Intramolecular Reactivity of *trans* [4+4] Photodimers of 2-Pyridones

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Dedicated to Paul A. Wender on the occasion of his 60th year

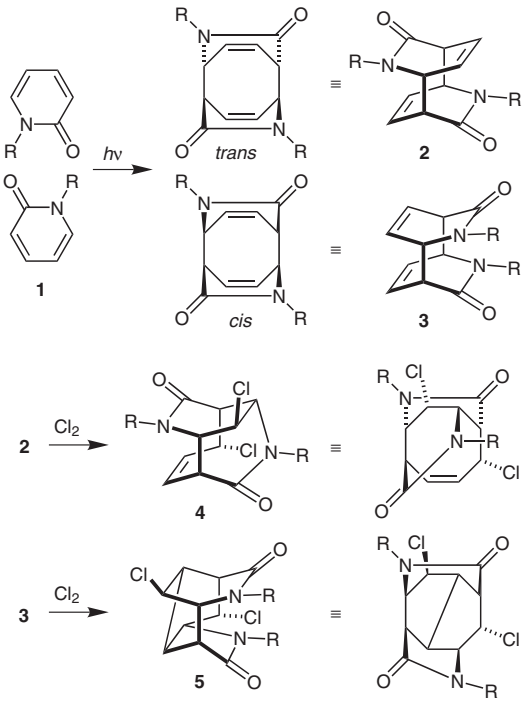
Abstract: Photodimers of 2-pyridones are cycloocta-1,5-dienes with two lactam bridges. These, and related structures, undergo halogenation to give rearranged products in which an amide nitrogen has intercepted an initial halonium ion. For the *trans* isomer, a transient four-membered azetidinium ion reacts via dealkylation, giving a dihalide-diamide product in high yield. This readily available intermediate reacts with nucleophiles in a process that begins with intramolecular amide N-alkylation, reforming the azetidinium intermediate. Reaction of this intermediate with the nucleophile can take two different paths, depending on the reversibility of the nucleophilic attack, with reversible nucleophiles giving N-dealkylation and irreversible nucleophiles reacting with the carbonyl group.

Key words: cycloadditions, dimerizations, ketones, photochemistry, pyridines

Photodimerization of 2-pyridones **1** yields highly functionalized cycloocta-1,5-dienes regioselectively and often with good stereoselectivity (Scheme 1). This singlet-mediated [4+4] cycloaddition is selective for head-to-tail isomers **2** and **3**, frequently favoring *trans*-isomer **2** (Scheme 1).[1] Procedures for favoring either *trans*-**2** or *cis*-**3** have been described.[2–4]

Each of these conformationally rigid structures has been found to undergo transannular reactions with amide nitrogen migration when treated with chlorine (Scheme 1). Treatment of *trans*-dimer **2** with chlorine results in a 1,3-migration of one amide nitrogen to yield **4**, whereas a similar treatment of **3** leads to participation of both alkenes, creating a diquinane structure **5**, whose formation is also accompanied by migration of an amide nitrogen (Scheme 1).

Diquinane **5** has obvious applications in natural product synthesis,[5,6] but is derived from the less stable dimer **3** and is formed in moderate yield. In contrast, product **4** forms in high yield from the most common and most stable dimer **2**. We describe here groundwork for the use of this readily available intermediate: investigations into the halogenation of *trans*-**2** and related structures, and the reactivity of nucleophiles with product **4**, which contains both an allylic and a non-allylic secondary halide. A preliminary report on this work has appeared.[7]



Scheme 1 Photodimerization of 2-pyridones and chlorination of the *cis*- and *trans*-dimers

Formation of **4** from **2** involves an intermediate chloronium ion **6**, in which the chlorine has been added to the least-hindered face of one alkene group (Scheme 2). This chloronium ion is then intercepted by the amide nitrogen that lies on the other side. The resulting azetidinium amide **7** is reminiscent of a von Braun intermediate, primed to undergo dealkylation.[8,9] Three possible bonds can be broken in the next step, following paths a, b, and c (Scheme 2). In terms of orbital overlap, path a initially appeared to be the most likely; however, this potential product **8** is not observed, possibly because of the electronegative influence of the neighboring chloride. The von Braun reaction is well known for dealkylation of cyclic amines. This path b, however, would lead to the frustrated amide **9**, and it also not observed. Path c appears less obvious, but leads to the sole product **4** that is isolated (Scheme 2). Initially it was believed that the allylic nature of this position led to this site of reactivity; however, the actual reason is apparently more subtle (see below).

Three *N*-alkylpyridone dimers have been subjected to halogenation (Scheme 3, Table 1). Addition of chlorine to

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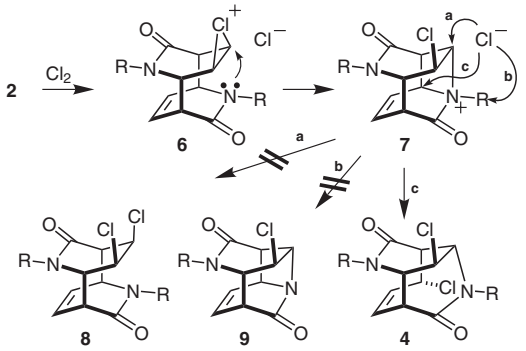
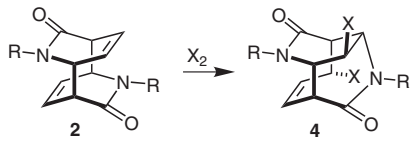


Scheme 2 Mechanism for chlorination of the *trans*-dimer **2**

the *N*-butyl dimer **2a** gave product **4a** in almost quantitative yield, with the structure confirmed by X-ray crystallography.[10] The more labile *N*-benzyl and *N*-(methoxymethyl) derivatives also gave the dichlorides **4c** and **4d** in high yield. Bromination of **2a** smoothly gave the dibromide **4b**.

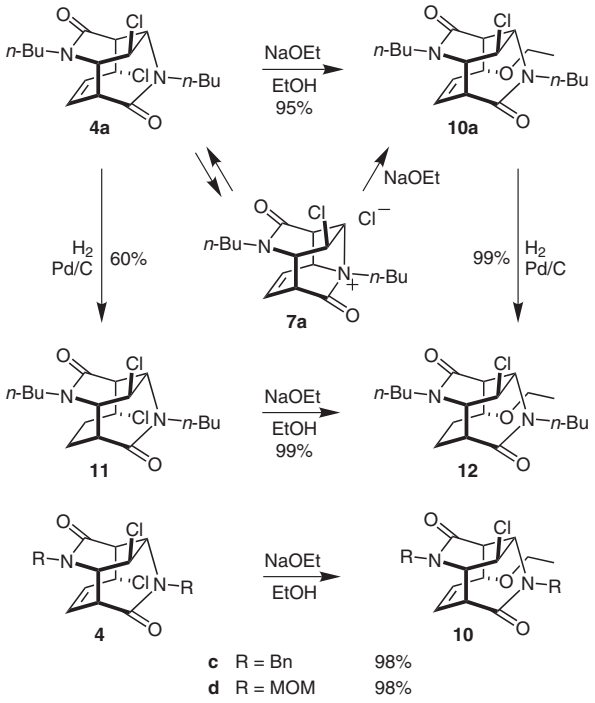


Scheme 3

Table 1 Yields of Dihalides **4**

Product **4**	R	X	Yield (%)
4a	*n*-Bu	Cl	99
4b	*n*-Bu	Br	70
4c	Bn	Cl	99
4d	MOM	Cl	99

Dihalides **4** present a unique array of functionality, with a secondary aliphatic halide and a secondary allylic halide, flanked by tertiary amides on both sides of the central cyclooctene. An initial probe of the reactivity of **4a** was conducted by treating this dichloride with sodium ethoxide (Scheme 4). Inspection of the structure of **4a** (Figure 1) reveals that S_N2 attack on both chlorides is blocked by an amide that straddles the space between them. The allylic nature of one chloride, however, suggested that S_N2' displacement might be an accessible pathway. This analysis proved incorrect, however, with ethoxide **10a** as the sole product formed. The nearly identical NMR spectra for **4a** and **10a**, except for the addition of the ethoxy signals, suggested analogous structures. Compound **10a**, whose structure was confirmed by X-ray crystallography,[11] is the apparent result of a double-inversion process. This process would entail an equilibrium between dichloro diamide **4a** and the azetidinium **7a**. The rate determining step, therefore, would likely be the internal displacement of the allylic chloride. It is notable that, once again, the



Scheme 4

ethoxide nucleophile attacks only one of several potential sites.

The reason for the surprising absence of an S_N2' attack of the nucleophile on the allylic chloride is revealed in the crystal structure of **4a** (Figure 1).[7] The carbon–chloride bond of the allylic chloride is nearly orthogonal to the π orbitals of the alkene. In addition, if the allylic chloride could be twisted to an S_N2' compatible conformation, an amide near the alkene face *syn* to the chloride may also hinder the S_N2' approach of the nucleophile.

Nevertheless, it was assumed that one influence of the allylic system was the enhancement of reactivity of the allylic bond of the azetidinium ion of intermediate **7**. This role was probed by hydrogenating the alkene of **4a** to give **11** (Scheme 4). The clean reduction of this alkene, without loss of the allylic chloride, is another indication of the conformational disjunction of normal allylic reactivity. Surprisingly, treatment of **11** with sodium ethoxide gave a clean conversion into a single product identical with **12**, formed by hydrogenation of **10a**.

Modeling of intermediate **7** found the rather symmetric structure shown in Figure 2.[12] The azetidinium ion has two bonds between carbon and nitrogen that would be broken by nucleophilic attack by paths a and c. In this analysis, the two bonds are nearly identical in length; the bond to be broken in nucleophilic attack via path a is longer by 0.005 Å. The selectivity for path c is therefore likely to be a consequence of the steric and electronic effect of the chloride substitution next to the azetidinium ion.

Investigation of the chlorination reaction was expanded to include the pyridone–naphthalene cycloadduct **15**,

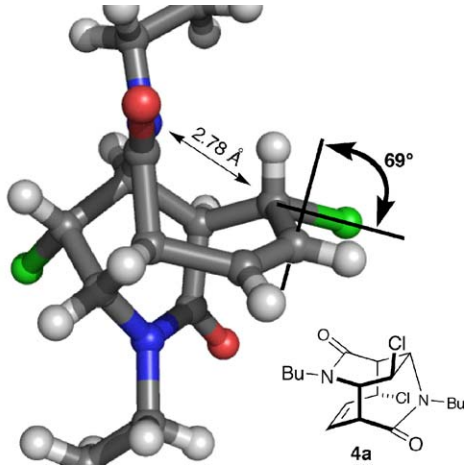


Figure 1 Partial crystal structure showing the dihedral angle of the allylic chloride in **4a** and the blockage of the S_N2 pathways by an amide

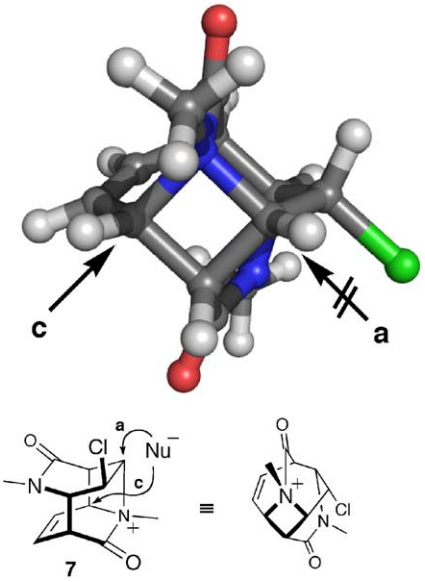
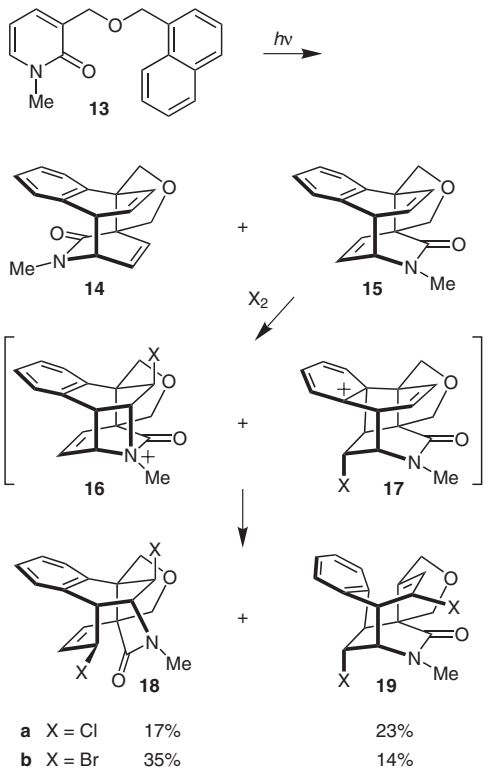


Figure 2 Calculated structure of azetidinium intermediate **7**

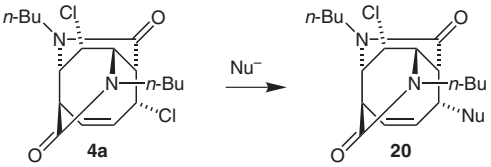
formed by irradiation of **13** and produced as a mixture with the *cis*-isomer **14** (Scheme 5). Substrate **15** has two non-equivalent alkenes, and there is little discrimination between them: two products were formed in this reaction and both were definitively proven by X-ray crystallography.[13] One product of this reaction is the equivalent of that described above, from chloronium ion interception by a nearby amide nitrogen. The resulting azetidinium ion **16** is then cleaved by chloride to give **18** (Scheme 5).

Where chlorination of the alternative alkene occurs, the chloronium is intercepted by the nearby aromatic ring, via cyclobutane **17** (Scheme 5). In this case, the structure of **19** suggests that the chloride opening of intermediate **17** occurs in an S_N2' fashion to give **19**. In this case, however, a direct S_N2 opening of cyclobutane **17** would yield a tertiary allylic chloride, which might be expected to rearrange to **19**. It is notable that there are two different phenyl migrations possible for **15**, one leading through **17** to **19** (Scheme 5). The alternative phenyl migration isomer is not observed.



Scheme 5 Products **18** and **19** produced by chlorination of **15**; both the amide nitrogen and the phenyl group migrate

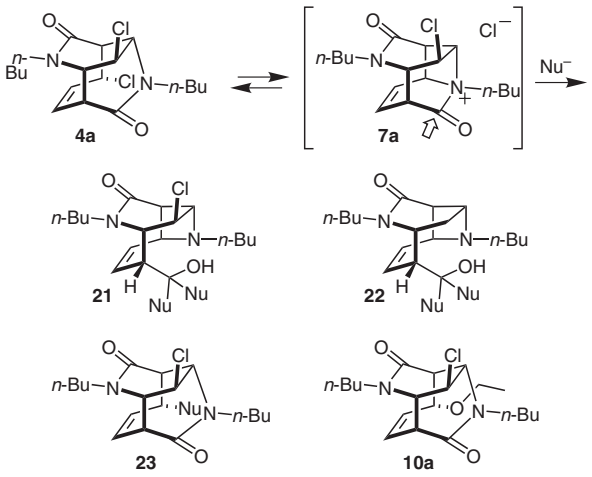
Nucleophilic substitution of the allylic chloride in **4a** was studied with nucleophiles in addition to ethoxide (Scheme 6). With nucleophiles that can add reversibly to a carbonyl, substitution of the chloride proceeded smoothly. The reaction with sodium methoxide gave substitution analogous to that of sodium ethoxide, although with a slightly reduced yield. Thiophenol and pyrrolidine, both in the presence of sodium hydride, gave sulfur and nitrogen displacement examples. Malononitrile also gave substitution in good yield.



	NuH	yield
a	MeOH	93%
b	PhSH	85%
c		88%
d		80%

Scheme 6 Substitution of the allylic chloride by soft nucleophiles

Harder nucleophiles revealed another reaction path, attacking the carbonyl group of the intermediate azetidinium **7a** (Scheme 7, Table 2). When the amide in **4a** displaces the chloride to give **7a**, the amide carbonyl becomes susceptible to nucleophilic attack (see arrow, Scheme 7). In the case of reversible nucleophiles such as ethoxide, addition to this acyl ammonium carbonyl is of little consequence. When the nucleophile addition is irreversible, however, the addition leads to formation of a ketone or aldehyde, which then suffers a second addition. Allyl Grignard addition proceeds in good yield, to give essentially one product **21a** (Scheme 7, Table 2). Other Grignard reagents (phenyl, ethyl, phenylethynyl) were less satisfactory, yielding mixtures of products, although these reactions were not optimized.



Scheme 7 Reaction of **4a** with irreversible nucleophiles

Table 2 Products of Reaction of **4a** with Irreversible Nucleophiles

Reagent	Nu	Products	Yield (%)			
			21	**22**	**23**	**10a**
AllMgCl	All	**21a**	60	–	–	–
$NaBH_4$, EtOH	H	**23b**, **10a**	–	–	30	50
$LiBH_4$, THF	H	**21b**, **22b**	16	35	–	–

With hydride as the nucleophile, the reaction was slower and produced a range of products (Scheme 7, Table 2). With sodium borohydride in ethanol at ambient temperature for eight hours, starting **4a** remained, but was fully consumed after an additional two hours at reflux. In this case, the major product was **10a**, by chloride displacement by solvent, with a lesser amount of the dechlorinated **23b** formed in substantial amounts (Scheme 7, Table 2). With lithium borohydride in THF for seven days, only azetidine products were isolated; however, two-thirds of this product included loss of the allylic chloride, to give **22b** (Scheme 7, Table 2). It is tempting to suggest that this product results from internal delivery of a hydride from the newly formed primary alcohol.

Photocycloaddition of 2-pyridones with themselves, or with other 1,3-diene equivalents (1,3-dienes, furan, naphthalene), yields well-functionalized cycloocta-1,5-dienes, often in high yield and with good regio- and stereoselectivity. When these cycloocta-1,5-diene products are treated with chlorine or bromine, transannular participation leads to novel structures. For the reactions of the *trans*-cycloadducts described here, capture of the intermediate halonium ion by the amide nitrogen forms a reactive four-membered ammonium intermediate that then reacts even with modest nucleophiles such as chloride, giving the product in high yield and as a single stereoisomer. When the halogenation substrate is the achiral pyridone dimer **4**, which has a center of symmetry, the product is chiral, with six contiguous stereogenic centers. The allylic halide is readily displaced with relatively soft nucleophiles, but this reaction is governed by one of the nearby amide nitrogens. These studies are continuing.

Et_2O, THF and CH_2Cl_2 were dried using a Glass Contour (now Seca Solvent Systems) purification system. Melting points were measured with a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker WM-400 spectrometer. Exact mass measurements were performed with a VG70SE instrument at Drexel University.

1-Benzylpyridin-2(1*H*)-one (1c)[14]

To a soln of 2-pyridone (7.1 g, 75 mmol) in MeOH (100 mL) was added K_2CO_3 (21 g, 150 mmol) and BnBr (13 mL, 112 mmol). The mixture was heated to reflux for 2.5 h, filtered, and concentrated. The residue was diluted with H_2O (150 mL) and extracted with EtOAc (4 × 50 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc).

Yield: 12.3 g (89%); colorless solid; R_f = 0.42 (hexanes–EtOAc, 1:2); mp 68 °C (Lit.[5] 72 °C).

^1H NMR (400 MHz, $CDCl_3$): δ = ca. 7.28–7.19 (m, 7 H), 6.56 (d, *J* = 9.2 Hz, 1 H), 6.08 (dd, *J* = 6.4, 1.2 Hz, 1 H), 5.09 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.0, 139.7, 137.6, 136.7, 129.2, 128.5, 128.3, 121.6, 106.6, 52.4.

1-(Methoxymethyl)pyridin-2(1*H*)-one (1d)[15]

To a soln of 2-pyridone (5.0 g, 53 mmol) in THF (200 mL) at 0 °C was added NaH (1.9 g, 79 mmol). After 0.5 h, MOMCl (4.8 mL, 63 mmol) was added, and the mixture was stirred at 0 °C for an additional 0.5 h. The soln was diluted with sat. NH_4Cl (100 mL), extracted with EtOAc (4 × 100 mL), dried (Na_2SO_4), and concentrated in vacuo.

Yield: 7.4 g (100%); oil; R_f = 0.47 (MeOH–CH_2Cl_2, 1:20).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.29 (m, 2 H), 6.48 (d, *J* = 8.4 Hz, 1 H), 6.13 (t, *J* = 6.4 Hz, 1 H), 5.24 (s, 2 H), 3.32 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.2, 140.3, 136.4, 121.7, 106.4, 78.5, 57.3.

(1*R,2*R**,5*S**,6*S**)-3,7-Dibenzyl-3,7-diazatricyclo[4.2.2.2^{2,5}]dodeca-9,11-diene-4,8-dione (2c)**

An 8.0 M soln of 1-benzylpyridin-2(1*H*)-one (**1c**; 12.0 g, 64.78 mmol) in MeOH (8 mL) was irradiated with a water-cooled Pyrex-

filtered 450-W medium-pressure mercury lamp for 3 d. The soln was concentrated in vacuo and the residue was washed with hexanes.

Yield: 3.6 g (30%); colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (m, 3 H), 7.07 (m, 2 H), 6.47 (t, *J* = 6.9 Hz, 1 H), 5.97 (t, *J* = 8.1 Hz, 1 H), 5.05 (d, *J* = 15.0 Hz, 1 H), 3.95 (m, 1 H), 3.53 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3, 136.3, 135.4, 130.7, 129.1, 128.4, 128.1, 55.4, 50.9, 50.7.

(1*R,2*R**,5*S**,6*S**)-3,7-Bis(methoxymethyl)-3,7-diazatricyclo[4.2.2.2^{2,5}]dodeca-9,11-diene-4,8-dione (2d)**

Neat 1-(methoxymethyl)pyridine-2(1*H*)-one (**1d**; 7.3 g, 52.46 mmol) was irradiated with a water-cooled Pyrex-filtered 450-W medium-pressure mercury lamp for 22 h. The colored impurities were removed by flash chromatography (MeOH–CH_2Cl_2, 5:100). Other impurities were washed out with Et_2O; this gave pure **2d**.

Yield: 700 mg (10%); colorless solid; R_f = 0.42 (MeOH–CH_2Cl_2, 1:20); mp 200 °C.

IR (KBr): 3054, 2928, 1670, 1265, 739 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.62 (t, *J* = 6.8 Hz, 1 H), 6.14 (t, *J* = 7.2 Hz, 1 H), 4.96 (d, *J* = 11.2 Hz, 1 H), 4.31 (m, 1 H), 4.15 (d, *J* = 10.4 Hz, 1 H), 3.63 (m, 1 H), 3.22 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3, 134.7, 131.3, 77.7, 56.7, 54.4, 50.5.

HRMS–FAB: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{18}N_2O_4$: 301.1164; found: 301.1155.

(1*R,4*S**,7*S**,8*S**,11*R**,12*R**)-2,10-Dibutyl-7,12-dichloro-2,10-diazatricyclo[6.4.0.0^{4,11}]dodec-5-ene-3,9-dione (4a)**

To a soln of **2a** (107 mg, 0.35 mmol) in CH_2Cl_2 (5 mL) was added a 0.46 M soln of Cl_2 in CH_2Cl_2 (0.9 mL, 0.41 mmol), and the mixture was stirred at r.t. for 1 h. The soln was diluted with sat. $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (4 × 30 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo.

Yield: 135 mg (100%); colorless solid; R_f = 0.57 (hexanes–EtOAc, 1:2); mp 165–167.5 °C.

IR (KBr): 2959, 2932, 2872, 1662, 1467, 1176, 753 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93 (dt, *J* = 12.0, 1.6 Hz, 1 H), 5.77 (t, *J* = 10.8 Hz, 1 H), 4.85 (q, *J* = 2.0 Hz, 1 H), 4.22 (dd, *J* = 4.0, 1.6 Hz, 1 H), 3.91–3.81 (m, 2 H), 3.66–3.58 (m, 3 H), 3.49 (dt, *J* = 10.0, 1.6 Hz, 1 H), 3.11–2.98 (m, 2 H), 1.56–1.23 (m, 8 H), 0.90 (t, *J* = 7.2 Hz, 3 H), 0.86 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 165.7, 137.1, 127.1, 60.1, 59.7, 58.1, 56.1, 51.1, 48.7, 48.2, 47.5, 30.1, 30.0, 20.7, 20.6, 14.1, 14.0.

(1*R,4*S**,7*S**,8*S**,11*R**,12*R**)-7,12-Dibromo-2,10-dibutyl-2,10-diazatricyclo[6.4.0.0^{4,11}]dodec-5-ene-3,9-dione (4b)**

To a soln of **2a** (50 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) was added Br_2 (11 μL, 0.22 mmol) in CH_2Cl_2, and the reaction mixture was stirred at r.t. for 1 h. The soln was diluted with sat. $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (hexanes–EtOAc, 1:1).

Yield: 53 mg (70%); colorless solid; R_f = 0.57 (1:1 hexanes–EtOAc); mp 168–170 °C.

IR (KBr): 2958, 2930, 2871, 1661, 1467, 1176, 737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.07 (d, *J* = 11.4 Hz, 1 H), 5.70 (td, *J* = 10.4, 2.4 Hz, 1 H), 4.95 (q, *J* = 2.4 Hz, 1 H), 4.32 (dd, *J* = 4.5, 1.2 Hz, 1 H), 3.92 (d, *J* = 10.2 Hz, 1 H), 3.87–3.56 (m, 5 H), 3.10 (m, 1 H), 2.91 (m, 1 H), 1.60–1.20 (m, 8 H), 0.88 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 165.4, 137.3, 127.4, 60.1, 57.8, 50.9, 50.8, 48.4, 47.8, 47.5, 44.8, 29.8, 29.7, 20.4, 20.2, 13.9, 13.8.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{26}N_2O_2Br_2$: 463.041879; found: 463.0410.

(1*R,4*S**,7*S**,8*S**,11*R**,12*R**)-2,10-Dibenzyl-7,12-dichloro-2,10-diazatricyclo[6.4.0.0^{4,11}]dodec-5-ene-3,9-dione (4c)**

To a soln of **2c** (3.0 g, 8.10 mmol) in CH_2Cl_2 (300 mL) was added a 0.23 M soln of Cl_2 in CH_2Cl_2 (39 mL, 8.9 mmol), and the mixture was stirred at r.t. for 1 h. The soln was diluted with sat. $NaHCO_3$ (200 mL) and extracted with CH_2Cl_2 (4 × 100 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo.

Yield: quantitative; colorless solid; R_f = 0.71 (hexanes–EtOAc, 1:2); mp 200–201 °C.

IR (KBr): 3475, 3314, 3055, 2980, 2926, 1660, 1452, 1264, 1172, 735 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.30 (m, 10 H), 5.94 (d, *J* = 11.4 Hz, 1 H), 5.40 (td, *J* = 11.1, 2.4 Hz, 1 H), 5.27 (d, *J* = 13.8 Hz, 1 H), 4.93 (d, *J* = 14.1 Hz, 1 H), 4.77 (m, 1 H), 4.35 (d, *J* = 14.4 Hz, 1 H), 4.10–3.90 (m, 4 H), 3.56 (d, *J* = 10.2 Hz, 1 H), 3.40 (t, *J* = 10.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165, 164, 132, 131, 130.4, 129.7, 129.2, 129.0, 60, 59.9, 58, 57, 53, 52, 51, 45.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{22}N_2O_2Cl_2$: 441.1136; found: 441.1143.

(1*R,4*S**,7*S**,8*S**,11*R**,12*R**)-7,12-Dichloro-2,10-bis(methoxymethyl)-2,10-diazatricyclo[6.4.0.0^{4,11}]dodec-5-ene-3,9-dione (4d)**

To a soln of **2d** (55 mg, 0.20 mmol) in CH_2Cl_2 (5 mL) was added dropwise a 0.63 M soln of Cl_2 in CH_2Cl_2 (0.38 mL, 0.24 mmol), and the resulting mixture was stirred at 0 °C for 0.5 h. The soln was diluted with sat. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (4 × 10 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo.

Yield: quantitative; colorless solid; R_f = 0.54 (MeOH–CH_2Cl_2, 1:20); mp 58–60 °C.

IR (KBr): 2940, 2834, 1674, 1456, 1173, 1080 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.02 (dt, *J* = 11.7, 1.5 Hz, 1 H), 5.86 (td, *J* = 10.8, 2.7 Hz, 1 H), 5.14 (q, *J* = 2.1 Hz, 1 H), 5.00 (d, *J* = 10.8 Hz, 1 H), 4.77 (s, 2 H), 4.52 (d, *J* = 10.5 Hz, 1 H), 4.38 (dd, *J* = 4.2, 1.5 Hz, 1 H), 4.15 (m, 2 H), 3.77 (t, *J* = 10.5 Hz, 1 H), 3.55 (d, *J* = 10.2 Hz, 1 H), 3.37 (s, 3 H), 3.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 167.0, 137.1, 127.0, 79.1, 78.2, 59.9, 59.0, 58.1, 57.6, 56.7, 56.2, 50.8, 47.5.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}N_2O_4Cl_2$: 349.0722; found: 349.0733.

(1*R,4*S**,7*S**,8*S**,11*R**,12*R**)-2,10-Dibutyl-7-chloro-12-ethoxy-2,10-diazatricyclo[6.4.0.0^{4,11}]dodec-5-ene-3,9-dione (10a)**

To a soln of **4a** (100 mg, 0.27 mmol) in absolute EtOH (5 mL) was added a 0.16 M soln of NaOEt in EtOH (2 mL, 0.32 mmol), and the mixture was heated at reflux for 3 h, cooled, and concentrated in vacuo. The residue was diluted with H_2O (20 mL) and extracted with EtOAc (4 × 30 mL). The combined organics were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (hexanes–EtOAc, 1:10).

Yield: 97 mg (95%); colorless solid; R_f = 0.66 (hexanes–EtOAc, 1:5); mp 144–146 °C.

IR (KBr): 3453, 2961, 2930, 2872, 1661, 1265, 738 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.85 (d, *J* = 12.8 Hz, 1 H), 5.75 (td, *J* = 10.4, 2.8 Hz, 1 H), 4.22 (dd, *J* = 4.4, 1.6 Hz, 1 H), 4.19 (q, *J* = 2.4 Hz, 1 H), 3.85 (m, 2 H), 3.63 (m, 4 H), 3.40 (q, *J* = 7.2 Hz, 1 H), 3.34 (d, *J* = 10.4 Hz, 1 H), 3.07 (m, 2 H), 1.37 (m, 2 H), 1.20 (m, 6 H), 1.20 (t, *J* = 6.8 Hz, 3 H), 0.90 (t, *J* = 7.2 Hz, 3 H), 0.84 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 166.5, 137.8, 125.4, 65.3, 60.2, 58.9, 58.0, 48.2, 48.1, 47.5, 46.4, 30.1, 30.0, 20.66, 20.59, 15.5, 14.1.

HRMS–FAB: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{31}N_2O_3Cl$: 405.19209; found: 405.1920.

(1*R,4*S**,7*S**,8*S**,11*R**,12*R**)-2,10-Dibenzyl-7-chloro-12-ethoxy-2,10-diazatricyclo[6.4.0.0^{4,11}]dodec-5-ene-3,9-dione (10c)**

To a soln of compound **4c** (60 mg, 0.14 mmol) in absolute EtOH (10 mL) was added 0.5 M NaOEt in EtOH (0.55 mL, 0.27 mmol), and the mixture was heated at reflux for 0.5 h. The soln was cooled and concentrated in vacuo. The residue was diluted with sat. NH_4Cl (20 mL) and extracted with EtOAc (4 × 30 mL). The combined organics were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (hexanes–EtOAc, 1:1.5).

Yield: 60 mg (98%); colorless solid; R_f = 0.34 (hexanes–EtOAc, 1:1); mp 192–193 °C.

IR (KBr): 3475, 3301, 3032, 2976, 2870, 1659, 1464, 1264, 1169, 1096, 732 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.30 (m, 10 H), 5.86 (d, *J* = 11.4 Hz, 1 H), 5.46 (td, *J* = 10.5, 2.7 Hz, 1 H), 5.12 (d, *J* = 14.1 Hz, 1 H), 4.67 (d, *J* = 13.8 Hz, 1 H), 4.55 (d, *J* = 14.4 Hz, 1 H), 4.15 (m, 2 H), 4.01 (m, 2 H), 3.90 (m, 1 H), 3.40 (m, 3 H), 3.07 (m, 1 H), 1.19 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 167.0, 137.3, 136.1, 135.7, 130.5, 129.6, 129.5, 128.94, 128.90, 128.4, 125.6, 65.2, 60.3, 58.6, 56.2, 51.8, 51.4, 47.2, 46.3, 15.6.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{27}N_2O_3Cl$: 451.1788; found: 451.1805.

(1*R,4*S**,7*S**,8*S**,11*R**,12*R**)-7-Chloro-12-ethoxy-2,10-bis(methoxymethyl)-2,10-diazatricyclo[6.4.0.0^{4,11}]dodec-5-ene-3,9-dione (10d)**

To a soln of compound **4d** (69 mg, 0.20 mmol) in absolute EtOH (5 mL) was added 0.5 M NaOEt in EtOH (0.6 mL, 0.30 mmol), and the mixture was heated at reflux for 1 h. The soln was cooled and concentrated in vacuo. The residue was diluted with sat. NH_4Cl (10 mL) and extracted with EtOAc (4 × 10 mL). The combined organics were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (MeOH–CH_2Cl_2, 5:100).

Yield: 70 mg (98%); colorless solid; R_f = 0.41 (MeOH–CH_2Cl_2, 1:20).

IR (KBr): 2934, 2873, 1671, 1456, 1384, 1173, 1083 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.91 (m, 2 H), 4.85 (d, *J* = 10.8 Hz, 1 H), 4.73 (q, *J* = 9.6 Hz, 2 H), 4.58 (d, *J* = 11.1 Hz, 1 H), 4.43 (s, 1 H), 4.32 (d, *J* = 4.5 Hz, 1 H), 4.15 (m, 2 H), 3.69 (m, 2 H), 3.45 (m, 2 H), 3.36 (s, 3 H), 3.35 (s, 3 H), 1.22 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 167.4, 138.1, 125.2, 78.7, 78.2, 77.5, 65.3, 60.0, 58.13, 58.09, 57.6, 56.6, 47.6, 46.3, 15.4.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{23}N_2O_5Cl$: 359.1373; found: 359.1356.

(1*R,4*S**,7*S**,8*S**,11*R**,12*R**)-2,10-Dibutyl-7,12-dichloro-2,10-diazatricyclo[6.4.0.0^{4,11}]dodecane-3,9-dione (11)**

To a soln of **4a** (125 mg, 0.33 mmol) in MeOH (2 mL) was added 10% Pd/C (36 mg, 0.033 mmol). The mixture was stirred at r.t. under H_2 (1.0 atm) for 5 h. The Pd/C was removed by filtration through Celite. The filtrate was concentrated in vacuo. The residue was purified by flash chromatography (hexanes–EtOAc, 1:1).

Yield: 74 mg (60%); colorless solid; R_f = 0.45 (hexanes–EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.30 (m, 2 H), 3.85 (m, 2 H), 3.65 (m, 2 H), 3.57 (d, *J* = 9.9 Hz, 1 H), 3.22–3.00 (m, 3 H), 2.30–1.95 (m, 4 H), 1.62–1.29 (m, 8 H), 0.95 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 167.0, 60.2, 58.9, 58.4, 55.4, 51.6, 49.3, 47.8, 45.1, 32.7, 29.5, 29.4, 26.5, 20.4, 20.3, 13.8, 13.7.

(1*R,4*S**,7*S**,8*S**,11*R**,12*R**)-2,10-Dibutyl-7-chloro-12-ethoxy-2,10-diazatricyclo[6.4.0.0^{4,11}]dodecane-3,9-dione (12)**

By reduction of 10a: To a soln of **10a** (64 mg, 0.16 mmol) in MeOH (2 mL) was added 10% Pd/C (18 mg). The mixture was stirred at r.t. under H_2 (1 atm) for 6 h. The mixture was filtered through Celite and concentrated in vacuo to give **12**; yield: quantitative.

From 11: To a soln of **11** (50 mg, 0.13 mmol) in absolute EtOH (3 mL) was added 0.5 M NaOEt in absolute EtOH (0.32 mL, 0.16 mmol), and the mixture was heated at reflux for 0.5 h. The soln was cooled and concentrated in vacuo. The residue was diluted with H_2O (10 mL) and extracted with EtOAc (4 × 20 mL). The combined organics were dried ($MgSO_4$) and concentrated to give **12**; yield: quantitative.

Colorless solid; R_f = 0.43 (hexanes–EtOAc, 1:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.27 (m, 1 H), 3.85–3.55 (m, 6 H), 3.40–2.88 (m, 5 H), 2.20 (m, 1 H), 1.95 (m, 2 H), 1.75 (m, 1 H), 1.55 (m, 3 H), 1.32 (m, 4 H), 1.15 (t, *J* = 6.6 Hz, 4 H), 0.90 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 168.5, 76.4, 64.6, 60.6, 58.4, 58.3, 49.1, 47.8, 47.6, 45.5, 29.6, 29.5, 28.6, 24.8, 20.4, 20.3, 15.3, 13.8, 13.7.

Dichlorides 18a and 19a

To a soln of **15** (157 mg, 0.56 mmol) in CH_2Cl_2 (10 mL) was added 0.46 M Cl_2 in CH_2Cl_2 (1.6 mL, 0.73 mmol), and the mixture was stirred at 0 °C for 1 h. The soln was diluted with sat. $NaHCO_3$ (30 mL) and extracted with EtOAc (4 × 40 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (hexanes–EtOAc, 2:1). This gave **18a** and **19a**.

Compound 18a

Yield: 33 mg (17%); colorless solid; R_f = 0.65 (hexanes–EtOAc, 1:1); mp 261–263 °C.

IR (KBr): 2924, 2853, 1666, 1478, 1087, 953, 741 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (m, 1 H), 7.31 (m, 2 H), 7.25 (m, 1 H), 5.33 (d, *J* = 10.8 Hz, 1 H), 5.20 (dd, *J* = 11.6, 2.4 Hz, 1 H), 5.04 (m, 1 H), 5.00 (dd, *J* = 9.2, 1.2 Hz, 1 H), 4.51 (d, *J* = 10.0 Hz, 1 H), 4.35 (s, 1 H), 4.05 (m, 3 H), 3.62 (d, *J* = 9.2 Hz, 1 H), 3.21 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 137.2, 135.6, 133.0, 131.7, 130.3, 128.0, 127.8, 124.2, 78.7, 73.9, 64.8, 61.4, 60.8, 60.5, 58.8, 48.8, 36.1.

HRMS–DCI: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}Cl_2NO_2$: 350.0714; found: 350.0722.

Compound 19a

Yield: 45 mg (23%); colorless solid; R_f = 0.49 (hexanes–EtOAc, 1:1); mp 182–184 °C.

IR (KBr): 3052, 2975, 2926, 2843, 1665, 1460, 1266, 1070, 734 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.14 (m, 2 H), 7.10 (dd, *J* = 7.2, 0.8 Hz, 1 H), 6.97 (dd, *J* = 7.2, 1.2 Hz, 1 H), 5.20 (dt, *J* = 7.2, 1.6 Hz, 1 H), 4.93 (d, *J* = 8.8 Hz, 1 H), 4.64 (td, *J* = 6.4, 2.0 Hz, 1 H), 4.25 (dd, *J* = 4.0, 1.2 Hz, 1 H), 4.18 (d, *J* = 13.2 Hz, 1 H), 3.97 (m, 2 H), 3.75 (dt, *J* = 12.8, 2.0 Hz, 1 H), 3.65 (d, *J* = 9.2 Hz, 1 H), 3.11 (s, 3 H), 3.06 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 146.8, 141.0, 134.6, 129.2, 128.8, 128.4, 126.3, 117.9, 79.0, 73.9, 64.7, 60.5, 59.8, 55.4, 52.4, 50.3, 40.8.

HRMS–FAB: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{17}NO_2Cl_2$: 372.0534; found: 372.0538.

Dibromides 18b and 19b

To a soln of **15** (72 mg, 0.25 mmol) in CH_2Cl_2 (10.0 mL) at 0 °C was added Br_2 (14.5 μL, 0.28 mmol) in CH_2Cl_2, and the mixture was stirred at 0 °C for 1 h. The soln was diluted with sat. $NaHCO_3$ (20 mL) and extracted with EtOAc (4 × 30 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (hexanes–EtOAc, 2:1); this gave **18b** and **19b**.

Compound 18b

Yield: 39 mg (35%); R_f = 0.51 (hexanes–EtOAc, 2:1); mp 225–227 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (m, 1 H), 7.44 (m, 2 H), 7.33 (m, 1 H), 5.63 (d, *J* = 11.7 Hz, 1 H), 5.31 (d, *J* = 1.5 Hz, 1 H), 5.25 (dd, *J* = 11.7, 2.4 Hz, 1 H), 5.10 (d, *J* = 9.0 Hz, 1 H), 4.60 (d, *J* = 10.2 Hz, 2 H), 4.28 (d, *J* = 10.8 Hz, 1 H), 4.20 (d, *J* = 10.8 Hz, 1 H), 4.08 (d, *J* = 10.2 Hz, 1 H), 3.74 (d, *J* = 9.3 Hz, 1 H), 3.32 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 138.4, 135.9, 132.7, 132.4, 130.2, 127.5, 127.4, 123.6, 78.7, 74.3, 61.8, 60.4, 58.4, 56.9, 51.7, 48.8, 35.8.

Compound 19b

Yield: 16 mg (14%); R_f = 0.32 (hexanes–EtOAc, 2:1); mp 105–107 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.24 (m, 2 H), 7.15 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.03 (dd, *J* = 7.6, 1.2 Hz, 1 H), 5.28 (d, *J* = 6.8 Hz, 1 H), 5.03 (d, *J* = 8.8 Hz, 1 H), 4.86 (t, *J* = 5.2 Hz, 1 H), 4.42 (dd, *J* = 4.4, 1.2 Hz, 1 H), 4.27 (d, *J* = 12.8 Hz, 1 H), 4.08–3.98 (m, 2 H), 3.85 (dt, *J* = 12.8, 2.0 Hz, 1 H), 3.73 (d, *J* = 9.2 Hz, 1 H), 3.27 (s, 1 H), 3.26 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 146.4, 141.8, 134.9, 129.2, 128.9, 128.4, 126.2, 118.5, 79.4, 73.9, 60.9, 56.8, 55.6, 53.4, 51.0, 49.3, 42.0.

HRMS–FAB: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{17}NO_2Br_2$: 495.9523; found: 459.9522.

(1*R,4*S**,7*S**,8*S**,11*R**,12*R**)-2,10-Dibutyl-7-chloro-12-methoxy-2,10-diazatricyclo[6.4.0.0^{4,11}]dodec-5-ene-3,9-dione (20a)**

To a soln of **4a** (100 mg, 0.27 mmol) in anhyd MeOH (5 mL) was added 0.16 M NaOMe in MeOH (2 mL, 0.32 mmol), and the mixture was heated at reflux for 30 h. The soln was cooled and concentrated in vacuo. The residue was diluted with sat. NH_4Cl (20 mL) and extracted with EtOAc (4 × 30 mL). The combined organics were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (hexanes–EtOAc, 1:2) to give **20a**.

Yield: 92 mg (93%); colorless solid; R_f = 0.25 (hexanes–EtOAc, 1:2); mp 63–66 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.90 (d, *J* = 12.0 Hz, 1 H), 5.83 (m, 1 H), 4.25 (dd, *J* = 4.0, 2.0 Hz, 1 H), 4.11 (m, 1 H), 3.93 (d, *J* = 10.0 Hz, 1 H), 3.86 (m, 1 H), 3.63 (m, 3 H), 3.42 (s, 3 H), 3.43–3.41 (m, 1 H), 3.12–3.01 (m, 2 H), 1.44–1.25 (m, 8 H), 0.94 (t, *J* = 7.5 Hz, 3 H), 0.88 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 166.6, 137.1, 125.7, 79.8, 60.3, 58.9, 58.3, 57.6, 48.4, 48.1, 47.6, 46.0, 30.1, 30.0, 20.7, 20.6, 14.1.

(1*R,4*S**,7*S**,8*S**,11*R**,12*R**)-2,10-Dibutyl-7-chloro-12-(phenylsulfanyl)-2,10-diazatricyclo[6.4.0.0^{4,11}]dodec-5-ene-3,9-dione (20b)**

To a suspension of NaH (12 mg, 0.5 mmol) in THF (2 mL) was added PhSH (35 μL, 0.34 mmol), and the mixture was stirred at 0 °C for 0.5 h. To this was added **4a** (106 mg, 0.28 mmol) in THF (2 mL) and the mixture was warmed to r.t. for 5 h. The soln was diluted with sat. NH_4Cl (10 mL) and extracted with EtOAc (4 × 20 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (hexanes–EtOAc, 2:1) to give **20b**.

Yield: 107 mg (85%); colorless solid; R_f = 0.56 (hexanes–EtOAc, 1:1); mp 157–158 °C.

IR (KBr): 3460, 3310, 2959, 2930, 2871, 1660, 1470, 1176, 737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (m, 2 H), 7.22 (m, 3 H), 5.81 (d, *J* = 12.0 Hz, 1 H), 5.74 (td, *J* = 10.0, 2.4 Hz, 1 H), 4.26 (dd, *J* = 4.4, 2.0 Hz, 1 H), 4.12 (d, *J* = 2.0 Hz, 1 H), 3.80 (m, 2 H), 3.62 (t, *J* = 9.6 Hz, 1 H), 3.48 (m, 2 H), 3.37 (d, *J* = 9.6 Hz, 1 H), 3.13 (m, 2 H), 1.42 (m, 4 H), 1.27 (m, 4 H), 0.83 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 166.6, 136.4, 135.6, 132.4, 129.7, 128.1, 126.8, 60.4, 60.3, 58.0, 48.4, 48.1, 47.9, 30.4, 30.0, 20.7, 20.6, 14.14, 14.10.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{31}N_2O_2SCl$: 447.187303; found: 447.1865.

(1*R,4*S**,7*S**,8*S**,11*R**,12*R**)-2,10-Dibutyl-7-chloro-12-(1-pyrrolidino)-2,10-diazatricyclo[6.4.0.0^{4,11}]dodec-5-ene-3,9-dione (20c)**

To a suspension of NaH (15 mg, 0.62 mmol) in THF (1 mL) was added pyrrolidine (25 μL, 0.30 mmol), and the mixture was stirred at 0 °C for 0.5 h. To this was added **4a** (75 mg, 0.20 mmol) in THF (2 mL), and the mixture was warmed to 60–70 °C overnight. The soln was diluted with H_2O (10 mL) and extracted with EtOAc (4 × 20 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (MeOH–CH_2Cl_2, 5:100) to give **20c**.

Yield: 72 mg (88%); pale yellow oil; R_f = 0.69 (MeOH–CH_2Cl_2, 1:16).

IR (KBr): 2959, 2932, 2872, 1659, 1467, 1177, 733 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93 (d, *J* = 11.6 Hz, 1 H), 5.75 (td, *J* = 11.2, 2.8 Hz, 1 H), 4.26 (dd, *J* = 4.4, 1.2 Hz, 1 H), 3.86 (d, *J* = 10.0 Hz, 1 H), 3.80 (m, 1 H), 3.64–3.47 (m, 5 H), 3.03 (m, 2 H), 2.73 (m, 4 H), 1.74 (m, 4 H), 1.52–1.22 (m, 8 H), 0.89 (t, *J* = 7.2 Hz, 3 H), 0.84 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2, 166.0, 136.1, 125.6, 62.6, 60.8, 59.9, 57.8, 51.9, 48.5, 48.1, 47.7, 46.3, 30.1, 30.0, 24.0, 20.7, 20.6, 14.1, 14.06.

HRMS–FAB: *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{34}N_3O_2Cl$: 430.2237; found: 430.2234.

(1*R,4*S**,7*S**,8*S**,11*R**,12*R**)-2,10-Dibutyl-7-chloro-12-(dicyanomethyl)-2,10-diazatricyclo[6.4.0.0^{4,11}]dodec-5-ene-3,9-dione (20d)**

To a suspension of NaH (23 mg, 0.93 mmol) in THF (2 mL) was added malononitrile (23 μL, 0.35 mmol), and the mixture was stirred at 0 °C for 0.5 h. To this was added **4a** (100 mg, 0.27 mmol)

in THF (3 mL), and the mixture was warmed to r.t. overnight. The soln was diluted with H_2O (20 mL) and extracted with EtOAc (4 × 30 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (hexanes–EtOAc, 1.5:1) to give **20d**.

Yield: 87 mg (80%); colorless solid; R_f = 0.56 (hexanes–EtOAc, 1:1); mp 72–74 °C.

IR (KBr): 2961, 2932, 2874, 2257, 1651, 1473, 1180 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.98 (td, *J* = 10.4, 2.8 Hz, 1 H), 5.75 (dt, *J* = 11.6, 1.6 Hz, 1 H), 4.65 (d, *J* = 12.0 Hz, 1 H), 4.30 (dd, *J* = 4.4, 1.6 Hz, 1 H), 3.93 (dt, *J* = 10.0, 1.2 Hz, 1 H), 3.86 (m, 1 H), 3.73 (t, *J* = 10.8 Hz, 1 H), 3.60 (m, 1 H), 3.34 (m, 1 H), 3.25 (dt, *J* = 11.2, 1.6 Hz, 1 H), 3.14 (m, 3 H), 1.38 (m, 2 H), 1.30 (m, 6 H), 0.92 (t, *J* = 7.6 Hz, 3 H), 0.86 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 165.6, 130.3, 130.0, 112.9, 112.4, 59.44, 59.41, 57.7, 48.3, 48.2, 47.8, 44.6, 41.5, 30.1, 29.8, 27.7, 20.64, 20.61, 14.1.

HRMS–FAB: *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{27}N_4O_2Cl$: 425.1720; found: 425.1723.

(1*R,3*R**,6*S**,7*R**,10*S**,11*S**)-6-(1-Allyl-1-hydroxybut-3-enyl)-2,8-dibutyl-11-chloro-2,8-diazatricyclo[5.3.1.0^{3,10}]undec-4-en-9-one (21a)**

To a soln of **4a** (100 mg, 0.26 mmol) in THF (2 mL) was added 2.0 M AllMgCl (0.30 mL, 0.60 mmol) in THF, and the mixture was stirred at 0 °C for 0.5 h. The soln was diluted with sat. NH_4Cl (20 mL) and extracted with EtOAc (4 × 30 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (hexanes–EtOAc, 3:1) to give **21a**. [The structure of **21a** was determined by X-ray crystallography of the hydrochloride salt (mp 173–175 °C).]

Yield: 68 mg (60%); colorless oil; R_f = 0.35 (hexanes–EtOAc, 2.5:1).

IR (KBr): 3052, 2961, 2932, 2864, 1666, 1265, 739 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.72 (s, 1 H), 6.05 (dd, *J* = 12.5, 7.5 Hz, 1 H), 5.90 (m, 2 H), 5.79 (dd, *J* = 11.5, 8.5 Hz, 1 H), 5.23–5.10 (m, 5 H), 4.08 (d, *J* = 8.5 Hz, 1 H), 3.84–3.77 (m, 3 H), 3.60 (d, *J* = 7.5 Hz, 1 H), 3.16 (t, *J* = 8.5 Hz, 1 H), 2.74 (m, 3 H), 2.61 (dt, *J* = 14.0, 2.0 Hz, 1 H), 2.45 (dd, *J* = 14.0, 5.0 Hz, 1 H), 2.24 (m, 2 H), 1.52 (m, 2 H), 1.40–1.25 (m, 6 H), 0.90 (m, 6 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1, 134.6, 134.4, 132.6, 132.2, 118.4, 118.2, 74.5, 64.3, 62.2, 60.7, 57.7, 56.0, 49.7, 46.3, 45.2, 43.7, 37.5, 29.9, 29.3, 20.7, 20.6, 14.2, 14.1.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{37}N_2O_2Cl$: 421.26218; found: 421.2634.

(1*R,3*R**,6*S**,7*R**,10*S**,11*S**)-2,8-Dibutyl-6-(hydroxymethyl)-2,8-diazatricyclo[5.3.1.0^{3,10}]undec-4-en-9-one (22b)**

To a soln of **4a** (106 mg, 0.28 mmol) in THF (5 mL) at 0 °C was added 2.0 M $LiBH_4$ in THF (0.18 mL, 0.37 mmol). The mixture was warmed to r.t. and stirred for 1 week. The soln was diluted with sat. NH_4Cl (20 mL) and extracted with EtOAc (4 × 30 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography; this gave **21b** and **22b**.

Compound 21b

Flash chromatography (hexanes–EtOAc, 1:3); yield: 15 mg (16%); colorless oil; R_f = 0.76 (EtOAc).

IR (KBr): 3416, 2959, 2932, 2872, 1643, 1468 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.08 (dd, *J* = 3.5, 10.5 Hz, 1 H), 5.90 (br, 1 H), 5.61 (dd, *J* = 3.0, 10.0 Hz, 1 H), 4.57 (q, *J* = 3.0 Hz, 1 H), 3.95 (m, 1 H), 3.88 (m, 1 H), 3.78 (d, *J* = 11.5 Hz, 1 H), 3.73 (m, 1 H), 3.64 (t, *J* = 6.5 Hz, 2 H), 3.27 (td, *J* = 7.0, 2.0 Hz, 1 H), 2.96 (q, *J* = 4.5 Hz, 1 H), 2.70–2.54 (m, 3 H), 1.62–1.20 (m, 8 H), 0.88 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 133.1, 131.0, 66.6, 63.8, 61.9, 61.6, 56.5, 56.2, 52.1, 46.4, 44.6, 31.1, 29.2, 20.9, 20.7, 14.2, 14.1.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{29}N_2O_2Cl$: 339.1839; found: 339.1833.

Compound 22b

Flash chromatography ($MeOH–CH_2Cl_2$, 4:100); yield: 30 mg (35%); colorless oil; R_f = 0.45 ($MeOH–CH_2Cl_2$, 4:100).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.80 (br, 1 H), 6.12 (dd, *J* = 10.0, 6.8 Hz, 1 H), 5.55 (dd, *J* = 10.4, 6.8 Hz, 1 H), 3.91–3.71 (m, 5 H), 3.59 (t, *J* = 7.2 Hz, 1 H), 3.14 (t, *J* = 5.6 Hz, 1 H), 2.87 (m, 1 H), 2.55–2.42 (m, 3 H), 2.25–2.21 (m, 1 H), 2.01 (d, *J* = 11.6 Hz, 1 H), 1.57–1.22 (m, 8 H), 0.90 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.7, 133.6, 129.6, 64.4, 64.0, 61.3, 56.1, 48.3, 46.1, 43.3, 33.3, 30.7, 29.7, 20.8, 20.5, 14.2, 14.1.

(1*R,3*R**,6*S**,7*R**,10*S**,11*S**)-2,8-Dibutyl-11-chloro-6-(hydroxymethyl)-2,8-diazatricyclo[5.3.1.0^{3,10}]undec-4-en-9-one (23b)**

To a soln of **4a** (100 mg, 0.26 mmol) in absolute EtOH (2 mL) at 0 °C was added $NaBH_4$ (14 mg, 0.37 mmol). The mixture was warmed to r.t. overnight and then heated at reflux for 2 h. The soln was concentrated, and the residue was diluted with H_2O (20 mL) and then extracted with EtOAc (4 × 30 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (hexanes–EtOAc, 1:2) gave **10a**; yield: 51 mg (50%); and **23b**; yield: 27 mg (30%).

Compound 23b

R_f = 0.23 (hexanes–EtOAc, 1:1).

IR (KBr): 3503, 2961, 2932, 2872, 1653, 1473, 1431 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.76 (m, 2 H), 4.28 (dd, *J* = 4.8, 1.6 Hz, 1 H), 3.83–3.78 (m, 1 H), 3.72 (d, *J* = 10.0 Hz, 1 H), 3.61–3.53 (m, 2 H), 3.45 (m, 1 H), 3.14–3.04 (m, 3 H), 2.67 (m, 1 H), 2.36 (d, *J* = 18.4 Hz, 1 H), 1.55–1.25 (m, 8 H), 0.86 (m, 6 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6, 167.3, 133.0, 126.6, 60.4, 59.9, 58.2, 48.3, 47.9, 43.3, 30.3, 29.9, 29.8, 20.6, 20.6, 14.1

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{28}N_2O_2Cl$: 339.1839; found: 339.1836

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(11) Compound **10a** crystallized in the rhombohedral space group *R*–3, with a = 25.354 (2) Å, b = 25.354 (2) Å, c = 18.437 (2) Å, and Z = 18. Direct solution using 4159 unique reflections with SHELXL-97 gave a final R_1 = 0.0707 and R_2 = 0.1980.
(12) This structure was calculated by initially building a structure with a carbon atom in place of the positively charged nitrogen, and minimizing the structure using molecular mechanics. The resulting structure was then modified by replacing the carbon with a positively charged nitrogen and minimizing the structure using PM3 (MOPAC). The calculation was performed using WebMO (www.webmo.net). Images were generated with PyMOL (pymol.sourceforge.net).
(13) Compound **18a** crystallized in the monoclinic space group $P2_1/n$, with a = 8.8752 (11) Å, b = 16.318 (2) Å, c = 13.575 (2) Å, β = 90.9270 (10)°, V = 1965.7 (5) Å^3, and Z = 4. Direct solution using 3180 unique reflections with SHELXL-97 gave a final R_1 = 0.0372 and R_2 = 0.0816. Compound **19a** crystallized in the orthorhombic space group $Pca2_1$, with a = 20.5701 (10) Å, b = 9.1456 (4) Å, c = 16.8463 (8) Å, V = 3169.2 (3) Å^3, and Z = 8. Direct solution using 6546 unique reflections with SHELXL-97 gave a final R_1 = 0. 0316 and R_2 = 0. 0794.
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