Functionalized Azamacrocycles and Large-Ring α-Amino Esters by One-Pot Syntheses from Methyl 2-Siloxy-2-vinylcyclopropanecarboxylates

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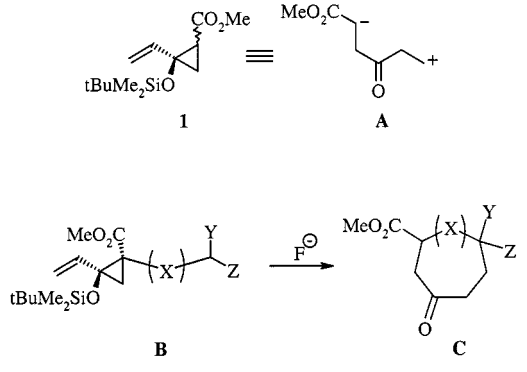
Siloxycyclopropane **1** served as starting material for intermediate alkylation products **2**, **7**, **11**, **14**, and **17**, which were elongated to provide a variety of precursor compounds bearing terminal *N*-benzyl groups. These substrates were subjected to a cesium fluoride-promoted ring-opening/ring-closure sequence to afford azamacrocycles **19**, **21**, **22**, **23**, **25**, **26**, **27**, and **28** in moderate to good yields. The cyclic products have different ring sizes and numbers of nitrogen atoms, and may incorporate *meta*-substituted benzene or pyridine units. A second approach employed glycine derivative **29** as the key building block for construction of precursors **31** and **34**, which on fluoride treatment furnished macrocyclic α-amino esters **32** and **35**, respectively, in moderate yields. A few reactions, such as transformations into macrocyclic pyridazinone derivatives **37** and **38**, illustrate the potential of the synthesized azamacrocycles for preparation of complex compounds. Our concept for construction of macrocyclic compounds using siloxycyclopropane **1** as zwitterionic synthon **A** has thus successfully been extended to the synthesis of a variety of highly functionalized azamacrocycles.

Introduction

The preparation of medium- and large-sized ring systems is a permanent challenge[1−7] for synthetic chemists, as such systems are widespread, ranging from naturally occurring compounds to macrocyclic synthetic receptors or ligands.[8−13] Ring systems containing two or more nitrogen atoms are potentially useful because of their ability to act as ligands and in some cases to mimic enzymatic functions.[14−15] Their synthesis using direct cyclization has hardly been reported.[16−19] Over the years, our laboratory has had a special interest in the reactivity of donor-acceptor substituted cyclopropane derivatives such as methyl 2-siloxy-2-vinylcyclopropanecarboxylate (**1**), the potential of which for a variety of chemical transformations is well documented.[20] The key feature of its synthetic use is its equivalence to the 1,5-zwitterionic synthon **A** (Scheme 1).



Scheme 1

Compound **1** may be deprotonated and substituted by treatment with electrophiles at C(1), while the vinyl group may be transformed by fluoride-induced ring-cleavage into an enone unit capable of accepting nucleophiles at the terminal carbon. These useful properties of **1** have hence paved the way to a number of interesting products.[21−26]

We have recently published one-pot syntheses of medium- to large-ring carbocycles **C**, in which the key step is an intramolecular Michael addition (IMA).[27−30] The precursor siloxycyclopropanes **B** contain remote pronucleophilic units CYZ at suitable distances from the cyclopropane core; these add to the enone generated in situ on fluoride treatment by desilylation and ring-opening of **B** (Scheme 1). More recently, we have described an extension of this methodology to nitrogen-containing large-ring systems involving the benzylamino group as the nucleophilic terminus.[31] This new route provides direct access to a variety of functionalized azamacrocycles with varying ring sizes, together with control over the number of nitrogen atoms in the ring. In this paper we wish to provide full details of these cyclization reactions. The extension of this concept to α-amino esters is presented, followed by a few typical reactions of the azamacrocycles, demonstrating the potential of this approach for syntheses of highly functionalized large-ring compounds.

Results

Syntheses of Precursor Compounds

Alkylation of siloxycyclopropane **1** in the presence of LDA with an excess of dihalides such as 1,4-dibromobutene furnished the known bromide **2**.[32] We found that benzylamine was the best amine substrate for the proposed syntheses of azamacrocycles. Thus, treatment of **2** in a concentrated solution of benzylamine in dichloromethane afforded

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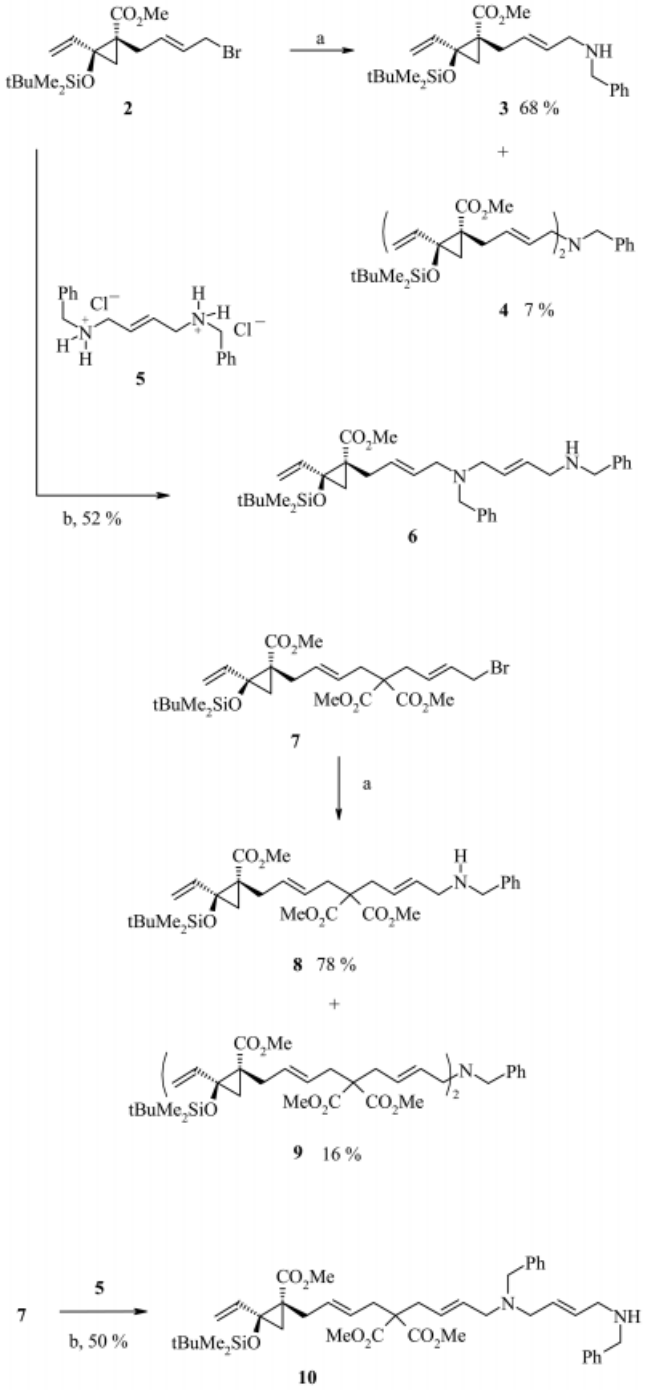
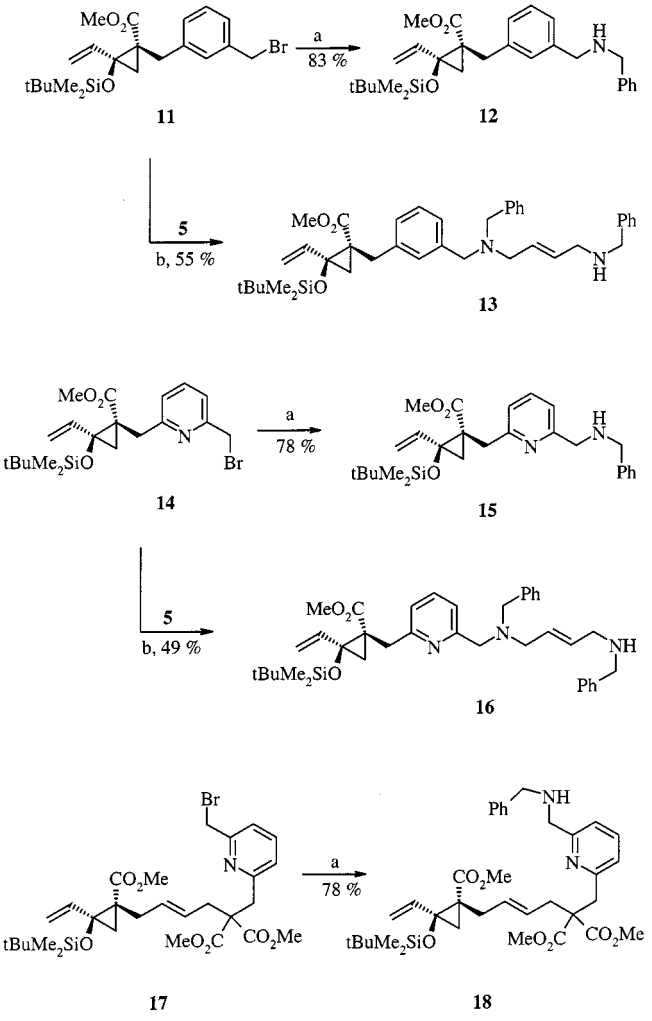
the corresponding amine **3** in 68% yield, together with the dialkylated product **4**,[33] formed in small amounts (Scheme 2). The two compounds could easily be separated by column chromatography. An excess of benzylamine was required to minimize the amount of undesired double alkylation. The precursor diamine **6** was prepared in moderate yield by alkylation of 1,4-(dibenzylamino)butene dihydrochloride salt **5**[34] with bromide **2** in the presence of potassium carbonate. Small amounts of a dialkylation product were detected, but not isolated in pure form. Similarly,



Scheme 2. a) $PhCH_2NH_2$, CH_2Cl_2, room temp., 3 h; b) K_2CO_3, CH_3CN, room temp. to reflux, 24 h



Scheme 3. a) $PhCH_2NH_2$, CH_2Cl_2, room temp., 3 h; b) K_2CO_3, CH_3CN, room temp. to reflux, 24 h

bromide **7**[29] was benzylaminated to afford the extended derivative **8** in 78% yield, again together with the inevitably formed dialkylated product **9**. Bromide **7** was also treated with the diammonium salt **5** in the presence of potassium carbonate to furnish the long-chain diamine **10** in 50% yield.

We also prepared precursors **12**, **13**, **15**, **16**, and **18**, incorporating benzene and pyridine spacer units, which should allow preparation of cyclophane derivatives. Hence, starting with the previously described siloxycyclopropane **11**,[30] we obtained **12** in 83% yield and diamine **13** in 55% yield under the established conditions (Scheme 3). Similarly, upon alkylation with benzylamine or diammonium salt **5**, the related (bromomethyl)pyridylmethyl-substituted cyclopropane **14**[30] furnished the required cyclization precursors **15** and **16** in good yields. The amine **18**, with a longer pyridine-containing spacer, was also prepared in 78% yield from elongated siloxycyclopropane derivative **17**.[30]

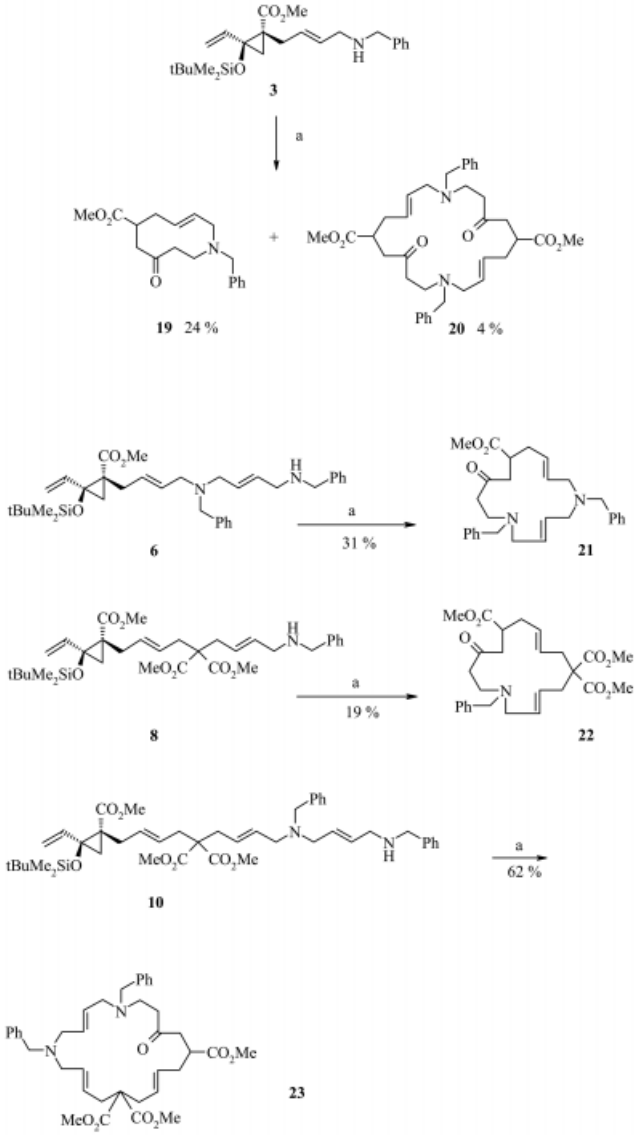
Cyclization Reactions

With the intermediate amines in hand, we studied the cyclization reactions. These involve cesium fluoride-induced

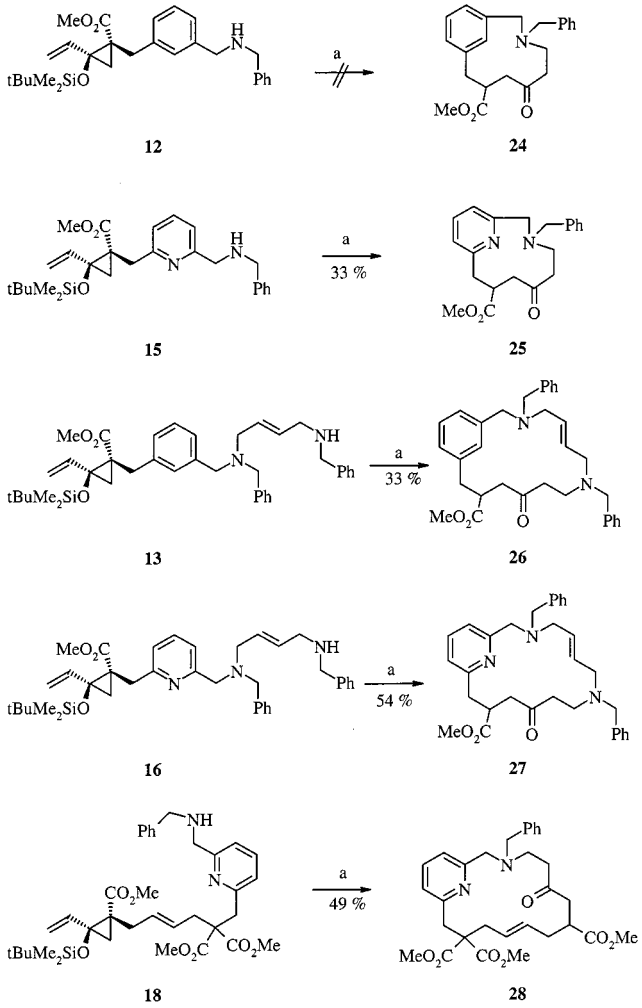
desilylation of the siloxy group, subsequent ring-cleavage of the cyclopropane and attack of the terminal nitrogen nucleophile on the enone generated in situ. Thus, amine **3** was slowly added over 25 h to a highly diluted (500 mL·mmol^{-1}), warmed (90 °C) suspension of cesium fluoride and TEBA (triethylbenzylammonium chloride) in dimethylformamide. Workup and purification of the resulting residue by chromatography afforded the expected azecine derivative **19** (24%) and its dimer **20** (4%, one diastereomer) (Scheme 4). Although the yield of **19** seems low it is nevertheless remarkable, since formation of ten-membered rings is usually rather unfavourable.[35] Our attempts to cyclize the corresponding tosylamine, the primary amine or an alcohol related to **3** failed to provide the expected heterocyclic compounds.[36] We also have to mention that an experiment with **3** as precursor under less dilute conditions did not provide higher yields of the interesting diazamacrocycle **20**; oligomers were formed in large quantities instead. The missing quantities in the mass balance in all the experiments described here are probably oligomers, formation of which through intermolecular reactions could not be avoided even under the high-dilution conditions employed. Further loss of material may be due to saponification and/or condensation reactions of the carbonyl groups induced by fluoride.

Encouraged by the positive result with **3** as starting material, we employed other benzylamine-substituted precursor compounds for the anticipated azamacrocycle syntheses. When amine **6** was subjected to the conditions described above, the corresponding 15-membered macrocycle **21** was isolated in 31% yield. Similarly, amine **8** afforded the corresponding functionalized macrocycle **22**, although in relatively low yield. We could not detect or isolate even traces of dimers or higher oligomers in any of these reactions. However, when the long-chain amine **10** was cyclized in the presence of CsF under similar conditions, the 20-membered azamacrocycle **23** was obtained in surprisingly high yield (62%).[37]

In order to synthesize azacyclophanes, we first attempted to cyclize dibenzylamine derivative **12** (Scheme 5). However, we could not detect the desired azacyclophane **24**, nor its dimer, nor higher oligomers, as has been observed in the



Scheme 4. a) CsF, TEBA, DMF, 90 °C, 22−25 h

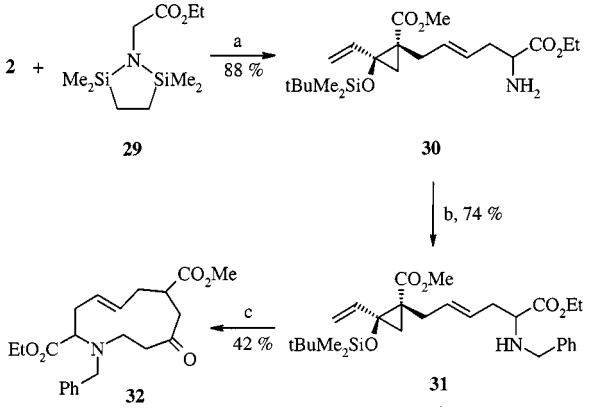


Scheme 5. a) CsF, TEBA, DMF, 90 °C, 22−25 h

case of a similar compound with a malonic ester as terminus. We attribute the failure to obtain **24** to the strain developed in its formation. Interestingly, this effect is considerably diminished when the benzene ring of precursor **12** is substituted by a pyridine unit. Thus, cesium fluoride-promoted reaction of compound **15** furnished the corresponding pyridinophane **25** as the sole product, in 33% yield. A possible explanation for the difference between the formation of a benzocyclophane and that of the corresponding pyridinophane has been discussed in our previous publication.[30] Cyclization of the long-chain diamine **13** afforded the desired azacyclophane **26** with moderate efficiency (33% yield). Further examples such as **16** and **18**, incorporating *meta*-substituted pyridine units as spacers, demonstrated smooth formation of the azapyridinophanes **27** and **28** in good yields (54% and 49%).

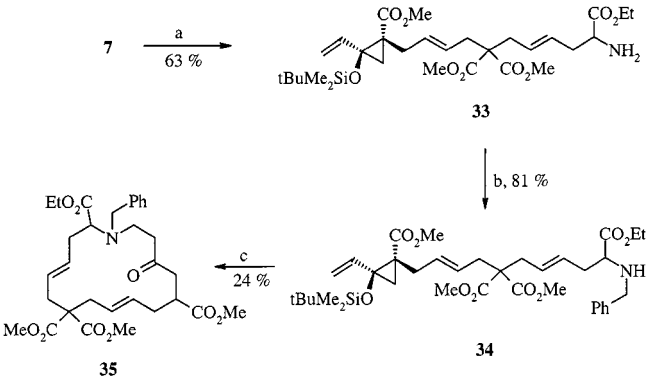
Synthesis of Macrocyclic α-Amino Esters

A second approach was used to open a pathway to macrocyclic α-amino esters. The enolate generated from *N*-disilylated glycine derivative **29**[38] by treatment with LDA was alkylated, with siloxycyclopropane **2** used as the electrophile (Scheme 6). After purification by column chromatography on silica gel (which apparently causes *N*-desilylation), substitution product **30** was isolated in high yield as the expected 1:1 mixture of two diastereomers. The primary amino group of **30** was smoothly benzylated by formation of the corresponding Schiff base with benzaldehyde, followed by reduction with sodium borohydride.[39] Thus, cyclization precursor **31** was obtained in good yield. Its treatment with cesium fluoride under the above conditions caused transformation to the 11-membered ring compound **32** in 42% yield. As expected, this compound was isolated as a 1:1 mixture of two diastereomers.



Scheme 6. a) i. LDA, −78 °C, ii. Silica gel; b) i. PhCHO, $MgSO_4$, ii. $NaBH_4$, MeOH, room temp.; c) CsF, TEBA, DMF, 90 °C, 25 h

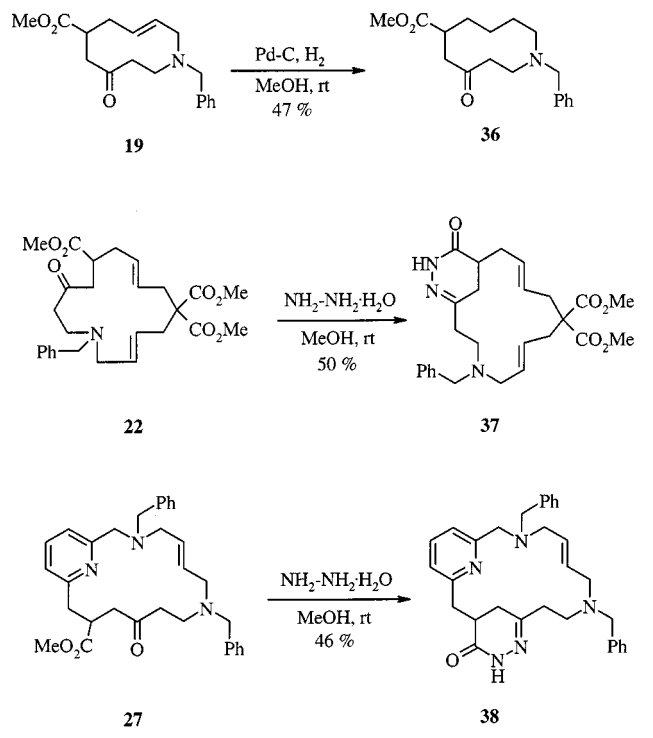
The analogous sequence applied to the extended siloxycyclopropane derivative **7** furnished α-amino ester **33** and its *N*-benzylated derivative **34** in good yields (Scheme 7). Cyclization of **34** provided 16-membered azamacrocycle **35** in low yield. The reactions resulting in **32** and **35** have not so far been optimized. We believe that this new approach to macrocyclic α-amino esters deserves some interest, since **32** and **35** may be regarded as highly functionalized expanded proline derivatives.



Scheme 7. a) i. **29**, LDA, −78 °C, ii. silica gel; b) i. PhCHO, $MgSO_4$, ii. $NaBH_4$, MeOH, room temp.; c) CsF, TEBA, DMF, 90 °C, 28 h

Reactions of Azamacrocycles

The simplest derivative in our series of azamacrocycles, compound **19**, could be converted into saturated azecane derivative **36** by hydrogenation in the presence of Pd-C. The *N*-benzyl group is not affected under these conditions, but the moderate yield of 47% does not preclude the formation of other products, lost during workup and purification (Scheme 8). A second transformation made use of the γ-oxo ester moiety of azamacrocycles **22** and **27**. Upon treatment with hydrazine hydrate in a solution of methanol, these compounds were converted into the macrocyclic pyridazinone[40] derivatives **37** and **38**. Again, the yields were



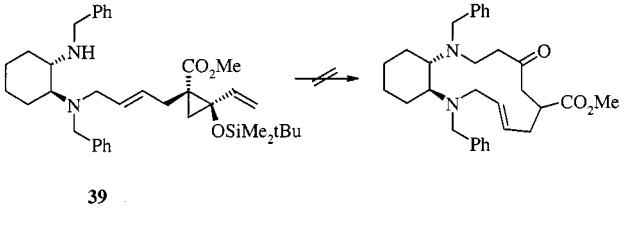
Scheme 8

only moderate, which may be due to formation of other condensation products of higher molecular weight in these examples. Nevertheless, the synthesis of unusual pyridazinone derivatives is notable, since this class of compounds is known to be of considerable pharmaceutical interest.[41]

Discussion

As mentioned above, we had previously studied macrocyclizations of compounds with dimethyl malonate units as C-nucleophilic termini, and now several closely related derivatives with benzylamino groups as N-nucleophilic termini have been investigated. It is therefore tempting to compare the efficiencies in both series, but there seems to be no general rule. Starting material **3** provided the azamacrocycle **19** in 24% yield and its dimer in 4% yield, whereas the related dimethyl malonate precursor gave the ten-membered carbocyclic compound in only 11% yield, but its dimer and trimer in 24% and 8% yields.[28] The cyclization of benzylamine derivative **10** to diazamacrocycle **23** is considerably more efficient (62% yield) than that of the corresponding all-carbon precursor with two dimethyl malonate units, which provides the 20-membered ring in 40% yield. On the other hand, the quite respectable yield for cyclization of **18** into **28** (49% yield) is even surpassed by the related transformation of the malonate precursor into the corresponding pyridinocyclophane, which proceeded in an excellent 78% yield.[30] However, these comparisons should be regarded with some reservations, since the mass balances of the cyclizations studied are often rather low. Thus, product loss during workup or purification can never be ruled out.

It should also briefly be mentioned that precursor compounds **39** and **40**, prepared by analogous routes, did not provide any cyclized compounds under the standard reaction conditions (Scheme 9). Apparently, steric hindrance caused by branching near the nucleophilic terminus completely prevents ring-formation with these compounds.



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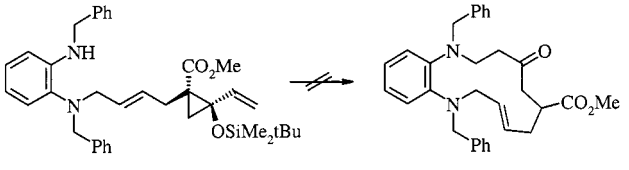

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Scheme 9

Conclusion

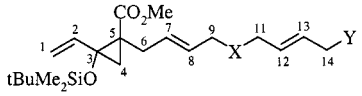
We have demonstrated here that our concept of sequential fluoride-promoted ring-opening/ring-closure in the presence of terminal pronucleophilic units was smoothly extendable to the preparation of a fair number of highly functionalized azamacrocycles. Though yields are variable, the transformations may certainly be optimized further. The highly flexible building block system developed permits the syntheses of compounds with variable ring sizes, differing number of incorporated nitrogen atoms, and various functional groups. Many spacer units may be incorporated between the protected enone unit provided by the siloxycyclopropane part derived from **1** and the nucleophilic terminus. Taking into account the difficulties involved in the generation of large-membered heterocycles, due to unfavourable enthalpic and entropic effects,[42] our method could be very useful.

Since the new macroheterocycles incorporate γ-oxo ester moieties, they may be exploited for further transformations, but also − with participation of double bonds or the aromatic units − for transannular reactions. Thanks to these various opportunities, these azamacrocycles may also serve as templates for diversity-orientated syntheses. We are currently introducing dipeptides and small oligopeptides as spacer units into the precursor compounds to obtain products of higher complexity. After cyclization, conformationally restricted peptidomimetics[43] should be made available.

Experimental Section

^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker instruments (AC 250, AC 300, or DRX 500) in $CDCl_3$ solution. The chemical shifts are given relative to TMS from the solvent ($CDCl_3$) signal (δ_H = 7.25, δ_C = 77.0). The 2D NMR COSY, HSQC (heteronuclear single quantum coherence), and HMBC (heteronuclear multiple quantum correlation) spectra were recorded on the DRX 500 spectrometer with an inverse TBI probe-head using pulsed two-field gradients. The final resolution of the 2D spectra was 2.5 Hz per point for ^{1}H and 20.5 Hz per point for ^{13}C.

To facilitate comparison of NMR spectroscopic data, the numbering of C and H atoms used for the siloxycyclopropanes **3**, **4**, **6**, **8**, **9**, **10**, **12**, **13**, **15**, **16**, and **18** is as depicted below (Scheme 10), independent of the systematic nomenclature of the compounds.



Scheme 10

IR spectra were measured with a Nicolet 205 FT-IR spectrometer and 5 SXC Nicolet FT-IR spectrometer using a DTGS detector. Mass spectra were recorded on a Varian MAT 711 or MAT 311 A spectrometer.

All reactions were performed under argon atmosphere in flame-dried flasks, and the reagents were introduced by syringe. All solvents were dried by standard methods. Silica gel (0.040−0.063 mm, Merck−Schuchardt) was used for column chromatography. Commercially available (*E*)-1,4-dibromo-2-butene and α,α′-dibromo-*m*-xylene were used as received. Benzylamine (Merck) was distilled before use. Other starting materials were synthesized as described in the literature [siloxycyclopropanes **2**,[32] **7**,[29] **11**, **14**, **17**,[30] diammonium salt **5**,[34] 2,6-bis(bromomethyl)pyridine[44]].

General Procedure A for *N*-Alkylation of Benzylamine: The alkyl bromide (1.0 equiv.) was added at room temperature to a stirred solution of benzylamine (10.0 equiv.) in dichloromethane (5 mL·mmol^{-1}). After 3 h, the reaction mixture was diluted with dichloromethane (10 mL·mmol^{-1}) and washed with saturated $NaHCO_3$ solution. The organic layer was dried with $MgSO_4$ and the solvent was evaporated. The residue was purified by column chromatography as described in the individual experiments.

General Procedure B for *N*-Alkylation of Ammonium Salt 5: The alkyl bromide (1.0 equiv.) and the diammonium salt **5** (2.0 equiv.) were added to a stirred suspension of anhyd. K_2CO_3 (5 equiv.) in dry acetonitrile (20 mL·mmol^{-1}). The reaction mixture was stirred at room temperature for 12 h, refluxed for a further period of 12 h, cooled, and poured into ice water, followed by extraction with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water and brine and then dried with Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography as described in the individual experiments.

General Procedure C for Fluoride-Induced Cyclization: A solution of siloxycyclopropyl-substituted amine (1.0 equiv.) in dry DMF (50 mL) was slowly added to a warm suspension (90 °C) of cesium fluoride (3.0 equiv.) and benzyltriethylammonium chloride (1.5 equiv.) in dry DMF (≈ 500 mL·mmol^{-1} siloxycyclopropyl compound). The addition was performed by syringe pump, over a period of time listed in each experiment. After evaporation of all volatile components (16 mbar, 70 °C), the residue was diluted with saturated aqueous NH_4Cl solution and extracted with ethyl acetate (5 × 20 mL). The combined organic layers were washed with brine and dried with $MgSO_4$. Removal of the solvent was followed by evaporation of the remaining DMF (0.01 mbar, 50 °C). The residue was purified by chromatography as indicated in the individual experiments.

Synthesis of Amine 3: According to general procedure A, cyclopropyl bromide **2** (2.00 g, 5.00 mmol) was treated with benzylamine (5.50 g, 25.0 mmol) in dichloromethane (20 mL), followed by purification using silica gel column chromatography (hexane/EtOAc, 1:1) to give the corresponding amine **3** (1.40 g, 68%) as a light yellow liquid and dialkylamine **4** (0.12 g, 7%) as the second fraction (elution with hexane/EtOAc, 1:9). − IR (film): $\tilde{\nu}$ = 3470−3005 cm^{-1} (N−H, =C−H), 2990−2740 (C−H), 1725 (CO_2Me), 1640 (C=C). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24−7.12 (m, 5 H, Ph), 5.72 (dd, *J* = 17.0, 10.5 Hz, 1 H, 2-H), 5.52 (m_c, 2 H, 7-H, 8-H), 5.18 (dd, *J* = 17.0, 1.0 Hz, 1 H, 1-H), 5.02 (dd, *J* = 10.5, 1.0 Hz, 1 H, 1-H), 3.67 (s, 2 H, C*H*$_2$Ph), 3.53 (s, 3 H, CO_2Me), 3.12 (m_c, 2 H, 9-H), 2.81 (br. dd, *J* = 15.5, 6.0 Hz, 1 H, 6-H), 2.13 (br. dd, *J* = 15.5, 6.0 Hz, 1 H, 6-H), 1.75 (d, *J* = 6.0 Hz, 1 H, 4-H), 1.43 (br. s, 1 H, NH), 0.94 (d, *J* = 6.0 Hz, 1 H, 4-H), 0.82 (s, 9 H, *t*Bu), 0.02, 0.00 (2 s, 6 H, $SiMe_2$). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 172.1, 51.9 (s, q, CO_2Me), 140.3, 129.6, 128.4, 128.2 (s, 3 d, Ph), 136.7 (d, C-2), 129.8, 126.9 (2 d, C-7, C-8), 115.2 (t, C-1), 65.1 (s, C-3), 53.2, 51.1 (2 t, *C*H$_2$Ph, C-9), 37.5 (s, C-5), 31.7, 23.6 (2 t, C-6, C-4), 25.8, 18.2 (q, s, *t*Bu), −3.4, −3.6 (2 q, $SiMe_2$). − $C_{24}H_{36}NO_3Si$ (414.6): calcd. C 69.52, H 8.75, N 3.37; found C 69.40, H 9.15, N 3.81.

Compound 4: IR (film): $\tilde{\nu}$ = 3090−2890 cm^{-1} (=C−H, C−H), 1730 (CO_2Me), 1670 (C=C). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17−7.07 (m, 5 H, Ph), 5.57 (dd, *J* = 17.0, 10.5 Hz, 2 H, 2-H), 5.46 (m_c, 4 H, 7-H, 8-H), 5.14 (dd, *J* = 17.0, 1.5 Hz, 2 H, 1-H), 4.97 (dd, *J* = 10.5, 1.5 Hz, 2 H, 1-H), 3.46 (s, 6 H, CO_2Me), 3.38 (m_c, 2 H, C*H*$_2$Ph), 2.88 (m_c, 4 H, 9-H), 2.78 (dd, *J* = 15.5, 6.5 Hz, 2 H, 6-H), 2.11 (dd, *J* = 15.5, 6.5 Hz, 2 H, 6-H), 1.71 (d, *J* = 6.3 Hz, 2 H, 4-H), 0.90 (d, *J* = 6.3 Hz, 2 H, 4-H), 0.79 (s, 18 H, *t*Bu), 0.02, 0.00 (2 s, 12 H, $SiMe_2$). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.8, 51.7 (s, q, CO_2Me), 139.4, 128.9, 128.7, 126.6 (s, 3 d, Ph), 136.7, 130.7 (2 d, C-2, C-8), 128.0 (d, C-7), 115.1 (t, C-1), 64.9 (s, C-3), 57.0, 55.3 (2 t, *C*H$_2$Ph, C-9), 37.4 (s, C-5), 31.7, 23.6 (2 t, C-6, C-4), 25.8, 18.1 (q, s, *t*Bu), −3.5, −3.7 (2 q, $SiMe_2$). − $C_{41}H_{65}NO_6Si_2$ (724.1): calcd. C 68.00, H 9.04, N 1.93; found C 68.28, H 8.83, N 2.32.

Synthesis of Diamine 6: According to general procedure B, cyclopropyl bromide **2** (0.83 g, 2.12 mmol) in dry acetonitrile (50 mL) was treated with diammonium salt **5** (1.43 g, 4.24 mmol) in the presence of K_2CO_3 (1.46 g, 10.6 mmol), followed by workup and purification using silica gel column chromatography (hexane/EtOAc, 1:9) to afford **6** (633 mg, 52%) as a light yellow liquid. − IR (film): $\tilde{\nu}$ = 3340 cm^{-1} (N−H), 3085−2800 (=C−H, C−H), 1730 (CO_2Me), 1640 (C=C). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20−7.08 (m, 10 H, 2 Ph), 5.70 (dd, *J* = 17.1, 10.5 Hz, 1 H, 2-H), 5.56 (m_c, 2 H, 8-H, 12-H), 5.47 (m_c, 2 H, 7-H, 13-H), 5.14 (dd, *J* = 17.1, 1.0 Hz, 1 H, 1-H), 4.98 (dd, *J* = 10.5, 1.0 Hz, 1 H, 1-H), 3.66 (s, 2 H, C*H*$_2$Ph), 3.46 (s, 3 H, CO_2Me), 3.46−3.42 (m, 2 H, C*H*$_2$Ph), 3.14−2.91 (m, 6 H, 14-H, 11-H, 9-H), 2.78 (dd, *J* = 15.3, 5.0 Hz, 1 H, 6-H), 2.09 (dd, *J* = 15.3, 5.0 Hz, 1 H, 6-H), 1.71 (d, *J* = 6.3 Hz, 1 H, 4-H), 1.61 (br. s, 1 H, NH), 0.90 (d, *J* = 6.3 Hz, 1 H, 4-H), 0.79 (s, 9 H, *t*Bu), 0.00, −0.03 (2 s, 6 H, $SiMe_2$). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 172.0, 51.8 (s, q, CO_2Me), 140.2, 139.5, 128.9, 128.4, 128.2, 128.1, 126.9, 126.7 (2 s, 6 d, Ph), 136.7 (d, C-2), 131.5, 130.9, 129.6, 128.6 (4 d, C-13, C-12, C-8, C-7), 115.2 (t, C-1), 65.1 (s, C-3), 57.3, 55.5, 55.2, 53.2, 50.8 (5 t, 2 *C*H$_2$Ph, C-14, C-9, C-11), 37.5 (s, C-5), 31.8, 23.7 (2 t, C-6, C-4), 25.8, 18.2 (q, s, *t*Bu), −3.4, −3.6 (2 q, $SiMe_2$). − MS (EI, 80 eV): *m*/*z* (%) = 574 (7) [M$^+$], 483 [M$^+$ − 91] (7), 91 (100). − HRMS: calcd. for $C_{35}H_{50}N_2O_3Si$: 574.35972; found 574.35896.

Synthesis of Amine 8: Following general procedure A, cyclopropyl bromide **7** (2.63 g, 4.53 mmol) was treated with benzylamine (4.86 g, 45.3 mmol) in dichloromethane (50 mL). Subsequent workup and purification by column chromatography (silica gel, hexane/EtOAc, 1:4) afforded **8** (2.10 g, 78%) as a light yellow liquid, along with dialkylamine **9** (0.40 g, 16%) as the second fraction (elution with hexane/EtOAc, 1:1). − IR (film): $\tilde{\nu}$ = 3445 cm^{-1} (N−H), 3090−3030 (=C−H), 3000−2860 (C−H), 1735 (CO_2Me), 1620 (C=C). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19−7.10 (m, 5 H, Ph), 5.69 (dd, *J* = 17.0, 10.5 Hz, 1 H, 2-H), 5.52−5.18 (m, 4 H, 7-H, 8-H, 12-H, 13-H), 5.14 (dd, *J* = 17.0, 1.0 Hz, 1 H, 1-H), 4.97 (dd, *J* = 10.5, 1.0 Hz, 1 H, 1-H), 3.62 (s, 2 H, C*H*$_2$Ph), 3.56, 3.51, 3.49 (3 s, 9 H, 3 CO_2Me), 3.07 (m_c, 2 H, 14-H), 2.72 (dd, *J* = 15.5, 6.5 Hz, 1 H, 6-H), 2.47 (m_c, 4 H, 9-H, 11-H), 2.06 (dd, *J* = 15.5, 6.5 Hz, 1 H, 6-H), 1.69 (d, *J* = 6.0 Hz, 1 H, 4-H), 1.31 (br. s, 1 H, NH), 0.88 (d, *J* = 6.0 Hz, 1 H, 4-H), 0.79 (s, 9 H, *t*Bu), 0.00, −0.03 (2 s, 6 H, $SiMe_2$). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.5, 170.8, 52.0, 51.6 (2 s, 2 q, CO_2Me), 140.1, 132.0, 128.1, 127.9 (s, 3 d, Ph), 136.5, 133.1 (2 d, C-2, C-7), 126.6, 125.6, 124.8 (3 d, C-8, C-12, C-13), 114.9 (t, C-1), 64.8 (s, C-3), 57.7 (s, C-10), 52.8, 50.5 (2 t, *C*H$_2$Ph, C-14), 37.1 (s, C-5), 35.6, 35.1, 31.5 (3 t, C-9, C-

11, C-6), 25.6, 17.9 (q, s, *t*Bu), 23.4 (t, C-4), −3.7, −3.8 (2 q, $SiMe_2$). − MS (EI, 80 eV): *m*/*z* (%) = 599 (7) [M^+], 508 [M^+ − 91] (5), 73 (100). − HRMS: calcd. for $C_{33}H_{49}NO_7Si$: 599.32783; found 599.32759.

Compound 9: IR (film): $\tilde{\nu}$ = 3090−2860 cm^{-1} (C−H, =C−H), 1735 (CO_2Me), 1640 (C=C). − ^1H NMR (300 MHz, $CDCl_3$): δ = 7.19−7.10 (m, 5 H, Ph), 5.69 (dd, *J* = 17.0, 10.5 Hz, 2 H, 2-H), 5.48−5.13 (m, 8 H, 7-H, 8-H, 12-H, 13-H), 5.17 (dd, *J* = 17.0, 1.5 Hz, 2 H, 1-H), 5.00 (dd, *J* = 10.5, 1.5 Hz, 2 H, 1-H), 3.55 (s, 12 H, 4 CO_2Me), 3.50 (s, 6 H, 2 CO_2Me), 3.37 (br. s, 2 H, CH_2Ph), 2.84 (m_c, 4 H, 14-H), 2.73 (dd, *J* = 15.5, 6.5 Hz, 2 H, 6-H), 2.45 (m_c, 8 H, 9-H, 11-H), 2.02 (dd, *J* = 15.5, 6.5 Hz, 2 H, 6-H), 1.69 (d, *J* = 6.3 Hz, 2 H, 4-H), 0.87 (d, *J* = 6.3 Hz, 2 H, 4-H), 0.78 (s, 18 H, *t*Bu), 0.00, −0.03 (2 s, 12 H, $SiMe_2$). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.8, 171.1, 52.3, 51.9 (2 s, 2 q, CO_2Me), 139.3, 132.1, 127.1, 126.8 (s, 3 d, Ph), 136.7, 132.2, 128.8, 128.8, 125.1 (5 d, C-2, C-7, C-8, C-12, C-13), 115.2 (t, C-1), 65.1 (s, C-3), 58.1 (s, C-10), 57.2, 55.2 (2 t, CH_2Ph, C-14), 35.7, 35.5, 31.8 (3 t, C-9, C-11, C-6), 25.8, 18.2 (q, s, *t*Bu), 23.6 (t, C-4), −3.5, −3.6 (2 q, $SiMe_2$). − $C_{59}H_{89}NO_{14}Si_2$ (1092.6): calcd. C 64.86, H 8.21, N 1.28; found C 62.77, H 7.85, N 1.61; no correct elemental analysis was obtained for this minor component.

Synthesis of Diamine 10: According to general procedure B, cyclopropyl bromide **7** (1.00 g, 1.74 mmol) in dry acetonitrile (20 mL) was treated with diammonium salt **5** (1.18 g, 3.48 mmol) in the presence of K_2CO_3 (1.20 g, 8.70 mmol), followed by purification using silica gel column chromatography (hexane/EtOAc, 1:4) to afford **10** (642 mg, 50%) as a light yellow liquid. − IR (film): $\tilde{\nu}$ = 3360 cm^{-1} (N−H), 3090−3030 (=C−H, C−H), 1735 (CO_2Me), 1640 (C=C). − ^1H NMR (300 MHz, $CDCl_3$): δ = 7.30−7.19 (m, 10 H, Ph), 5.79 (dd, *J* = 17.3, 10.6 Hz, 1 H, 2-H), 5.69−5.26 (m, 6 H, =CH), 5.22 (dd, *J* = 17.3, 1.4 Hz, 1 H, 1-H), 5.07 (dd, *J* = 10.6, 1.4 Hz, 1 H, 1-H), 3.76 (s, 2 H, CH_2Ph), 3.67, 3.59 (2 s, 9 H, 3 CO_2Me), 3.51 (s, 2 H, CH_2Ph), 3.24 (m_c, 2 H, 19-H), 3.00 (m_c, 4 H, 14-H, 16-H), 2.82 (dd, *J* = 15.4, 6.6 Hz, 1 H, 6-H), 2.55 (m_c, 4 H, 9-H, 11-H), 2.15 (dd, *J* = 15.4, 6.6 Hz, 1 H, 6-H), 1.79 (d, *J* = 5.8 Hz, 1 H, 4-H), 1.49 (br. s, 1 H, NH), 0.96 (d, *J* = 5.8 Hz, 1 H, 4-H), 0.88 (s, 9 H, *t*Bu), 0.09, 0.06 (2 s, 6 H, $SiMe_2$). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.7, 171.0, 52.1, 51.7 (2 s, 2 q, CO_2Me), 140.2, 139.4, 128.7, 128.1, 126.9, 126.8, 126.7 (2 s, 5 d, Ph), 136.6 (d, C-2), 132.1, 132.0, 131.6, 129.3, 128.3, 124.9 (6 d, =CH), 115.1 (t, C-1), 65.0 (s, C-3), 57.9 (s, C-10), 57.4 (t, C-19), 55.3, 55.1 (2 t, C-14, C-16), 53.2, 50.7 (2 t, CH_2Ph), 37.3 (s, C-5), 35.6, 35.4 (2 t, C-9, C-11), 31.7, 18.1 (2 t, C-6, C-4), 25.8, 14.1 (q, s, *t*Bu), −3.5, −3.7 (2 q, $SiMe_2$). − $C_{44}H_{62}N_2O_7Si$ (759.1): calcd. C 69.62, H 8.23, N 3.69; found C 68.99, H 8.02, N 3.42.

Synthesis of Amine 12: According to general procedure A, cyclopropyl bromide **11** (1.10 g, 2.50 mmol) was treated with benzylamine (2.68 g, 25.0 mmol) in dichloromethane (30 mL), followed by purification using silica gel column chromatography (hexane/EtOAc, 1:4) to give the corresponding amine **12** (967 mg, 83%) as a light yellow liquid. − IR (film): $\tilde{\nu}$ = 3345 cm^{-1} (N−H), 3065−2890 (=C−H, C−H), 1730 (CO_2Me), 1640 (C=C). − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.49−7.18 (m, 9 H, Ar), 5.93 (dd, *J* = 17.3, 10.0 Hz, 1 H, 2-H), 5.48 (dd, *J* = 17.3, 1.0 Hz, 1 H, 1-H), 5.20 (dd, *J* = 10.0, 1.0 Hz, 1 H, 1-H), 3.82, 3.81 (2 s, 2 H each, NCH_2), 3.60, 2.92 (2 d, *J* = 14.9 Hz, 1 H each, 6-H), 3.58 (s, 3 H, CO_2Me), 2.00 (d, *J* = 5.8 Hz, 1 H, 4-H), 1.71 (br. s, 1 H, NH), 1.28 (d, *J* = 5.8 Hz, 1 H, 4-H), 1.00 (s, 9 H, *t*Bu), 0.17, 0.16 (2 s, 6 H, $SiMe_2$). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 171.7, 51.6 (s, q, CO_2Me), 140.3, 140.2, 140.1, 128.8, 128.2, 128.0, 127.0, 126.7, 125.8 (3 s, 6 d, Ar), 136.6 (d, C-2), 115.3 (t, C-1), 65.0 (s, C-3), 53.0, 52.9 (2 t, N−CH_2), 38.5 (s, C-5), 34.1 (t, C-6), 25.7, 18.1 (q, s, *t*Bu), 23.8 (t, C-4), −3.4, −3.6 (2 q, $SiMe_2$). − MS (EI, 80 eV): *m*/*z* (%) = 465 (4) [M^+], 480 [M^+ − 57] (3), 360 [M^+ − 105] (17), 73 (100). − HRMS: calcd. for $C_{28}H_{39}NO_3Si$: 465.26992; found 465.26632.

Synthesis of Diamine 13: According to general procedure B, cyclopropyl bromide **11** (2.00 g, 4.60 mmol) in dry acetonitrile (25 mL) was treated with diammonium salt **5** (3.10 g, 9.28 mmol) in the presence of K_2CO_3 (3.20 g, 23.0 mmol), followed by purification using silica gel column chromatography (hexane/EtOAc, 1:4) to afford **13** (1.58 g, 55%) as a light yellow liquid. − IR (film): $\tilde{\nu}$ = 3340 cm^{-1} (N−H), 3085−2710 (=C−H, C−H), 1730 (CO_2Me), 1680, 1640 (C=C). − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.39−7.06 (m, 14 H, Ar), 5.85 (dd, *J* = 17.0, 11.2 Hz, 1 H, 2-H), 5.70 (m_c, 2 H, =CH), 5.29 (dd, *J* = 17.0, 1.5 Hz, 1 H, 1-H), 5.12 (dd, *J* = 11.2, 1.5 Hz, 1 H, 1-H), 3.77 (s, 2 H, CH_2Ph), 3.52 (s, 3 H, CO_2Me), 3.57−3.03 (m, 9 H, N−CH_2, 6-H), 2.83 (d, *J* = 15.4 Hz, 1 H, 6-H), 1.91 (d, *J* = 5.8 Hz, 1 H, 4-H), 1.25 (br. s, 1 H, NH), 1.18 (d, *J* = 5.8 Hz, 1 H, 4-H), 0.92 (s, 9 H, *t*Bu), 0.14, 0.12 (2 s, 6 H, $SiMe_2$). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 171.7, 50.8 (s, q, CO_2Me), 140.2, 140.0, 139.9, 139.8, 129.2, 128.9, 128.7, 128.6, 128.4, 127.3, 127.2, 127.0, 126.8 (4 s, 9 d, Ar), 136.9 (d, C-2), 130.9, 130.6 (2 d, =CH), 115.7 (t, C-1), 65.4 (s, C-3), 58.2, 58.1, 55.5, 53.2, 52.0 (5 t, NCH_2), 38.9 (s, C-5), 34.4 (t, C-6), 26.1, 18.5 (q, s, *t*Bu), 24.2 (t, C-4), −3.1, −3.2 (2 q, $SiMe_2$). − MS (EI, 80 eV): *m*/*z* (%) = 624 (6) [M^+], 533 [M^+ − 91] (4), 91 (100). − HRMS: calcd. for $C_{39}H_{52}N_2O_3Si$: 624.37472; found 624.37121.

Synthesis of Amine 15: Following general procedure A, cyclopropyl bromide **14** (471 mg, 1.07 mmol) was treated with benzylamine (1.15 g, 10.7 mmol) in dichloromethane (25 mL). Workup and purification by column chromatography (silica gel, hexane/EtOAc, 3:7) afforded **15** (390 mg, 78%) as a light yellow liquid. − IR (film): $\tilde{\nu}$ = 3325 cm^{-1} (N−H), 3085−2860 (=C−H, C−H), 1725 (CO_2Me), 1640 (C=C), 1590, 1575 (pyridine). − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.48 (t, *J* = 7.5 Hz, 1 H, pyr-H), 7.37−7.18 (m, 5 H, Ph), 7.01, 6.93 (2 d, *J* = 7.5 Hz each, 2 H, pyr-H), 5.88 (dd, *J* = 16.9, 10.3 Hz, 1 H, 2-H), 5.30 (dd, *J* = 16.9, 1.5 Hz, 1 H, 1-H), 5.11 (dd, *J* = 10.3, 1.5 Hz, 1 H, 1-H), 3.83, 3.81 (2 s, 2 H each, NCH_2), 3.69, 3.04 (2 d, *J* = 16.1 Hz, 1 H each, 6-H), 3.52 (s, 3 H, CO_2Me), 2.37 (br. s, 1 H, NH), 1.92 (d, *J* = 6.6 Hz, 1 H, 4-H), 1.20 (d, *J* = 6.6 Hz, 1 H, 4-H), 0.89 (s, 9 H, *t*Bu), 0.12, 0.09 (2 s, 6 H, $SiMe_2$). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 172.2, 51.7 (s, q, CO_2Me), 159.7, 158.7 (2 s, C-pyr), 140.3, 128.3, 128.2, 126.8 (s, 3 d, Ph), 136.7, 136.3, 120.6, 119.5 (4 d, C-2, C-pyr), 115.3 (t, C-1), 65.4 (s, C-3), 54.2, 53.4 (2 t, NCH_2), 37.3 (s, C-5), 36.7 (t, C-6), 25.8, 18.2 (q, s, *t*Bu), 24.2 (t, C-4), −3.4, −3.5 (2 q, $SiMe_2$). − MS (EI, 80 eV): *m*/*z* (%) = 466 (60) [M^+], 407 [M^+ − 59] (13), 375 [M^+ − 91] (36), 212 (100). − HRMS: calcd. for $C_{27}H_{38}N_2O_3Si$: 466.26517; found 466.26531.

Synthesis of Diamine 16: According to general procedure B, cyclopropyl bromide **14** (1.50 g, 3.40 mmol) in dry acetonitrile (25 mL) was treated with diammonium salt **5** (2.30 g, 6.80 mmol) in the presence of K_2CO_3 (2.34 g, 17.0 mmol), followed by purification using silica gel column chromatography (hexane/EtOAc, 1:4) to afford **16** (1.02 g, 49%) as a light yellow liquid. − IR (film): $\tilde{\nu}$ = 3340 cm^{-1} (N−H), 3085−2800 (=C−H, C−H), 1725 (CO_2Me), 1640 (C=C). − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.52 (t, *J* = 7.7 Hz, 1 H, pyr-H), 7.39−7.17 (m, 11 H, Ph, pyr-H), 7.01 (d, *J* = 7.7 Hz, 1 H, pyr-H), 5.90 (dd, *J* = 17.3, 10.6 Hz, 1 H, 2-H), 5.72 (m_c, 2 H, =CH), 5.33 (dd, *J* = 17.3, 1.4 Hz, 1 H, 1-H), 5.15 (dd, *J* = 10.6, 1.4 Hz, 1 H, 1-H), 3.76 (s, 3 H, CO_2Me), 3.76, 3.69, 3.61 (3 br s, 6 H, N−CH_2), 3.76−3.52 (m, 2 H, NCH_2), 3.20−3.00 (m, 4

H, NCH_2, 6-H), 1.93 (d, J = 5.8 Hz, 1 H, 4-H), 1.64 (br. s, 1 H, NH), 1.27 (d, J = 5.8 Hz, 1 H, 4-H), 0.89 (s, 9 H, *t*Bu), 0.13, 0.11 (2 s, 6 H, $SiMe_2$). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 172.1, 51.8 (s, q, CO_2Me), 159.4, 159.2 (2 s, C-pyr), 140.2, 139.5 (2 s, Ph), 136.8, 136.3 (2 d, C-2, C-pyr), 131.5, 129.5, 128.7, 128.3, 128.1, 126.8, 126.7 (7 d, =CH, Ph), 120.3, 119.9 (2 d, C-pyr), 115.1 (t, C-1), 65.3 (s, C-3), 59.6, 57.9, 55.5, 53.2, 50.7 (5 t, NCH_2), 37.1 (s, C-5), 36.8 (t, C-6), 25.8, 18.1 (q, s, *t*Bu), 24.4 (t, C-4), −3.5 (q, $SiMe_2$). − MS (EI, 80 eV): *m*/*z* (%) = 625 (22) [M^+], 361 (100). − HRMS: calcd. for $C_{38}H_{51}N_3O_3Si$: 625.36997; found 625.36933. − $C_{38}H_{51}N_3O_3Si$ (625.9): calcd. C 72.91, H 8.21, N 6.71; found C 72.66, H 7.97, N 6.76.

Synthesis of Amine 18: Following general procedure A, cyclopropyl bromide **17** (740 mg, 1.18 mmol) was treated with benzylamine (1.27 g, 11.8 mmol) in dichloromethane (25 mL). Workup and purification by column chromatography (silica gel, hexane/EtOAc, 1:4) afforded **18** (590 mg, 78%) as a light yellow liquid. − IR (film): $\tilde{\nu}$ = 3325 cm^{-1} (N−H), 3060−2860 (=C−H, C−H), 1735 (CO_2Me), 1640, 1590 (C=C). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.49 (t, J = 7.7 Hz, 1 H, pyr-H), 7.39−7.21 (m, 5 H, Ph), 7.03 (d, J = 7.7 Hz, 1 H, pyr-H), 6.93 (d, J = 7.7 Hz, 1 H, pyr-H), 5.79 (dd, J = 16.7, 10.3 Hz, 1 H, 2-H), 5.30 (m_c, 2 H, 7-H, 8-H), 5.24 (dd, J = 16.7, 1.0 Hz, 1 H, 1-H), 5.08 (dd, J = 10.3, 1.0 Hz, 1 H, 1-H), 3.77 (s, 4 H, NCH_2), 3.64, 3.63 (2 s, 9 H, 3 CO_2Me), 3.36 (s, 2 H, 11-H), 2.81 (br. dd, J = 17.2, 4.4 Hz, 1 H, 6-H), 2.48 (m_c, 2 H, 9-H), 2.16 (br. s, 1 H, NH), 2.15 (br. dd, J = 17.2, 4.4 Hz, 1 H, 6-H), 1.80 (d, J = 5.8 Hz, 1 H, 4-H), 0.97 (d, J = 5.8 Hz, 1 H, 4-H), 0.90 (s, 9 H, *t*Bu), 0.10, 0.08 (2 s, 6 H, $SiMe_2$). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 171.9, 171.4, 52.3, 51.9 (2 s, 2 q, CO_2Me), 158.9, 156.4 (2 s, C-pyr), 140.0, 128.3, 128.3, 126.8 (s, 3 d, Ph), 136.7, 136.4 (2 d, C-pyr, C-2), 132.2 (d, C-7), 125.4 (d, C-8), 122.3, 120.0 (2 d, C-pyr), 115.2 (t, C-1), 65.1 (s, C-3), 57.5 (s, C-10), 54.3, 53.5 (2 t, NCH_2), 39.3 (t, C-11), 37.5 (s, C-5), 35.3, 31.8 (2 t, C-6, C-9), 25.8, 18.2 (q, s, *t*Bu), 13.6 (t, C-4), −3.4, −3.6 (2 q, $SiMe_2$). − MS (EI, 80 eV): *m*/*z* (%) = 650 (32) [M^+], 619 [M^+ − 31] (26), 559 [M^+ − 91] (21), 237 (100). − HRMS: calcd. for $C_{36}H_{50}N_2O_7$: 650.33873; found 650.33809.

Methyl (*E*)-1-Benzyl-4-oxo-1,2,3,4,5,6,7,10-octahydroazecine-6-carboxylate (19): Following general procedure C, amine **3** (300 mg, 0.72 mmol) in DMF (50 mL) was treated with a warm suspension of CsF (330 mg, 2.17 mmol) and TEBA (247 mg, 1.08 mmol) in DMF (250 mL) for 22 h. Workup and purification by silica gel column chromatography (EtOAc/hexane, 1:9) afforded **19** (50 mg, 24%) as a thick, colourless liquid, along with dimer **20** (4 mg, 4%, colourless liquid, one diastereomer) as the second fraction. − IR (film): $\tilde{\nu}$ = 3085−2910 cm^{-1} (=C-H, C−H), 1735 (CO_2Me), 1705 (C=O), 1640 (C=C). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32−7.23 (m, 5 H, Ph), 5.59 (m_c, 1 H, 8-H), 5.25 (m_c, 1 H, 9-H), 3.69 (s, 3 H, CO_2Me), 3.65 (s, 2 H, C*H*$_2$Ph), 3.45−3.34 (m, 2 H, 10-H), 2.94−2.52 (m, 7 H, CH, CH_2), 2.47−2.26, 2.06−1.94 (2 m, 1 H each, CH_2). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 208.8 (s, C=O), 174.6, 51.9 (s, q, CO_2Me), 138.0, 128.8, 128.3, 127.1 (s, 3 d, Ph), 134.4, 130.2 (2 d, C-9, C-8), 62.2, 58.9 (2 t, *C*H$_2$Ph, C-10), 50.0, 45.3, 45.0 (3 t, C-2, C-5, C-3), 44.8 (d, C-6), 36.5 (t, C-7). − MS (EI, 70 eV): *m*/*z* (%) = 301 (14) [M^+], 210 [M^+ − CH_2Ph] (46), 91 (100). − $C_{18}H_{23}NO_3$ (301.4): calcd. C 71.73, H 7.69, N 4.65; found C 71.48, H 7.48, N 4.71.

Dimethyl (3*E*,13*E*)-1,11-Dibenzyl-8,18-dioxo-1,11-diazacycloeicosa-3,13-diene-6,16-dicarboxylate (20): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35−7.24 (m, 10 H, Ph), 5.63 (m_c, 2 H, 3-H, 13-H), 5.50 (m_c, 2 H, 4-H, 14-H), 3.79, 3.41 (AB system, J_{AB} = 13.0 Hz, 2 H each, C*H*$_2$Ph), 3.72 (s, 6 H, CO_2Me), 3.36−3.26, 3.14−3.02, 2.86−2.44, 2.39−2.30 (4 m, 2 H, 6 H, 12 H, 2 H, CH_2, CH). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 210.6 (s, C=O), 175.0, 51.9 (s, q, CO_2Me), 138.5 (s, Ph), 130.2, 130.0, 129.4, 129.0, 127.1 (5 d, Ph, C-3, C-4, C-13, C-14), 58.5 (t, *C*H$_2$Ph), 50.0, 48.4, 42.7 (3 t, C-2, C-5, C-10, C-12, C-15, C-20), 38.8 (d, C-16, C-6), 37.9 (t, C-7, C-17), 26.9 (t, C-9, C-19). − MS (FAB): *m*/*z* (%) = 603 [M^+ + 1] (4), 91 (100).

Methyl (3*E*,8*E*)-1,6-Dibenzyl-13-oxo-1,6-diazacyclopentadeca-3,8-diene-11-carboxylate (21): According to general procedure C, diamine **6** (456 mg, 0.79 mmol) was cyclized in the presence of CsF (362 mg, 2.38 mmol) and TEBA (270 mg, 1.19 mmol) in dry DMF (450 mL) for 24 h, followed by workup and column chromatography using silica gel (EtOAc/hexane, 4:6) to yield **21** (110 mg, 31%) as a colourless liquid. − IR (film): $\tilde{\nu}$ = 3085−2800 cm^{-1} (=C−H, C−H), 1735 (CO_2Me), 1715 (C=O), 1640 (C=C). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.40−7.22 (m, 10 H, Ph), 5.67 (m_c, 2 H, 3-H, 4-H), 5.52 (m_c, 2 H, 8-H, 9-H), 3.70 (s, 3 H, CO_2Me), 3.63−3.49 (m, 4 H, 2 C*H*$_2$Ph), 3.20−2.41, 2.27−2.13 (2 m, 14 H, 1 H, CH_2, CH). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 209.0 (s, C=O), 175.3, 51.9 (s, q, CO_2Me), 139.4, 138.9, 128.9, 128.8, 128.7, 128.2 (2 s, 4 d, Ph), 131.6, 130.9 (2 d, C-3, C-4), 127.0, 126.9 (2 d, C-8, C-9), 60.2 (t, C-2), 58.7 (t, C-5), 55.5, 55.4, 55.4 (3 t, 2 *C*H$_2$Ph, C-7), 48.9 (t, C-15), 42.3, 41.1 (2 t, C-10, C-12), 39.2 (d, C-11), 34.0 (t, C-14). − MS (EI, 80 eV): *m*/*z* (%) = 460 (14) [M^+], 429 [M^+ − 31] (18), 369 [M^+ − 91] (100). − HRMS: calcd. for $C_{29}H_{36}N_2O_3$: 460.27259; found 460.27058. − $C_{29}H_{36}N_2O_3$ (460.6): calcd. C 75.62, H 7.87, N 6.08; found C 73.90, H 7.48, N 5.62.

Trimethyl (3*E*,8*E*)-1-Benzyl-13-oxo-1-azacyclopentadeca-3,8-diene-6,6,11-tricarboxylate (22): Following general procedure C, amine **8** (1.25 g, 2.08 mmol) was cyclized in the presence of CsF (951 mg, 6.26 mmol) and TEBA (712 mg, 3.12 mmol) in dry DMF (750 mL) for 25 h, followed by workup and column chromatography using silica gel (EtOAc/hexane, 1:9) to yield **22** (191 mg, 19%) as a colourless liquid. − IR (film): $\tilde{\nu}$ = 3165−2610 cm^{-1} (=C−H, C−H), 1705 (CO_2Me), 1680 (C=C). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28−7.24 (m, 2 H, Ph), 7.21−7.18 (m, 3 H, Ph), 5.59−5.54 (m, 1 H, 3-H), 5.42−5.36 (m, 1 H, 9-H), 5.29 (m_c, 2 H, 8-H, 4-H), 3.66, 3.64 (2 s, 9 H, 3 CO_2Me), 3.56, 3.45 (AB system, J_{AB} = 14.0 Hz, 2 H, C*H*$_2$Ph), 2.95−2.78, 2.68−2.41, 2.19−2.13 (3 m, 6 H, 8 H, 1 H, CH_2, CH). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 208.7 (s, C=O), 175.0, 171.4, 171.0, 52.5, 52.3, 51.8 (3 s, 3 q, CO_2Me), 138.7, 131.0, 128.6, 128.2 (s, 3 d, Ph), 132.0 (d, C-3), 126.9, 126.6, 125.5 (3 d, C-9, C-4, C-8), 60.3 (s, C-6), 58.6, 55.8 (2 t, *C*H$_2$Ph, C-2), 49.5 (t, C-15), 41.9, 41.5 (2 t, C-5, C-7), 39.3 (d, C-11), 35.2, 35.1 (2 t, C-12, C-10), 33.7 (t, C-14). − MS (EI, 80 eV): *m*/*z* (%) = 485 (7) [M^+], 454 [M^+ − 31] (18), 394 [M^+ − 91] (59), 106 (100). − HRMS: calcd. for $C_{27}H_{35}NO_7$: 485.24135; found 485.24069.

Trimethyl (3*E*,8*E*,13*E*)-1,6-Dibenzyl-18-oxo-1,6-diazacycloeicosa-3,8,13-triene-11,11,16-tricarboxylate (23): Following general procedure C, diamine **10** (495 mg, 0.65 mmol) was cyclized in the presence of CsF (297 mg, 1.95 mmol) and TEBA (223 mg, 0.98 mmol) in dry DMF (450 mL) for 25 h, followed by workup and column chromatography using silica gel (EtOAc/hexane, 3:7) to yield **23** (258 mg, 62%) as a colourless liquid. − IR (film): $\tilde{\nu}$ = 3060−2800 cm^{-1} (=C−H, C−H), 1735 (CO_2Me), 1640 (C=C). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.32 (m_c, 10 H, 2 Ph), 5.74 (m_c, 2 H, =CH), 5.68−5.19 (m, 4 H, =CH), 3.71, 3.68 (2 s, 9 H, 3 CO_2Me), 3.57 (m_c, 4 H, 2 C*H*$_2$Ph), 3.20−2.78, 2.66−2.52, 2.49−2.22 (3 m, 10 H, 6 H, 3 H, CH_2, CH). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 208.3 (s, C=O), 174.7, 171.2, 171.1, 52.5, 51.9 (3 s, 2 q, CO_2Me), 139.2, 138.8 (2 s, Ph), 132.1, 130.8, 130.7, 128.9, 128.7, 128.2, 127.8, 127.6, 127.0, 126.9, 126.8 (11 d, Ph, =CH), 58.7, 58.7, 55.5, 54.9, 54.5 (5 t, 2 *C*H$_2$Ph, 3 CH_2), 57.0 (s, C-11), 48.8, 42.1, 41.0 (3 t, 3

CH_2), 39.3 (d, C-16), 35.3, 35.0, 34.4 (3 t, 3 CH_2). − MS (EI, 80 eV): *m*/*z* (%) = 644 (7) [M^+], 613 [M^+ − 31] (13), 553 [M^+ − 91] (52), 91 (100). − HRMS: calcd. for $C_{38}H_{48}N_2O_7$: 644.34615; found 644.34375.

Methyl 3-Benzyl-6-oxo-3,14-diazabicyclo[8.3.1]tetradeca-1(13),10(14),11-triene-8-carboxylate (25): According to general procedure C, amine **15** (320 mg, 0.69 mmol) was cyclized in the presence of CsF (315 mg, 2.07 mmol) and TEBA (236 mg, 1.03 mmol) in dry DMF (450 mL) for 22 h, followed by workup and column chromatography using silica gel (EtOAc/hexane, 1:1) to yield **25** (79 mg, 33%) as a colourless liquid. − IR (film): $\tilde{\nu}$ = 2955−2850 cm^{-1} (=C−H, C−H), 1730 (CO_2Me), 1710 (C=O). − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.47 (t, *J* = 7.5 Hz, 1 H, pyr-H), 7.40−7.22 (m, 5 H, Ph), 7.02, 6.76 (2 d, *J* = 7.5 Hz, each 1 H, pyr-H), 3.83 (m_c, 2 H, CH_2Ph), 3.80 (s, 2 H, 2-H), 3.75 (s, 3 H, CO_2Me), 3.34 (dd, *J* = 16.0, 3.7 Hz, 1 H, 9-H), 3.58−3.49, 3.20−2.98, 2.55−2.35 (3 m, 1 H, 4 H, 2 H, CH_2, CH), 2.77 (dd, *J* = 16.0, 1.5 Hz, 1 H, 9-H). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 207.3 (s, C=O), 175.8, 52.0 (s, q, CO_2Me), 157.9, 153.6 (2 s, C-1, C-10), 139.3 (d, C-12), 136.8, 128.9, 128.2, 126.9 (s, 3 d, Ph), 121.5, 120.5 (2 d, C-11, C-13), 59.5, 58.9 (2 t, C-2, CH_2Ph), 50.4 (t, C-4), 44.6, 42.5, 38.3 (3 t, C-9, C-7, C-5), 39.6 (d, C-8). − MS (EI, 80 eV): *m*/*z* (%) = 352 (55) [M^+], 261 [M^+ − 91] (31), 91 (100). − HRMS: calcd. for $C_{21}H_{24}N_2O_3$: 352.17869; found 352.17462.

Methyl (*E*)-3,8-Dibenzyl-11-oxo-3,8-diazabicyclo[13.3.1]nonadeca-1(18),5,15(19),16-tetraene-13-carboxylate (26): According to general procedure C, diamine **13** (520 mg, 0.83 mmol) was cyclized in the presence of CsF (379 mg, 2.49 mmol) and TEBA (283 mg, 1.24 mmol) in dry DMF (450 mL) for 22 h, followed by workup and column chromatography using silica gel (EtOAc/hexane, 2:3) to yield **26** (139 mg, 33%) as a colourless liquid. − IR (film): $\tilde{\nu}$ = 3085−2800 cm^{-1} (=C−H, C−H), 1735 (CO_2Me), 1710 (C=O), 1640 (C=C). − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.41−6.99 (m, 14 H, Ar), 5.75−5.54 (m, 2 H, 5-H, 6-H), 3.74−3.42 (m, 6 H, CH_2Ph, 2-H), 3.72 (s, 3 H, CO_2Me), 3.25−2.75, 2.68−2.42 (2 m, 9 H, 4 H, CH_2, CH). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 208.9 (s, C=O), 175.0, 51.8 (s, q, CO_2Me), 140.3, 139.4, 138.8, 138.3 (4 s, Ar), 131.1, 129.3, 129.0, 128.9, 128.7, 128.4, 128.2, 128.1, 127.6, 126.9, 126.9, 126.2 (12 d, Ar, C-5, C-6), 59.5, 58.6, 57.7, 55.7, 53.9 (5 t, C-2, CH_2Ph, C-4, C-7), 48.4, 41.8 (2 t, C-9, C-14), 41.3 (d, C-13), 41.2, 32.2 (2 t, C-12, C-10). − MS (EI, 80 eV): *m*/*z* (%) = 510 (12) [M^+], 479 [M^+ − 31] (8), 453 [M^+ − 57] (11), 419 [M^+ − 91] (100). − HRMS: calcd. for $C_{33}H_{38}N_2O_3$: 510.28702; found 510.28824.

Methyl (*E*)-3,8-Dibenzyl-11-oxo-3,8,19-triazabicyclo[13.3.1]nonadeca-1(18),5,15(19),16-tetraene-13-carboxylate (27): According to general procedure C, diamine **16** (240 mg, 0.38 mmol) was cyclized in the presence of CsF (175 mg, 1.15 mmol) and TEBA (130 mg, 0.57 mmol) in dry DMF (500 mL) for 22 h, followed by workup and column chromatography using silica gel (EtOAc/hexane, 2:3) to yield **27** (104 mg, 54%) as a colourless liquid. − IR (film): $\tilde{\nu}$ = 3085−2800 cm^{-1} (=C−H, C−H), 1735 (CO_2Me), 1700 (C=O), 1640 (C=C). − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.54 (t, *J* = 7.7 Hz, 1 H, pyr-H), 7.42−7.17 (m, 11 H, Ph, pyr-H), 6.98 (d, *J* = 7.7 Hz, 1 H, pyr-H), 5.73−5.62, 5.54−5.43 (2 m, 2 H, 5-H, 6-H), 3.75 (m_c, 4 H, 2 CH_2Ph), 3.67 (s, 3 H, CO_2Me), 3.52 (s, 2 H, 2-H), 3.48−2.84 (m, 9 H, CH, CH_2), 2.74 (m_c, 2 H, 12-H), 2.58 (m_c, 2 H, 10-H). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 208.8 (s, C=O), 174.9, 51.8 (s, q, CO_2Me), 159.1, 157.8 (2 s, C-pyr), 139.3, 138.9 (2 s, Ph), 136.6, 131.9 (2 d, C-5, C-6), 128.9, 128.7, 128.2, 128.1, 126.9, 126.9 (6 d, Ph), 128.6, 121.6, 120.7 (3 d, C-pyr), 59.5 (t, C-2), 58.6, 58.1 (2 t, CH_2Ph), 55.8, 54.2, 48.5 (3 t, C-4, C-7, C-9), 42.6, 40.9, 38.7 (3 t, C-14, C-12, C-10), 39.7 (d, C-13). − MS (EI, 80 eV): *m*/*z* (%) = 511 (4) [M^+], 480 [M^+ − 31] (1), 420 [M^+ − 91] (4), 91 (100). − HRMS: calcd. for $C_{32}H_{37}N_3O_3$: 511.28349; found 511.28333.

Trimethyl (*E*)-3-Benzyl-6-oxo-3,19-diazabicyclo[13.3.1]nonadeca-1(18),10,15(19),16-tetraene-8,13,13-tricarboxylate (28): According to general procedure C, amine **18** (590 mg, 0.90 mmol) was cyclized in the presence of CsF (413 mg, 2.72 mmol) and TEBA (309 mg, 1.36 mmol) in dry DMF (450 mL) for 22 h, followed by workup and column chromatography using silica gel (EtOAc/hexane, 3:7) to yield **28** (236 mg, 49%) as a colourless liquid. − IR (film): $\tilde{\nu}$ = 3060−2845 cm^{-1} (=C−H, C−H), 1740 (CO_2Me), 1700 (C=O), 1640 (C=C), 1590, 1580 (pyridine). − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.48 (t, *J* = 7.7 Hz, 1 H, pyr-H), 7.24 (m, 5 H, Ph), 6.94 (d, *J* = 7.7 Hz, 1 H, pyr-H), 6.83 (d, *J* = 7.7 Hz, 1 H, pyr-H), 5.68−5.48 (m, 2 H, 10-H, 11-H), 3.72, 3.71, 3.70 (3 s, 9 H, 3 CO_2Me), 3.70, 3.66 (AB system, J_{AB} = 13.2 Hz, 2 H, CH_2Ph), 3.57 (s, 2 H, 2-H), 3.44 (br. s, 2 H, 14-H), 3.06−2.46 (m, 10 H, 4-H, 5-H, 7-H, 9-H, 12-H), 2.32−2.21 (m, 1 H, 8-H). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 208.2 (s, C=O), 175.0, 171.0, 170.9, 52.4, 51.7 (3 s, 2 q, CO_2Me), 157.4, 156.5 (2 s, C-pyr), 138.7, 128.9, 128.1, 127.0 (s, 3 d, Ph), 136.3, 131.6 (2 d, C-11, C-10), 126.6, 122.5, 121.9 (3 d, C-pyr), 58.5, 58.0 (2 t, C-2, CH_2Ph), 58.2 (s, C-13), 48.9, 42.3, 41.0 (3 t, C-4, C-14, C-12), 39.2 (d, C-8), 39.1 (t, C-9), 34.3, 33.7 (2 t, C-5, C-7). − MS (EI, 80 eV): *m*/*z* (%) = 536 (23) [M^+], 505 [M^+ − 31] (10), 445 [M^+ − 91] (7), 91 (100). − HRMS: calcd. for $C_{30}H_{36}N_2O_7Si$: 536.25225; found 536.25177.

Synthesis of Amino Ester 30: Ester **29** (1.42 g, 5.78 mmol) was added, at −78 °C under argon atmosphere, to LDA (5.78 mmol) in THF (20 mL), and the reaction mixture was stirred for 1.5 h at this temperature. Cyclopropyl bromide **2** (1.50 g, 3.75 mmol) in THF (20 mL) was slowly added to the reaction mixture over a period of 10 min and the mixture was allowed to stir at −78 °C for 3 h. It was allowed to warm to room temperature and poured into saturated aqueous NH_4Cl solution (200 mL). The aqueous phase was extracted with ethyl acetate (3 × 20 mL) and the combined organic extracts were washed with brine (3 × 20 mL), dried (Na_2SO_4), and concentrated. Purification by flash chromatography using hexane/EtOAc (1:1) afforded **30** (1.36 g, 88%) as a colourless liquid (1:1 mixture of diastereomers). − IR (film): $\tilde{\nu}$ = 3380 cm^{-1} (N−H), 3095−2860 (=C−H, C−H), 1730 (CO_2Et, CO_2Me), 1640 (C=C). − ^1H NMR (300 MHz, $CDCl_3$): δ = 5.70 (dd, *J* = 17.0, 10.5 Hz, 1 H, 2-H), 5.45, 5.29 (2 m_c, 2 H, 7-H, 8-H), 5.14 (dd, *J* = 17.0, 1.0 Hz, 1 H, 1-H), 4.98 (dd, *J* = 10.5, 1.0 Hz, 1 H, 1-H), 4.05 (q, *J* = 7.2 Hz, 2 H, CO_2CH_2), 3.50 (s, 3 H, CO_2Me), 3.36 (t, *J* = 5.5 Hz, 1 H, 10-H), 2.75 (dd, *J* = 15.0, 6.0 Hz, 1 H, 6-H), 2.34−2.19 (m, 2 H, 9-H), 2.09 (dd, *J* = 15.0, 6.0 Hz, 1 H, 6-H), 1.70 (d, *J* = 6.5 Hz, 1 H, 4-H), 1.50 (br. s, 2 H, NH_2), 1.15 (t, *J* = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 0.89 (d, *J* = 6.5 Hz, 1 H, 4-H), 0.79 (s, 9 H, *t*Bu), 0.00, −0.02 (2 s, 6 H, $SiMe_2$). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 175.1, 51.8 (s, q, CO_2Me) 171.8, 60.7, 14.2 (s, t, q, $CO_2CH_2CH_3$), 136.6, 131.7, 126.1 (3 d, C-2, C-7, C-8), 115.1, 115.0 (2 t, C-1), 65.0, 64.9 (2 s, C-3), 54.0 (d, C-10), 37.9, 31.9, 31.8 (3 t, C-6, C-9), 37.4 (s, C-5), 18.1 (t, C-4), 25.7, 14.2 (q, s, *t*Bu), −3.5, −3.7 (2 q, $SiMe_2$). − $C_{21}H_{37}NO_5Si$ (411.6): calcd. C 61.27, H 9.06, N 3.40; found C 60.93, H 9.38, N 3.41.

Synthesis of *N*-Benzylated Amino Ester 31: Freshly distilled benzaldehyde (335 mg, 3.16 mmol) was added to the amino ester **30** (1.30 g, 3.16 mmol) in dry methanol (20 mL), followed by $MgSO_4$ (0.5 g). The reaction mixture was stirred for 1 h (monitored by TLC). After complete consumption of **30**, the reaction mixture was filtered and the filtrate was cooled to 0 °C. $NaBH_4$ (120 mg,

3.16 mmol) was added gradually over a period of 30−45 min. After stirring at room temperature for 2−3 h, the reaction mixture was poured into water and extracted with dichloromethane (3 × 20 mL), washed with brine, dried ($MgSO_4$), and concentrated. The residue, after purification by flash chromatography using hexane/EtOAc (3:7), afforded **31** (1.17 g, 74%, 3:2 mixture of diastereomers) as a colourless liquid. − IR (film): $\tilde{\nu}$ = 3340 cm^{-1} (N−H), 3085−2860 (=C−H, C−H), 1730 (CO_2Me, CO_2Et), 1640 (C=C). − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.31−7.13 (m, 5 H, Ph), 5.75 (dd, *J* = 17.2, 10.3 Hz, 1 H, 2-H), 5.59−5.31 (m, 2 H, 7-H, 8-H), 5.22 (dd, *J* = 17.2, 1.0 Hz, 1 H, 1-H), 5.07 (dd, *J* = 10.3, 1.0 Hz, 1 H, 1-H), 4.13 (q, *J* = 7.2 Hz, 2 H, CO_2CH_2), 3.78, 3.62 (AB system, J_{AB} = 12.9 Hz, 2 H, CH_2Ph), 3.52 (s, 3 H, CO_2Me), 3.27 (br. t, *J* = 6.5 Hz, 1 H, 10-H), 2.83 (dd, *J* = 15.5, 6.0 Hz, 1 H, 6-H), 2.35 (m_c, 2 H, 9-H), 2.15 (dd, *J* = 15.5, 6.0 Hz, 1 H, 6-H), 1.84 (br. s, 1 H, NH), 1.77 (d, *J* = 6.0 Hz, 1 H, 4-H), 1.23 (t, *J* = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 0.96 (d, *J* = 6.0 Hz, 1 H, 4-H), 0.90 (s, 9 H, *t*Bu), 0.10, 0.06 (2 s, 6 H, $SiMe_2$). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 174.3, 171.8, 60.4, 51.9, 51.7, 14.3 (2 s, t, 3 q, CO_2Me, CO_2Et), 139.8, 128.2, 128.1, 126.9 (s, 3 d, Ph), 136.7, 130.8, 126.4 (3 d, C-2, C-7, C-8), 115.1 (t, C-1), 65.0 (s, C-3), 60.5 (d, C-10), 51.8 (t, CH_2Ph), 37.4 (s, C-5), 36.5, 31.7 (2 t, C-6, C-9), 25.8, 18.1 (q, s, *t*Bu), 23.5 (t, C-4), −3.5, −3.7 (2 q, $SiMe_2$). − MS (EI, 80 eV): *m*/*z* (%) = 501 (3) [M^+], 428 [M^+ − 73] (4), 91 (100). − HRMS: calcd. for $C_{28}H_{43}NO_5Si$: 501.29105; found 501.29003.

2-Ethyl 7-Methyl (*E*)-1-Benzyl-9-oxo-1-azacycloundec-4-ene-2,7-dicarboxylate (32): According to general procedure C, amine **31** (220 mg, 0.44 mmol) was cyclized in the presence of CsF (200 mg, 1.31 mmol) and TEBA (150 mg, 0.66 mmol) in dry DMF (250 mL) for 30 h, followed by workup and column chromatography using silica gel (EtOAc/hexane, 1:3) to yield **32** (71 mg, 42%) as a colourless liquid (1:1 mixture of isomers). − IR (film): $\tilde{\nu}$ = 3065−2850 cm^{-1} (=C−H, C−H), 1730 (CO_2Me, CO_2Et), 1725 (C=O), 1640 (C=C). − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.41−7.22 (m, 5 H, Ph), 5.51−5.45, 5.38−5.29 (2 m, 1 H each, =CH), 5.02 (m_c, 1 H, =CH), 4.27−4.20 (m, 2 H, CO_2CH_2), 3.95, 3.89 (AB system, J_{AB} = 14.0 Hz, 1 H, CH_2Ph), 3.75, 3.74 (2 s, 3 H, CO_2Me), 3.59, 3.52 (AB system, J_{AB} = 13.2 Hz, 1 H, CH_2Ph), 3.42−2.57 (m, 7.5 H, CH_2), 2.36−1.57 (m, 4.5 H, CH, CH_2), 1.30, 1.28 (2 t, *J* = 7.7 Hz each, 3 H, CH_3). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 210.0, 208.1 (2 s, C=O), 175.6, 172.8, 172.5, 60.3, 60.2, 51.9, 14.5, 14.4 (3 s, 2 t, 3 q, CO_2Me, CO_2Et), 139.5, 138.6 (2 s, Ph), 130.6, 130.3, 130.0, 129.5, 129.3, 128.6, 128.5, 127.6, 127.2, 126.9 (10 d, Ph, =CH), 64.5 (d, C-2), 56.8, 55.7 (2 t, CH_2Ph, C-11), 47.2, 46.3, 44.3, 43.2, 41.9 (5 t, CH_2), 38.3, 38.1 (2 d, C-7), 36.1, 32.9, 32.4 (3 t, CH_2). − MS (EI 80 eV): *m*/*z* (%) = 387 (2) [M^+], 356 [M^+ − 31] (2), 314 [M^+ − 73] (30), 91 (100). − HRMS: calcd. for $C_{22}H_{29}NO_5$: 387.204573; found 387.20843.

Synthesis of Amino Ester 33: Ester **29** (1.89 g, 3.23 mmol) was added, at −78 °C under argon atmosphere, to LDA (4.83 mmol) in THF (20 mL), and the reaction mixture was stirred for 1.5 h at the same temperature. The cyclopropyl bromide **7** (927 mg, 1.61 mmol) in THF (20 mL) was slowly added to the reaction mixture over a period of 10 min and the mixture was allowed to stir at −78 °C for 3 h. It was allowed to warm to room temperature and poured into saturated aqueous NH_4Cl solution (200 mL). The aqueous phase was extracted with ethyl acetate (3 × 20 mL) and the combined organic extracts were washed with brine (3 × 20 mL), dried (Na_2SO_4), and concentrated. Purification by flash chromatography using hexane/EtOAc (1:1) afforded **33** (608 mg, 63%) as a colourless liquid (1:1 mixture of diastereomers). − IR (film): $\tilde{\nu}$ = 3380 cm^{-1} (N−H), 2955−2860 (=C−H, C−H), 1740 (CO_2Me, CO_2Et), 1640 (C=C). − ^1H NMR (250 MHz, $CDCl_3$): δ = 5.69 (dd, *J* = 16.7, 11.0 Hz, 1 H, 2-H), 5.48−5.09 (m, 4 H, 7-H, 8-H, 12-H, 13-H), 5.10 (dd, *J* = 16.7, 1.5 Hz, 1 H, 1-H), 4.95 (dd, *J* = 11.0, 1.5 Hz, 1 H, 1-H), 4.07−3.92 (m, 2 H, CO_2CH_2), 3.55, 3.54, 3.48 (3 s, 9 H, 3 CO_2Me), 3.32 (t, *J* = 6.6 Hz, 1 H, 15-H), 2.69 (dd, *J* = 15.0, 6.6 Hz, 1 H, 6-H), 2.40 (br. d, *J* = 6.5 Hz, 4 H, 9-H, 11-H), 2.33−2.15 (m, 2 H, 14-H), 2.02 (dd, *J* = 15.0, 6.6 Hz, 1 H, 6-H), 1.67 (d, *J* = 5.8 Hz, 1 H, 4-H), 1.51 (br. s, 2 H, NH_2), 1.57−1.07 (m, 3 H, $CO_2CH_2CH_3$), 0.86 (d, *J* = 5.8 Hz, 1 H, 4-H), 0.78 (s, 9 H, *t*Bu), −0.02, −0.04 (2 s, 6 H, $SiMe_2$). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 174.8, 171.5, 170.8, 60.4, 52.0, 51.6, 53.7, 14.0 (3 s, t, 4 q, CO_2Me, CO_2Et), 136.5, 132.2, 129.3, 127.9, 124.7 (5 d, C-2, C-7, C-8, C-12, C-13), 114.9 (t, C-1), 64.8 (s, C-3), 60.6 (d, C-15), 57.7 (s, C-10), 37.7 (s, C-5), 37.1, 35.3, 35.2 (3 t, C-6, C-9, C-11), 31.5 (t, C-14), 25.6, 17.9 (q, s, *t*Bu), 23.4 (t, C-4), −3.7, −3.9 (2 q, $SiMe_2$). − MS (EI, 80 eV): *m*/*z* (%) = 595 (13) [M^+], 564 [M^+ − 91] (19), 522 [M^+ − 73] (100). − $C_{30}H_{49}NO_9Si$ (595.8): calcd. C 66.43, H 7.74, N 4.30; found C 65.54, H 7.36, N 4.23.

Synthesis of *N*-Benzylated Amino Ester 34: Freshly distilled benzaldehyde (0.10 g, 0.92 mmol) was added to the amino ester **33** (0.55 g, 0.92 mmol) in dry methanol (15 mL), followed by $MgSO_4$ (0.25 g). The reaction mixture was stirred for 1 h (monitored by TLC). After complete consumption of **33**, the reaction mixture was filtered and the filtrate was cooled to 0 °C. $NaBH_4$ (40 mg, 1.00 mmol) was added gradually over a period of 30−45 min. After stirring at room temperature for 2−3 h, the reaction mixture was poured into water and extracted with dichloromethane (3 × 20 mL), washed with brine, dried ($MgSO_4$), and concentrated. The residue, after purification by flash column chromatography using hexane and EtOAc (1:1), afforded **34** (0.51 g, 81%, 3:2 mixture of diastereomers) as a colourless liquid. − IR (film): $\tilde{\nu}$ = 3365 cm^{-1} (N−H), 3030−2860 (=C−H, C−H), 1740 (CO_2Me), 1640 (C=C). − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.37−7.23 (m, 5 H, Ph), 5.80 (dd, *J* = 17.3, 10.6 Hz, 1 H, 2-H), 5.59−5.25 (m, 4 H, 7-H, 8-H, 12-H, 13-H), 5.25 (dd, *J* = 17.3, 1.4 Hz, 1 H, 1-H), 5.09 (dd, *J* = 10.6, 1.4 Hz, 1 H, 1-H), 4.17 (q, *J* = 7.1 Hz, 2 H, CO_2CH_2), 3.87, 3.65 (AB system, J_{AB} = 13.2 Hz, 2 H, CH_2Ph), 3.67, 3.62 (2 s, 9 H, CO_2Me), 3.28 (t, *J* = 6.6 Hz, 1 H, 15-H), 2.84 (dd, *J* = 15.4, 6.6 Hz, 1 H, 6-H), 2.54 (br. d, *J* = 6.5 Hz, 4 H, 9-H, 11-H), 2.36 (m_c, 2 H, 14-H), 2.16 (dd, *J* = 15.4, 6.6 Hz, 1 H, 6-H), 1.82 (br. s, 1 H, NH), 1.80 (d, *J* = 6.6 Hz, 1 H, 4-H), 1.27 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 0.99 (d, *J* = 6.6 Hz, 1 H, 4-H), 0.91 (s, 9 H, *t*Bu), 0.11, 0.08 (2 s, 6 H, $SiMe_2$). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 174.4, 171.8, 171.1, 60.6, 52.2, 51.9, 14.3 (3 s, t, 3 q, CO_2Et, CO_2Me), 139.8, 128.3, 128.2, 127.4 (s, 3 d, Ph), 136.7 (d, C-2), 132.2, 129.9, 127.0, 125.1 (4 d, C-7, C-8, C-12, C-13), 115.2 (t, C-1), 65.1 (s, C-3), 60.4 (d, C-15), 58.0 (s, C-10), 51.8 (t, CH_2Ph), 37.4 (s, C-5), 36.5, 35.6, 35.5 (3 t, C-14, C-9, C-11), 31.8 (t, C-6), 25.8, 18.2 (q, s, *t*Bu), 23.6 (t, C-4), −3.5, −3.6 (2 q, $SiMe_2$). − MS (EI, 80 eV): *m*/*z* (%) = 686 (1) [M^+ + 1], 685 (3) [M^+], 654 [M^+ − 31] (1), 612 [M^+ − 73] (100). − HRMS: calcd. for $C_{37}H_{55}NO_9Si$: 685.36461; found 685.36408. − $C_{30}H_{49}NO_9Si$ (685.9): calcd. C 64.79, H 8.08, N 2.04; found C 64.26, H 7.54, N 1.84.

2-Ethyl 7,7,12-Trimethyl (4*E*,9*E*)-1-benzyl-14-oxo-1-azacyclohexadeca-4,9-diene-2,7,7,12-tetracarboxylate (35): According to general procedure C, amine **34** (325 mg, 0.47 mmol) was cyclized in the presence of CsF (215 mg, 2.49 mmol) and TEBA (161 mg, 1.24 mmol) in dry DMF (500 mL) for 28 h, followed by workup and column chromatography using silica gel (EtOAc/hexane, 1:3) to yield **35** (63 mg, 24%) as a colourless liquid (1:1 mixture of isomers). − IR (film): $\tilde{\nu}$ = 3085−2850 cm^{-1} (=C−H, C−H), 1735 (CO_2Me, CO_2Et), 1730 (C=O), 1640 (C=C). − ^1H NMR

(250 MHz, $CDCl_3$): δ = 7.30−7.18 (m, 5 H, Ph), 5.59−5.35 (m, 2 H, 4-H, 5-H), 5.27−5.05 (m, 2 H, 9-H, 10-H), 4.25−4.06 (m, 2 H, OCH_2), 3.97, 3.85 (AB system, J_{AB} = 13.2 Hz, 1 H, CH_2Ph), 3.45, 3.37 (AB system, J_{AB} = 13.9 Hz, 1 H, CH_2Ph), 3.72, 3.71, 3.70, 3.68, 3.67, 3.66 (6 s, 9 H, 3 CO_2Me), 3.35−2.05 (m, 16 H, CH, CH_2), 1.31−1.23 (m, 3 H, CH_3). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 208.1, 207.6 (2 s, C=O), 175.1, 172.4, 172.0, 171.8, 171.5, 171.0, 60.2, 52.6, 52.6, 51.9, 14.5 (6 s, t, 4 q, CO_2Me, CO_2Et), 139.1, 138.9 (2 s, Ph), 132.0, 131.8, 131.3, 131.1 (4 d, C-4, C-10), 129.3, 128.9, 128.3, 128.2, 127.2, 126.7, 126.3, 124.6 (8 d, Ph, C-5, C-10), 62.7, 62.2 (2 d, C-2), 56.2, 55.9 (2 s, C-7), 55.7, 54.5 (2 t, CH_2), 46.6, 45.5, 42.8, 42.7, 41.3 (5 t, CH_2), 39.9, 38.7 (2 d, C-12), 35.0, 34.9, 34.8, 34.5, 33.7, 32.6, 32.0 (7 t, CH_2). − MS (EI, 80 eV): *m*/*z* (%) = 571 (1) [M^+], 540 [M^+ − 31] (11), 498 [M^+ − 73] (100). − HRMS: calcd. for $C_{31}H_{41}NO_9$: 571.27813; found 571.27863.

Methyl 1-Benzyl-4-oxoazecane-6-carboxylate (36): Pd−C (100 mg, 10% Pd) was added to **19** (95 mg, 0.31 mmol) in MeOH (10 mL). The reaction mixture was stirred under a hydrogen atmosphere for 48 h and then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography using silica gel (hexane/EtOAc, 4:1) to afford **36** (44 mg) in 47% yield. − IR (film): $\tilde{\nu}$ = 3065−2855 cm^{-1} (C−H, =C−H), 1735 (CO_2Me), 1700 (C=O). − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.42−7.23 (m, 5 H, Ph), 3.88−3.65 (m, 2 H, CH_2Ph), 3.68 (s, 3 H, CO_2Me), 3.53−3.11, 2.82−2.69, 2.48−1.91, 1.58−1.00 (4 m, 2 H, 2 H, 5 H, 6 H, CH_2, CH). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 214.8 (s, C=O), 174.4, 51.4 (s, q, CO_2Me), 139.8, 128.5, 128.0, 127.0 (s, 3 d, Ph), 56.0 (t, *C*H_2Ph), 54.3, 52.2, 46.3, 46.2 (4 t, CH_2), 40.4 (d, C-6), 35.3, 33.5, 29.8 (3 t, CH_2). − MS (EI, 80 eV): *m*/*z* (%) = 303 (3) [M^+], 212 [M^+ − 91] (1), 91 (100). − HRMS: calcd. for $C_{18}H_{25}NO_3$: 303.18343; found 303.18293.

Dimethyl 4-Benzyl-15-oxo-4,16,17-triazabicyclo[12.3.1]octadeca-1(17),6,11-triene-9,9-dicarboxylate (37): Compound **22** (101 mg, 0.21 mmol) was added to a solution of 80% hydrazine hydrate (14 mg, 0.28 mmol) in MeOH (5 mL). The reaction mixture was stirred for 16 h at room temperature before removal of the solvent under vacuum. Column chromatography using silica gel (hexane/EtOAc, 7:3) afforded **37** (49 mg, 50%) as a viscous oil. − IR (film): $\tilde{\nu}$ = 3240 cm^{-1} (N−H), 3030−2850 (C−H, =CH), 1730 (CO_2Me), 1680 (C=N, C=O). − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.38−7.20 (m, 5 H, Ph), 5.59−5.41 (m, 4 H, =CH), 3.71, 3.70 (2 s, 3 H each, 2 CO_2Me), 3.72−3.57 (m, 2 H, CH_2Ph), 2.99−2.20 (m, 11 H, CH_2, NH), 2.18−1.71 (m, 5 H, CH_2, CH). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.6, 171.5, 52.6, 52.5 (2 s, 2 q, CO_2Me), 169.5 (s, CONH), 153.6 (s, C=N), 140.8 (s, Ph), 130.6, 128.8, 128.7, 128.3, 127.8, 127.1, 126.9 (7 d, Ph, =CH), 58.5 (s, C-9), 57.6, 57.1, 56.5, 56.2, 51.1, 36.5, 36.1, 25.5 (8 t, CH_2), 35.9 (d, C-14). − MS (EI, 80 eV): *m*/*z* (%) = 467 (6) [M^+], 436 [M^+ − 31] (4), 376 [M^+ − 91] (34), 91 (100). − HRMS: calcd. for $C_{26}H_{33}N_3O_5$: 467.24202; found 467.24533.

10,15-Dibenzyl-5,6,10,15,21-pentaazatricyclo[15.3.1.1^{3,7}]docosa-1(21),6,12,17,19-pentaen-4-one (38): Compound **27** (69 mg, 0.13 mmol) was added to a solution of 80% hydrazine hydrate (10 mg, 0.20 mmol) in MeOH (5 mL). The reaction mixture was stirred for 16 h at room temperature before removal of the solvent under vacuum. Column chromatography using silica gel (hexane/EtOAc, 7:3) afforded **38** (29 mg, 46%) as a colourless solid (m.p. 161−163 °C, recrystallized from MeOH). − IR (KBr): $\tilde{\nu}$ = 3410 cm^{-1} (N−H), 2930−2850 (C−H, =CH), 1675 (C=O, C=N). − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.71−7.08 (m, 13 H, Ar), 6.33−6.15 (m, 1 H, =CH), 5.96 (m_c, 1 H, =CH), 4.10−3.59, 3.28−3.05, 2.82−2.56, 2.20−1.71 (4 m, 6 H, 4 H, 4 H, 6 H CH_2, CH). − MS (EI, 80 eV): *m*/*z* (%) = 493 (1) [M^+], 402 [M^+ − CH_2Ph] (1), 355 [M^+ − $C_7H_{10}N_2O$] (1), 91 (100). − HRMS: calcd. for $C_{31}H_{35}N_5O$: 493.28416; found 493.28420.

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[1] C. L. Kranemann, P. Eilbracht, *Eur. J. Org. Chem.* **2000**, 2367−2377.
[2] F. Denat, S. Brandes, R. Guilard, *Synlett* **2000**, 561−574.
[3] F. P. Schmidtchen, M. Berger, *Chem. Rev.* **1997**, *97*, 1609−1646.
[4] R. M. Izatt, K. Pawlak, J. S. Bradshaw, *Chem. Rev.* **1995**, *95*, 2529−2586.
[5] M. Ramaseshan, M. Robitaille, J. W. Ellingboe, Y. L. Dory, P. Deslongschamps, *Tetrahedron Lett.* **2000**, *41*, 4737−4742.
[6] P. Soucy, Y. L. Dory, P. Deslongschamps, *Synlett* **2000**, 1123−1126.
[7] B. R. Bear, K. J. Shea, *Org. Lett.* **2001**, *3*, 723−726.
[8] H. Graubaum, B. Costisella, R. Dambowsky, *J. Prakt. Chem.* **1998**, *340*, 165−170.
[9] E. Kimura, J. Koike, *Chem. Commun.* **1998**, 1495−1500.
[10] M. L. Turonek, P. Moore, H. J. Clase, N. W. Alcock, *J. Chem. Soc., Dalton Trans.* **1995**, 3659−3666.
[11] A. Bencini, M. I. Burguette, E. Garcia-Espana, S. V. Luis, J. F. Miravet, C. Soriano, *J. Org. Chem.* **1993**, *58*, 4749−4753.
[12] E. Kimura, *Top. Curr. Chem.* **1985**, *128*, 113−141.
[13] D. Parker, *Chem. Soc. Rev.* **1990**, *19*, 271−291.
[14] R. Krämer, *Angew. Chem.* **2000**, *112*, 4641−4642; *Angew. Chem. Int. Ed.* **2000**, *39*, 4469−4470.
[15] E. Kimura, *Tetrahedron* **1992**, *48*, 6175−6217.
[16] C. J. Roxburgh, *Tetrahedron* **1995**, *51*, 9767−9822.
[17] E. Kimura, T. Koieke, M. Takahashi, *J. Chem. Soc., Chem. Commun.* **1985**, 385−386.
[18] E. Kimura, *Pure & Appl. Chem.* **1989**, *61*, 823−828.
[19] D. Weibel, V. Gevorgyan, Y. Yamamoto, *J. Org. Chem.* **1998**, *63*, 1217−1220.
[20] Review: H.-U. Reißig, *Top. Curr. Chem.* **1988**, *144*, 73−135.
[21] E. L. Grimm, R. Zschiesche, H.-U. Reißig, *J. Org. Chem.* **1985**, *50*, 5543−5545.
[22] R. Zschiesche, E. L. Grimm, H.-U. Reißig, *Angew. Chem.* **1986**, *98*, 1104−1105; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1086−1087.
[23] R. Zschiesche, H.-U. Reißig, *Liebigs Ann. Chem.* **1988**, 1165−1168.
[24] J. Schnaubelt, R. Zschiesche, H.-U. Reißig, H. J. Lindner, J. Richter, *Liebigs Ann. Chem.* **1993**, 61−70, references cited therein.
[25] J. Schnaubelt, B. Frey, H.-U. Reißig, *Helv. Chim. Acta* **1999**, *82*, 666−676 and references cited therein.
[26] B. Frey, J. Schnaubelt, H.-U. Reißig, *Eur. J. Org. Chem.* **1999**, 1377−1384.
[27] J. Schnaubelt, A. Ullmann, H.-U. Reißig, *Synlett* **1995**, 1223−1225.
[28] A. Ullmann, J. Schnaubelt, H.-U. Reißig, *Synthesis* **1998**, 1052−1066.
[29] A. Ullmann, J. Schnaubelt, H.-U. Reißig, O. Rademacher, *Eur. J. Org. Chem.* **1998**, 2541−2549.
[30] A. Ullmann, M. Gruner, H.-U. Reißig, *Chem. Eur. J.* **1999**, *5*, 187−197.

[31] P. K. Patra, H.-U. Reißig, *Synlett* **2001**, 33−36.
[32] I. Reichelt, H.-U. Reißig, *Liebigs Ann. Chem.* **1984**, 531−551.
[33] Compounds **4** and **9** are formed as 1:1 mixtures of diastereomers that cannot be distinguished by spectroscopic methods, due to the large distance between the corresponding stereogenic centres.
[34] A. F. DeRose, A. W. Weston, German Patent 1016265, 1959; *Chem. Abstr.* **1958**, *52*, 6413.
[35] G. Rousseau, *Tetrahedron* **1995**, *51*, 2777−2849.
[36] A. Ullmann, Dissertation, Technische Universität Dresden, **1998** and: P. K. Patra, H.-U. Reißig, unpublished results.
[37] In ref. 30 we have discussed the possibility of a favourable cesium effect, but we have found no clear evidence that this cation is responsible for high-yield cyclizations.
[38] S. Djuric, J. Venit, P. Magnus, *Tetrahedron Lett.* **1981**, *22*, 1787−1790.
[39] A. Barco, S. Benetti, G. Spalluto, A. Casolari, G. P. Pollini, V. Zanirato, *J. Org. Chem.* **1992**, *57*, 6279−6286.
[40] Similar reactions from our group: I. Reichelt, H.-U. Reißig, *Synthesis* **1984**, 786−787.
[41] H. Frank, G. Heinisch, *Pharmacologically Active Pyridazines*, in: *Progress in Medicinal Chemistry* (Eds.: G. P. Ellis, D. K. Luscombe), Elsevier, Amsterdam, **1990**, Part 1, Vol. 27, pp. 1 and *ibid.* (Eds.: G. P. Ellis, G. B. West), Elsevier, Amsterdam, **1992**, Part 2, Vol. 29, pp. 141.
[42] C. Galli, L. Mandolini, *Eur. J. Org. Chem.* **1998**, 3117−3125.
[43] A. Giannis, T. Kolter, *Angew. Chem.* **1993**, *105*, 1303−1306; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1244−1267.
[44] M. Newcomb, G. W. Gokel, D. J. Cram, *J. Am. Chem. Soc.* **1974**, *96*, 6810−6811.

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