{7,8}$ = 8.5 Hz, $^4J_{6,8}$ = 1.2 Hz, H-8$_{(II)}$); 7.30–7.04 (m, 6H$_{(I)}$, 8H$_{(II)}$, H-7$_{(I)}$, Ph$_{(I)}$, H-5$_{(II)}$,6$_{(II)}$,7$_{(II)}$, Ph$_{(II)}$); 7.06 (d, 1H, $^3J_{2,3}$ = 7.6 Hz, H-2$_{(I)}$); 6.88 (d, 1H, $^3J_{2,3}$ = 7.6 Hz, H-2$_{(II)}$); 6.77 (d't', 1H, $^3J_{5,6}$ = $^3J_{6,7}$ = 7.6 Hz, $^4J_{6,8}$ = 1.2 Hz, H-6$_{(I)}$); 6.33 (dd, 1H, $^3J_{5,6}$ = 7.6 Hz, $^4J_{5,7}$ = 1.6 Hz, H-5$_{(I)}$); 5.60 (dd, 1H, $^3J_{2,3}$ = 7.6 Hz, $^3J_{3,4}$ = 6.0 Hz, H-3$_{(I)}$); 5.19 (dd, 1H, $^3J_{2,3}$ = 7.6 Hz, $^3J_{3,4}$ = 6.0 Hz, H-3$_{(II)}$); 4.17 (dd, 1H, $^3J_{4,9}$ = 7.8 Hz, $^3J_{3,4}$ = 6.0 Hz, H-4$_{(II)}$); 3.95 (dd, 1H, $^3J_{4,9}$ = 9.5 Hz, $^3J_{3,4}$ = 6.0 Hz, H-4$_{(I)}$); 3.87 (s, 3H, OMe$_{(I)}$); 3.76 (s, 3H, OMe$_{(II)}$); 3.72 (d, 1H, $^3J_{4,9}$ = 7.8 Hz, H-9$_{(II)}$); 3.52 (d, 1H, $^3J_{4,9}$ = 9.5 Hz, H-9$_{(I)}$). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.9 (COOH$_{(I)}$); 177.8 (COOH$_{(II)}$); 152.8 (NCO$_{(I)}$); 152.5 (NCO$_{(II)}$); 137.0 (C-8a$_{(I)}$); 136.7 (C-8a$_{(II)}$); 135.5 (*i*-Ph$_{(I)}$); 134.7 (*i*-Ph$_{(II)}$); 129.2 (C-5$_{(I)}$); 129.1, 128.9 (*o*-Ph$_{(I),(II)}$); 128.7 (C-4a$_{(II)}$); 128.4 (C-5$_{(II)}$); 128.3, 128.0 (*m*-Ph$_{(I),(II)}$); 128.1, 128.1 (C-2$_{(I),(II)}$); 127.7 (C-4a$_{(I)}$); 127.6 (*p*-Ph$_{(I)}$); 127.4 (*p*-Ph$_{(II)}$); 126.9 (C-7$_{(II)}$); 126.4 (C-7$_{(I)}$); 125.0 (C-6$_{(II)}$); 124.2 (C-6$_{(I)}$); 121.5 (C-8$_{(II)}$); 121.1 (C-8$_{(I)}$); 111.6 (C-3$_{(I)}$); 110.0 (C-3$_{(II)}$); 58.2 (C-9$_{(II)}$); 57.9 (C-9$_{(I)}$); 53.3 (OMe$_{(II)}$); 53.1 (OMe$_{(I)}$); 42.2 (C-4$_{(I)}$); 41.1 (C-4$_{(II)}$). IR (Nujol, cm^{-1}): $\tilde{\nu}$ = 3155 (br), 2945 (m), 1729 (m), 1708 (m), 1339 (m), 1239 (w), 1353 (s), 764 (w). MS (CI pos.; 70 eV) *m*/*z* (%) = 323.0 ([M + 1]$^+$, 80), 244 (12), 220 (66), 188 (100), 130 (15), 85 (33). HRMS (CI neg.): calcd for $C_{19}H_{16}NO_4$ ([M]$^-$): 322.1074; found: 322.1075.

Typical procedure for the preparation of azoxabicyclo[3.3.1]nonanones 8

To a CH_2Cl_2 solution (6 mL) of **7a** (0.100 g, 0.35 mmol) and I_2 (0.17 g 0.70 mmol) was added a saturated solution of $NaHCO_3$ (3.5 mL) and the solution was stirred for 12 h at 20 °C. The excess of iodine was removed by addition of a saturated aqueous solution of sodium sulfite (20 mL). The organic and the aqueous layers were separated. The latter was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo.* The residue was purified by chromatography (silica gel, hexane → hexane–EtOAc = 2 : 1) to give **8a** (0.110 g, 86%) as a yellow oil.

Methyl 13-iodo-11-oxo-10-propyl-12-oxa-8-azatricyclo[7.3.1.0^{2,7}]-trideca-2,4,6-triene-8-carboxylate (8a). Starting with a 1 : 1 diastereomeric mixture of **7a** (0.090 g, 0.31 mmol), iodine (0.086 g, 0.34 mmol) and a saturated aqueous $NaHCO_3$ solution (3.6 mL) in CH_2Cl_2 (7.0 mL), **8a** (*syn*/*anti* = 1 : 1) (0.110 g, 86%) was isolated as a yellow oil. The product contained a small amount of hydrolyzed silyl enol ether which could not be separated. ^{1}H NMR (500 MHz, $CDCl_3$) (2 diastereomers, dr = 1 : 1): δ = 7.78 (br, 1H, H-8); 7.38 (m, 1H, H-7); 7.35–7.31 (m, 2H, H-5,7); 7.17 (m, 2H, H-6,6); 5.62 (br, 1H, H-2); 5.35–5.27 (m, 4H, H-2,3,4,4); 4.92 ('t', 1H, $^3J_{2,3} = {}^3J_{3,4}$ = 3.0 Hz, H-3); 3.88 (s, 3H, OMe); 3.78 (s, 3H, OMe); 2.90–2.86 (m, 1H, H-9); 2.74 (m, 1H, H-9); 1.91–1.84 (m, 1H, H-10); 1.66–1.36 (m, 7H, H-10,11); 0.95 (t, 3H, ^3J = 7.3 Hz, Me); 0.90 (t, 3H, ^3J = 7.3 Hz, Me). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.3 (COO); 155.3 (NCO); 136.3, 133.3 (C-8a); 131.2, 130.4 (C-7); 129.6 (C-5); 127.8, 127.7 (br) (C-5,8); 126.9 (br), 125.4 (C-6); 124.4 (C-8); 123.0 (C-4a); 81.4, 77.5 (C-4); 55.4, 55.2 (C-2); 53.8 (OMe); 45.3, 43.3 (br) (C-9); 31.0, 27.3 (C-10); 20.8, 20.3 (C-11); 14.0, 13.8 (Me). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3432 (br), 2923 (w), 1698 (s), 1494 (m), 1213 (m), 921 (w), 703 (s). MS (EI, 70 eV): *m*/*z* (%) = 415.0 (M$^+$, 17), 314 (28), 288 (62), 204 (100), 188 (27), 144 (27), 128 (21). HRMS (EI): calcd for $C_{16}H_{18}INO_4$ ([M]$^+$): 415.0275; found: 415.0268.

Methyl 13-iodo-10–0ctyl-11-oxo-12-oxa-8-azatricyclo[7.3.1.0^{2,7}]-trideca-2,4,6-triene-8-carboxylate (*anti*-8b). Starting with *anti*-**7b** (0.147 g, 0.41 mmol), iodine (0.133 g, 0.45 mmol) and a saturated aqueous $NaHCO_3$ solution (4.0 mL) in CH_2Cl_2 (7.0 mL), *anti*- **8b** (0.103 g, 52%) was isolated as a brownish solid; mp. 101–102 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (br 'd', 1H, $^3J_{7,8}$ = 8.5 Hz, H-8); 7.39 (ddd, 1H, $^3J_{7,8}$ = 8.5 Hz, $^3J_{6,7}$ = 7.5 Hz, $^4J_{5,7}$ = 1.5 Hz, H-7); 7.35 (dd, 1H, $^3J_{5,6}$ = 7.7 Hz, $^4J_{5,7}$ = 1.5 Hz, H-5); 7.15 (d't', 1H, $^3J_{5,6}$ = 7.7 Hz, $^3J_{6,7}$ = 7.5 Hz, $^4J_{6,8}$ = 1.0 Hz, H-6); 5.34 ('t', 1H, $^3J_{3,4}$ = 3.0 Hz, $^4J_{2,4}$ = 2.5 Hz, H-4); 4.98 (br, 1H, H-2); 4.77 ('t', 1H, $^3J_{3,4} = {}^3J_{2,3}$ = 3.0 Hz, H-3); 3.89 (s, 3H, OMe); 2.73 (ddd, 1H, $^3J_{9,10(a)}$ = 8.5 Hz, $^3J_{9,10(b)}$ = 4.5 Hz, $^3J_{2,9}$ = 1.0 Hz, H-9); 1.91 (m, 1H, H-10(a); 1.77 (m, 1H, H-10(b)); 1.53, 142 (2 m, 2H, H-11(a),(b)); 1.36–1.23 (m, 10H, 5 CH_2); 0.88 (t, 3H, ^3J = 7.0 Hz, Me). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.5 (COO); 154.2 (NCO); 134.0 (C-8a); 131.5 (C-5); 130.7 (C-7); 124.6 (C-6); 123.0 (C-8); 121.7 (C-4a); 77.6 (C-4); 56.8 (C-2); 53.6 (OMe); 47.4 (C-9); 33.2 (C-10); 31.8, 29.3, 29.3, 29.2 (CH_2); 26.7 (C-11); 22.6 (C-16); 17.8 (C-3); 14.0 (Me). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3416 (br), 2916 (s), 1771 (s), 1716 (s), 1442 (m), 1331 (s), 1166 (m), 950 (m), 759 (m). MS (EI, 70 eV): *m*/*z* (%) = 485.0 (M$^+$, 74), 314 (82), 204 (20), 188 (100), 144 (30), 129 (15). HRMS (EI): calcd for $C_{21}H_{28}NIO_4$ ([M]$^+$): 485.10575; found: 4485.10581.

Methyl 13-iodo-11-oxo-12-phenyl-10-oxa-8-azatricyclo[7.3.1.0^{2,7}]-trideca-2,4,6-triene-8-carboxylate (8c). Starting with **7c** (0.300 g, 0.93 mmol, dr = 1.2 : 1), iodine (0.260 g, 1.02 mmol) and a saturated aqueous $NaHCO_3$ solution (10.0 mL) in CH_2Cl_2 (15.0 mL), **8c** (0.210 g, 50%) was isolated as light yellow solid; mp. 73 °C (2 diastereomers, dr = 1 : 1). A sample of diastereomerically pure *anti*-**8c** could be separated. Data of *anti*-**8c**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27 (dd, 1H, $^3J_{7,8}$ = 8.5 Hz, $^4J_{6,8}$ = 1.0 Hz, H-8); 7.44 (m, 2H, *m*-Ph); 7.39–7.35 (m, 2H, H-7, *p*-Ph); 7.28 (m, 3H, H-5, *o*-Ph); 7.21 (d't', 1H, $^3J_{5,6} = {}^3J_{6,7}$ = 7.3 Hz, $^4J_{6,8}$ = 1.0 Hz, H-6); 6.84 (dd, 1H, $^3J_{2,3}$ = 3.8 Hz, $^4J_{2,4}$ = 2.0 Hz, H-2); 4.94 (dd, 1H, $^3J_{2,3}$ = 3.8 Hz, $^3J_{3,4}$ = 2.2 Hz, H-3); 4.18 (d, 1H, $^3J_{4,9}$ = 2.2 Hz, H-9); 3.93 (s, 3H, OMe); 3.55 ('q', 1H, $^3J_{4,9} = {}^3J_{3,4}$ = 2.2 Hz, $^4J_{2,4}$ = 2.0 Hz, H-4). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.2 (COO); 153.5 (NCO); 136.6 (*i*-Ph); 132.2 (C-8a); 129.5 (C-5); 129.4 (*m*-Ph); 129.3 (C-7); 128.2 (*p*-Ph); 127.6 (*o*-Ph); 125.1 (C-6); 124.6 (C-4a); 122.0 (C-8); 84.4 (C-2); 57.8 (C-9); 53.9 (OMe); 48.0 (C-4); 12.8 (C-3). MS (CI; 70 eV) *m*/*z* (%) = 449.0 (M$^+$, 9), 321(53), 219 (34), 203 (100), 159 (32), 129 (54), 90 (25). HRMS (CI): calcd for $C_{19}H_{16}NIO_4$ ([M]$^+$): 449.0119; found: 449.0113.

Acknowledgements

Financial support from the state of Mecklenburg-Vorpommern (Landesgraduiertenstipendium for A. S.), from Boehringer-Ingelheim Pharma AG, and from the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

References

1 A. Brook, *Silicon in Organic, Organometallic, and Polymer Chemistry*, Wiley-Interscience, New York, 1999.
2 (*a*) T. Mukaiyama, K. Banno and K. Narasaka, *J. Am. Chem. Soc.*, 1974, **96**, 7503; (*b*) T. Mukaiyama, *Org. React.*, 1982, **28**, 203.
3 K. Takai and C. H. Heathcock, *J. Org. Chem.*, 1985, **50**, 3247.
4 (*a*) M. Bellassoued, E. Chelain, J. Collot, H. Rudler and J. Vaissermann, *Chem. Commun.*, 1999, 187; (*b*) H. Rudler, V. Comte, E. Garrier, M. Bellassoued, E. Chelain and J. Vaissermann, *J. Organomet. Chem.*, 2001, **621**, 284; (*c*) H. Rudler, P. Harris, A. Parlier, F. Cantagrel, B. Denise, M. Bellassoued, E. Chelain and J. Vaissermann, *J. Organomet. Chem.*, 2001, **624**, 186.
5 H. Rudler, A. Harris, F. Cantagrel and M. Bellassoued, *Chem. Commun.*, 2000, 771.
6 H. Rudler, C. Alvarez, A. Parlier, E. Perez, B. Denise, Y. Xu and J. Vaissermann, *Tetrahedron Lett.*, 2004, **45**, 2409.
7 S. Rotzoll, E. Ullah, H. Görls and P. Langer, *Tetrahedron*, 2007, **63**, 2647.
8 E. Ullah and P. Langer, *Synthesis*, 2005, 3189.
9 E. F. V. Scriven, 'Pyridines and their Benzo Derivatives', *Reactivity at Ring Atoms*, ed. A. J. Boulton and A. McKillop, in *Comprehensive Heterocyclic Chemistry*, Elsevier Science, Oxford, 1984, vol. 2, part 2A, ch. 2.05, p. 165.
10 (*a*) W. Bradley and S. Jeffrey, *J. Chem. Soc.*, 1954, 2770; (*b*) F. Diaba, C. Le Houerou, M. Grignon-Dubios and P. Gerval, *J. Org. Chem.*, 2000, **65**, 907; (*c*) R. Yamaguchi, B. Hatano, T. Nakaysau and S. Kozima, *Tetrahedron Lett.*, 1997, **38**, 403; (*d*) K. Akiba, Y. Nishihara and M. Wada, *Tetrahedron Lett.*, 1983, **24**, 5269; (*e*) F. Diaba, C. Le Houerou, M. Grignon-Dubois, B. Rezzonico and P. Gerval, *Eur. J. Org. Chem.*, 2000, 2915; (*f*) T. Itoh, K. Nagata, M. Miyazaki, K. Kameoka and A. Ohsawa, *Tetrahedron*, 2001, **57**, 8827; (*g*) A. R. Katritzky, S. Zhang, T. Kurz and M. Wang, *Org. Lett.*, 2001, **3**, 2807; (*h*) D. L. Comins, M. J. Sandelier and T. A. Grillo, *J. Org. Chem.*, 2001, **66**, 6829; (*i*) J. S. Yadav,

B. V. S. Reddy, M. K. Gupta, A. Prabhakar and B. Jagadeesh, *Chem. Commun.*, 2004, 2124.
11 P. Langer, *Eur. J. Org. Chem.*, 2007, 2233.
12 (*a*) H. Rudler, B. Denise, A. Parlier and J.-C. Daran, *Chem. Commun.*, 2002, 940; (*b*) H. Rudler, B. Denise, A. Parlier and J.-C. Daran, *Eur. J. Org. Chem.*, 2005, 3724.
13 S. Rotzoll, E. Ullah, C. Fischer, D. Michalik, A. Spannenberg and P. Langer, *Tetrahedron*, 2006, **62**, 12084.
14 For a review of 1,3-bis(trimethylsilyloxy)-1,3-dienes, see:P. Langer, *Synthesis*, 2002, 441.
15 A. Schmidt, J.-P. Gütlein, A. Preuss, U. Albrecht, H. Reinke and P. Langer, *Synlett*, 2005, 2489.
16 A. Schmidt, J.-P. Gütlein and P. Langer, *Tetrahedron Lett.*, 2007, **48**, 2067.
17 A. Schmidt, J.-P. Gütlein, S. Mkrtchyan, H. Görls and P. Langer, *Synlett*, 2007, 1305.
18 E. Ullah, S. Rotzoll, A. Schmidt, D. Michalik and P. Langer, *Tetrahedron Lett.*, 2005, **46**, 8997.
19 (*a*) C. Ainsworth and Y.-N. Kuo, *J. Organomet. Chem.*, 1972, **46**, 73; (*b*) A. Wissner, *J. Org. Chem.*, 1979, **44**, 4617.

