A one-pot, three-step process for the
diastereoselective synthesis of
aminobicyclo[4.3.0]nonanes using consecutive
palladium(II)- and ruthenium(II)-catalysis†

Mohamed A. B. Mostafa, Mark. W. Grafton, Claire Wilson and Andrew Sutherland*

A diastereoselective synthesis of highly substituted aminobicyclo[4.3.0]nonanes has been attained using a
one-pot multi-bond forming process. A four-step synthetic route was developed for the efficient syn-
thesis of a series of C-7 substituted hept-2-en-6-yn-1-ols. These compounds were then investigated as
substrates for a one-pot, three-step tandem process involving a palladium(ii)-catalysed Overman
rearrangement, a ruthenium(ii)-catalysed ring closing enyne metathesis reaction followed by a hydrogen
bond directed Diels–Alder reaction. The optimisation of the one-pot process has allowed the rapid prepa-
ration of a library of aminobicyclo[4.3.0]nonanes with significant molecular complexity and up to four
stereogenic centres.

Introduction

A recent trend in identifying lead-hit compounds and small-
molecule probes for medicinal chemistry and chemical biology
has been the replacement of sp²-rich aromatic and hetero-
aromatic compounds with sp³-rich compounds.1 Partially satu-
rated compounds with a higher degree of saturation have more
suitable physicochemical properties such as solubility and
allow a more efficient examination of three-dimensional
chemical space.1,2 In this regard, saturated and partially satu-
rated forms of amino substituted bicyclo[4.3.0]nonanes have
exhibited wide-ranging biological and pharmacological pro-
properties.3 In particular, these compounds are found as com-
ponents of natural products such as the guanidine alkaloid
netamine A (1)4 and the antitumour antibiotic (+)-ptilocaulin
(2) (Fig. 1).5 Amino-indanes are found as constituents of a
range of medicinal agents including (+)-indatraline (3),6 a
monoamine transporter inhibitor and rasagiline (Azilect), a
drug used for the treatment of Parkinson’s disease.7 Other
amino-indane structural analogues can inhibit the prolifer-
ation of malignant cells8 and are used to treat HIV infections
and AIDS.9

Due to these wide-ranging pharmacological activities, a
number of synthetic approaches have been developed for the
general preparation of these compounds.5,10–13 Diastereo-
selective syntheses have been achieved using an intra-
molecular 1,3-dipolar cycloaddition between an oxime and a
cyclohexene5 and, using a Ru(ii)-catalysed allenic cycloisomer-
isation of an alkynone, followed by a Diels–Alder reaction of the resulting 2-alkyllidene-3-vinylcyclopentenone.10 Other
diastereoselective syntheses include the C–H activation of a
hexahydroindene that gave the corresponding secondary
organoborane, which was then aminated to give the amino
substituted bicyclo[4.3.0]nonane in good overall yield.11

As part of a research programme to develop new methods
for rapid access to drug-like polycyclic scaffolds, we recently
reported the diastereoselective synthesis of amino substituted
bicyclo[4.3.0]nonanes using a one-pot multistep process involv-
ing a thermally-mediated Overman rearrangement of alkyne
derived allylic alcohols, followed by a ring closing enyne

Fig. 1 Biologically active amino bicyclo[4.3.0]nonanes and indanes.
metathesis (RCEYM) reaction of the resulting enyne and a hydrogen bond directed Diels–Alder reaction (Scheme 1). Using a range of dienophiles, this allowed the late-stage synthesis of a library of partially saturated indane ring systems. More recently the one-pot method has been extended to include a cross-metathesis step leading to the rapid preparation of C-4 substituted analogues with up to five stereogenic centres. While this approach permitted the facile preparation of a range of amino substituted bicyclo[4.3.0]nonanes, we found that some of the one-pot processes required particularly long reaction times and this was in part due to using thermal conditions to implement the Overman rearrangement (36 h). In previous studies, we found that alkene and alkyne derived allylic trichloroacetimidates would not undergo effective palladium(II)-catalysed rearrangements due to binding of the catalyst to the unsaturated side-chains. We were interested in exploring the structural requirements of alkyne derived allylic alcohols that could block catalyst side-chain binding and perform a Pd(II)-catalysed Overman rearrangement as part of a more rapid one-pot process leading to new C-5 substituted aminobicyclo[4.3.0]nonanes. We now report the synthesis of a series of C-7 substituted hept-2-en-6-yn-1-ols and the evaluation of these compounds to undergo a Pd(II)-catalysed Overman rearrangement.

**Results and discussion**

To investigate the requirements of alkyne substituents to block catalyst binding during a Pd(II)-catalysed Overman rearrangement, a series of C-7 substituted hept-2-en-6-yn-1-ols were prepared in four steps from pent-4-yn-1-ol (Scheme 2).
the conditions required for metal catalysed rearrangement of allylic trichloroacetamides bearing mono-substituted unsaturated side-chains. The rearrangement of disubstituted alkyne derived allylic trichloroacetamides was next investigated. While a methyl substituent is relatively small, the use of this group was sufficient to partially retard catalyst binding and allow rearrangement using only 10 mol% of catalyst at 20 °C (entry 2). This gave allylic trichloroacetamide 21 in 55% yield after 24 h. Using aryl groups with substantially more bulk proved effective and allowed the efficient synthesis of the corresponding allylic trichloroacetamides 22–24 in high yields after a 12 h reaction time (entries 3–5). Interestingly, the yields were independent of the electronic nature of the aryl groups indicating that the steric bulk of these substituents is primarily responsible for preventing binding of the catalyst to the alkyne moiety.

Having identified the structural requirements and optimal conditions for an efficient Overman rearrangement, these were incorporated into a one-pot multi-reaction process including a Ru(II)-catalysed RCEYM step and a Diels–Alder reaction for the preparation of novel aminobicyclo[4.3.0] nonanes (Scheme 3). Preliminary attempts at the one-pot preparation of 25 from phenyl substituted allylic alcohol 17 using Grubbs 2nd generation catalyst (7 mol%) for the RCEYM step and N-phenyl maleimide as a dienophile for the Diels–Alder step, under previously developed conditions for these reactions gave low yields of 25 (~25%). Analysis of the 1H NMR spectrum of the reaction mixture showed the presence of the 1,6-enyne 22, indicating that the RCEYM step had not gone to completion. This was unsurprising as disubstituted, bulky alkyynes often show suppressed reactivity during RCEYM reactions. Methods for improving this step were investigated. A combination of the use of 1,7-octadiene as an in situ source of ethylene and a higher reaction temperature (from 75 to 90 °C) resulted in an accelerated RCEYM reaction, allowing complete conversion of 1,6-enyne 22 to the corresponding cyclopentyl exo-diene. Using these modified conditions as part of the one-pot process gave 5-phenyl aminobicyclo[4.3.0]nonane 25 as a single diastereomer in 51% overall yield from allylic alcohol 17 (Scheme 3). As previously reported for the Diels–Alder reaction of trichloroacetamide

<table>
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<th>Time (h)</th>
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<td>4-NO2C6H4 (18)</td>
<td>20</td>
<td>12</td>
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*Isolated yields from allylic alcohols 15–19. A second portion of catalyst was added after 24 h (20 mol% in total).

Scheme 3 One-pot synthesis of aminobicyclo[4.3.0]nonanes 25–33.
derived cyclic exo-dienes, the reaction proceeds via a hydrogen bonding directed endo transition state, generating the syn-products with excellent diastereoselectivity (>20:1).

The relative stereochemistry of 25 was confirmed by difference NOE experiments, which showed the syn relationship of the hydrogen atoms at C-3a, C-8, C-8a and C-8b. For comparison, use of the optimised one-pot process was applied to methyl substituted allylic alcohol 16 which gave 26 in 23% overall yield. The significantly lower yield for 26 is a consequence of the less efficient Overman rearrangement for this analogue. Using phenyl derived allylic alcohol 17, the scope of the one-pot multistep process was explored using various dienophiles. In all cases, the compounds were formed as single diastereomers in good yields over the four steps (40–56%). It should be noted that the non-symmetrical dienophile, methyl acrylate gave indane 29 as a single regioisomer. This again is a direct consequence of the hydrogen bonding directed endo transition state.

As well as developing a one-pot synthesis of aminobicyclo[4.3.0]nonanes using consecutive Pd(II)- and Ru(II)-catalysis, another major objective of this research programme was to probe the effect of electron-deficient and electron-rich aryl substituted alkenes on the outcome of the RCEYM step and the subsequent one-pot process. While 1,6-enynes bearing electron-deficient alkyne substituents have been shown to have a detrimental effect on RCEYM reactions, examples with electron-poor aryl groups have given excellent yields under forcing conditions. Using (2E)-7-(4'-nitrophenyl)hept-2-en-6-yn-1-ol (18) as a substrate for the one-pot multistep process and N-phenyl maleimide as the dienophile, the alkyne substituted aminobicyclo[4.3.0]nonane 30 as a single diastereomer in 69% yield. In a similar fashion, use of 4-phenyl-1,2,4-triazole-3,5-dione, tetracyanoethylene or methyl acrylate as a single diastereomer in 69% yield. Despite the resistance of the tetra-substituted alkene to undergo hydrogenation, oxidation of the moiety was readily observed. For example, reaction of 25 with osmium tetroxide in the presence of TMEDA under Donohoe conditions gave dihydroxyl derivative 39 as a single stereoisomer in quantitative yield after only 3 h. Based on the shape of aminobicyclo[4.3.0]nonane 25, it was expected that reactions of the alkene would take place from the more exposed convex face of the molecule. This was confirmed by X-ray crystallography. The (3aS*,5R*,5aR*,8R*,8aR*,8bR*)-stereoisomer 39 was found to crystallise in the triclinic space group P1 and the structure clearly shows the syn relationship.

Having synthesised a novel library of aminobicyclo[4.3.0]nonanes, a preliminary study was conducted to explore further functionalisation of these compounds and in particular, the reactivity of the tetra-substituted alkene moiety. Initially, hydrogenation of 25 was attempted under standard conditions (Scheme 5). However, after 48 h, partial reduction of the trichloromethyl group was the only change detected, giving the dichloroacetamide in 48% yield. Despite the resistance of the tetra-substituted alkene to undergo hydrogenation, oxidation of the moiety was readily observed. For example, reaction of 25 with osmium tetroxide in the presence of TMEDA under Donohoe conditions gave dihydroxy derivative 39 as a single stereoisomer in quantitative yield after only 3 h. Based on the shape of aminobicyclo[4.3.0]nonane 25, it was expected that reactions of the alkene would take place from the more exposed convex face of the molecule. This was confirmed by X-ray crystallography. The (3aS*,5R*,5aR*,8R*,8aR*,8bR*)-stereoisomer 39 was found to crystallise in the triclinic space group P1 and the structure clearly shows the syn relationship.

Optimised RCEYM step, one-pot reactions using allylic alcohol 19 still gave modest yields of the 4-methoxyphenyl substituted aminobicyclo[4.3.0]nonane 34. As such, the preparation of this series of compounds was conducted as two separate processes. Following efficient large-scale preparation of allylic trichloroacetamidate 24 (Table 1), this was subjected to a one-pot, two-step process involving the low temperature RCEYM step and a Diels–Alder reaction with various electron-deficient dienophiles (Scheme 4). This allowed the synthesis of 4-methoxyphenyl substituted aminobicyclo[4.3.0]nonanes 34–37 as single diastereomers in good yields over the two steps.

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of the hydrogen atoms at C-3a, C-8, C-8a and C-8b and the hydroxyl groups at C-5 and C-5a (Fig. 2). 30,31 In a similar fashion, reaction of 25 with m-CPBA gave epoxide 40 as a single diastereomer in 65% yield.

**Conclusions**

In summary, a series of C-7 substituted hept-2-en-6-yn-1-ols have been examined as substrates for the one-pot diastereoselective synthesis of sp³-rich aminobicyclo[4.3.0]nonanes. The presence of the C-7 groups allowed an effective Pd(II)-catalysed Overman rearrangement to proceed. Incorporation of this transformation into a one-pot, three-step process involving a Ru(II)-catalysed RCEYM reaction and a hydrogen bonding directed Diels-Alder reaction gave a range of aminobicyclo[4.3.0]nonanes in good overall yields. The effect of the electronic nature of the aryl substituent on the RCEYM step was also studied and while an electron-poor analogue could be used as a substrate for the one-pot process using forcing conditions for the RCEYM step, the electron-rich cyclopentyl exo-diene was found to undergo decomposition during the multi-step process. Nevertheless, a series of 4-methoxyphenyl substituted aminobicyclo[4.3.0]nonanes could be prepared efficiently using a one-pot, two-step process from the allylic trichloroacetamide. The reactivity of these novel compounds was also explored and aminobicyclo[4.3.0]nonane 25 was readily oxidised, generating dihydroxy and epoxide derivatives as single diastereomers in high yields. The combination of the one-pot, three-step multireaction process with the oxidations allowed the rapid preparation of these sp³-rich, drug-like polycyclic scaffolds with six stereogenic centres. With the development of an effective one-pot synthesis of these compounds using a Pd(II)-catalysed rearrangement, work is currently underway to incorporate chiral Pd(II)-catalysts for their asymmetric synthesis and preparation of natural product targets.

**Experimental**

All reagents and starting materials were obtained from commercial sources and used as received. All dry solvents were purified using a PureSolv 500 MD solvent purification system. All reactions were performed under an atmosphere of argon unless otherwise mentioned. Flash column chromatography was performed using Fisher matrix silica 60. Macherey-Nagel aluminium-backed plates pre-coated with silica gel 60 (UV254) were used for thin layer chromatography and were visualised by staining with KMnO₄. ¹H NMR and ¹³C NMR spectra were obtained using a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to TMS (δH 0.00 and δC 0.0) or residual chloroform (δH 7.26 and δC 77.2) as standard. Proton and carbon assignments are based on two-dimensional COSY and DEPT experiments, respectively. Mass spectra were obtained using a JEOL JMS-700 spectrometer for EI and CI or a Bruker Microtof-q for ESI. Infrared spectra were obtained neat using a Shimadzu IRPrestige-21 spectrometer. Melting points were determined on a Reichert platform melting point apparatus.

**5-Phenylpent-4-yn-1-ol (5)**

Bis(triphenylphosphine)palladium(II) dichloride (0.022 g, 0.031 mmol) and copper iodide (0.012 g, 0.062 mmol) were dissolved in triethylamine (43 mL) and iodobenzene (0.42 mL, 3.71 mmol) was added and stirred at room temperature for 0.1 h. Pent-4-yn-1-ol (4) (0.26 g, 3.09 mmol) was added and the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was concentrated in vacuo. Purification of the resulting residue by flash column chromatography (petroleum
ether/ethyl acetate, 3:1) gave 5-phenylpent-4-yn-1-ol (5)
(0.48 g, 95%) as a colourless oil. Spectroscopic data was
consistent with the literature.\textsuperscript{32} δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 1.59
(1H, br s, OH), 1.86 (2H, quin, J 6.5 Hz, 2-H\textsubscript{2}), 2.54 (2H, t, J 6.5 Hz, 3-H\textsubscript{2}), 3.82 (2H, t, J 6.5 Hz, 1-H\textsubscript{2}), 7.24-7.30 (3H, m, 3 × ArH), 7.36-7.42 (2H, m, 2 × ArH); δ\textsubscript{C} (101 MHz, CDCl\textsubscript{3})
16.0 (CH\textsubscript{2}), 31.4 (CH\textsubscript{2}), 61.7 (CH\textsubscript{2}), 81.1 (C), 89.4 (C), 123.8 (C),
127.7 (CH), 128.2 (2 × CH), 131.6 (2 × CH); m/z (Cl) 161
(MH\textsuperscript{+}, 100%), 133 (20), 117 (28), 113 (13), 85 (28), 69 (39).

5-(4-Nitrophenyl)pent-4-yn-1-ol (6)\textsuperscript{33}
5-(4-Nitrophenyl)pent-4-yn-1-ol (6) was synthesised as
described for 5-phenylpent-4-yn-1-ol (5) using pent-4-yn-1-ol
(4) (0.26 g, 3.09 mmol) and 4-iodo-1-nitrobenzene (0.92 g,
3.71 mmol). Purification by flash column chromatography
(petroleum ether/diethyl ether (4 × 25 mL). The organic layers were combined,
dried (MgSO\textsubscript{4}), filtered and concentrated to give an orange oil. Purification by
flash column chromatography (petroleum ether/diethyl ether,
17 : 3) (1.50 g, 17.8 mmol) in
acetonitrile (60 mL) was then prepared and
stirred for a further 1 h. The Swern solution was concentrated in \textit{vacuo},
then the Horner Wadsworth Emmons solution was added and
the reaction mixture was stirred at room temperature
overnight. The reaction was quenched with a saturated solution
of ammonium chloride (45 mL) and concentrated to give an
orange residue, which was then extracted with diethyl ether
(4 × 60 mL). The organic layers were combined, dried (MgSO\textsubscript{4}),
filtered and concentrated to give an orange oil. Purification by
flash column chromatography (petroleum ether/diethyl ether,
7 : 3) gave ethyl (2E)-hept-2-en-6-ynoate (10) (2.45 g, 91%) as a
yellow oil. Spectroscopic data was consistent with the litera-
ture.\textsuperscript{35} δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 1.30 (3H, t, J 7.1 Hz, OCH\textsubscript{2}CH\textsubscript{3}),
2.01 (1H, t, J 2.5 Hz, 7-H), 2.34-2.39 (2H, m, 5-H\textsubscript{2}), 2.41-2.48 (2H, m, 4-H\textsubscript{2}),
4.20 (2H, q, J 7.1 Hz, OCH\textsubscript{2}CH\textsubscript{3}), 5.90 (1H, dt, J 15.7, 1.5 Hz, 2-H), 6.97 (1H, dt, J 15.7, 6.7 Hz, 3-H);
δ\textsubscript{C} (126 MHz, CDCl\textsubscript{3}) 14.3 (CH\textsubscript{i}), 17.4 (CH\textsubscript{a}), 31.0 (CH\textsubscript{b}),
60.3 (CH\textsubscript{c}), 69.4 (CH), 82.7 (C), 122.6 (CH), 146.3 (CH\textsubscript{a}), 166.4 (C); m/z (EI) 153
(MH\textsuperscript{+}, 100%), 139 (5), 113 (10), 97 (5), 81 (15),
69 (15).

Ethyl (2E)-oct-2-en-6-ynoate (11)\textsuperscript{36}
Ethyl (2E)-oct-2-en-6-ynoate (11) was synthesised as described
for ethyl (2E)-hept-2-en-6-ynoate (10) using hex-4-yn-1-ol (9)
(0.17 g, 1.68 mmol). Purification by flash column chromatogra-
phy (petroleum ether/diethyl ether, 8 : 2) gave ethyl (2E)-oct-2-en-
6-ynoate (11) (0.27 g, 95%) as a colourless oil. \textit{v}_{\text{max}}/\text{cm}^{-1}
(neat) 2921 (CH\textsubscript{3}), 1721 (C=O), 1657, 1368, 1265, 1157, 1039,
975; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 1.29 (3H, t, J 7.1 Hz, OCH\textsubscript{2}CH\textsubscript{3}), 1.77
(3H, t, J 2.3, 8-H\textsubscript{1}), 2.25-2.32 (2H, m, 5-H\textsubscript{2}), 2.34-2.41 (2H, m,
4-H\textsubscript{2}), 4.19 (2H, q, J 7.1 Hz, OCH\textsubscript{2}CH\textsubscript{3}), 5.87 (1H, dt, J 15.7, 1.5 Hz,
2-H), 6.98 (1H, dt, J 15.7, 6.6 Hz, 3-H); δ\textsubscript{C} (126 MHz, CDCl\textsubscript{3}) 3.4 (CH\textsubscript{i}),
14.2 (CH\textsubscript{a}), 17.7 (CH\textsubscript{b}), 31.6 (CH\textsubscript{c}), 60.2 (CH\textsubscript{d}), 76.6 (C),
77.5 (C), 121.2 (CH\textsubscript{a}), 147.1 (CH\textsubscript{b}), 166.5 (C); m/z (EI) 189.0883
(MNa\textsuperscript{+}). C\textsubscript{10}H\textsubscript{14}NaO\textsubscript{3} requires 189.0886.

Ethyl (2E)-7-phenylpent-4-yn-1-ol (12)\textsuperscript{36}
Ethyl (2E)-7-phenylpent-4-yn-1-ol (12) was synthesised as described for ethyl (2E)-hept-2-en-6-ynoate (10) using 5-phenyl-
pent-4-yn-1-ol (5) (0.64 g, 3.96 mmol). Purification by flash
column chromatography (petroleum ether/diethyl ether, 17 : 3)
gave ethyl (2E)-7-phenylhept-2-en-6-ynoate (12) (0.86 g, 95%) as a yellow oil. Spectroscopic data was consistent with the literature. Ethyl (2E)-7-(4′-nitrophenyl)hept-2-en-6-ynoate (13) was synthesised as described for ethyl (2E)-hept-2-en-6-ynoate (10) using 5-(4′-nitrophenyl)pent-4-yn-1-ol (6) (0.46 g, 2.24 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 8:2) gave ethyl (2E)-7-(4′-nitrophenyl)hept-2-en-6-ynoate (13) (0.86 g, 95%) as a yellow solid. Mp 56–58 °C;

\( \nu_{\text{max}} / \text{cm}^{-1} \) (neat) 2960, 1714 (C=O), 1591 (C=O), 1509, 1340, 1154, 854, 750; \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 1.30 (3H, t, J 7.1 Hz, OCH\(_2\)CH\(_3\)), 2.50–2.57 (2H, m, 4-H\(_2\)), 2.60–2.66 (2H, m, 5-H\(_2\)), 4.21 (2H, q, J 7.1 Hz, OCH\(_2\)CH\(_3\)), 5.94 (1H, dt, J 15.7, 1.5 Hz, 2-H), 7.02 (1H, dt, J 15.7, 6.7 Hz, 3-H); 7.49–7.54 (2H, m, 2′-H and 6′-H); 8.14–8.18 (2H, m, 3′-H and 5′-H); \( \delta_{\text{C}} \) (101 MHz, CDCl\(_3\)) 14.3 (CH\(_3\)), 18.4 (CH\(_2\)), 31.4 (CH\(_2\)), 60.2 (CH\(_2\)), 81.7 (C), 88.3 (C), 122.5 (CH), 123.6 (C), 127.8 (CH), 128.2 (2 × CH), 131.6 (2 × CH), 146.6 (CH), 166.3 (C); \( m/z \) (EI) 229 (M\(^+\)) 100%, 155 (7), 113 (13), 81 (25), 69 (34).

Ethyl (2E)-7-(4′-methoxyphenyl)hept-2-en-6-ynoate (14) Ethyl (2E)-7-(4′-methoxyphenyl)hept-2-en-6-ynoate (14) was synthesised as described for ethyl (2E)-hept-2-en-6-ynoate (10) using 5-(4′-methoxyphenyl)pent-4-yn-1-ol (7) (0.55 g, 2.89 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 8:2) gave ethyl (2E)-7-(4′-methoxyphenyl)hept-2-en-6-ynoate (14) (0.70 g, 94%) as a yellow oil. Spectroscopic data was consistent with the literature. Ethyl (2E)-7-(4′-nitrophenyl)hept-2-en-6-ynoate (13) (0.56 g, 3.36 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 1:1) gave (2E)-oct-2-en-6-yn-1-ol (16) (0.36 g, 87%) as a colourless oil. Spectroscopic data was consistent with the literature. Ethyl (2E)-7-(4′-methoxyphenyl)hept-2-en-6-ynoate (14) (0.67 g, 2.45 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 13:7) gave (2E)-7-phenylhept-2-en-6-yn-1-ol (17) (0.54 g, 98%) as a colourless oil. Spectroscopic data was consistent with the literature. Ethyl (2E)-7-(4′-nitrophenyl)hept-2-en-6-yn-1-ol (18) (2.28 g, 15.0 mmol) was dissolved in diethyl ether (80 mL) and cooled to –78 °C. Dibal-H (1 M in hexane) (33.0 mL, 33.0 mmol) was added dropwise and the reaction mixture was stirred at –78 °C for 3 h, before warming to room temperature overnight. The solution was cooled to 0 °C and quenched by the addition of a saturated solution of Rochelle salt (50 mL) and warmed to room temperature with vigorous stirring for 1 h, producing a white precipitate that was filtered through a pad of Celite® and washed with diethyl ether (3 x 75 mL). The filtrate was then dried (MgSO\(_4\)) and filtered and concentrated in vacuo. Purification by flash column chromatography (petroleum ether/diethyl ether, 6:4) gave (2E)-hept-2-en-6-yn-1-ol (15) (1.44 g, 87%) as a pale yellow oil. Spectroscopic data was consistent with the literature. Ethyl (2E)-7-(4′-nitrophenyl)hept-2-en-6-yn-1-ol (18) (0.47 g, 83%) as a dark green solid. Mp 64–66 °C;

\( \nu_{\text{max}} / \text{cm}^{-1} \) (neat) 3374 (OH), 2924 (CH), 1516, 1316, 131.6 (2 × CH); \( m/z \) (EI) 186 (M\(^+\)) 13%, 167 (12), 155 (11), 142 (16), 128 (9), 115 (100), 105 (10), 84 (14).

(2E)-7-(4′-Nitrophenyl)hept-2-en-6-yn-1-ol (18) (2E)-7-(4′-Nitrophenyl)hept-2-en-6-yn-1-ol (18) was synthesised as described for (2E)-hept-2-en-6-yn-1-ol (15) using ethyl (2E)-7-(4′-nitrophenyl)hept-2-en-6-ynoate (13) (0.67 g, 2.45 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 6:4) gave (2E)-7-(4′-nitrophenyl)hept-2-en-6-yn-1-ol (18) (0.47 g, 83%) as a dark green solid. Mp 64–66 °C;

\( \nu_{\text{max}} / \text{cm}^{-1} \) (neat) 3374 (OH), 2924 (CH), 1516, 1316, 131.6 (2 × CH); \( m/z \) (EI) 185 (M\(^+\)) 22%, 230 (20), 185 (27), 145 (100), 130 (6), 102 (13), 83 (11).
δ_C (101 MHz, CDCl_3) 19.6 (CH_3), 31.1 (CH_2), 63.5 (CH_2), 79.8 (C), 95.6 (C), 123.5 (2 × CH), 130.4 (CH), 130.8 (CH), 130.9 (C), 132.3 (2 × CH), 146.7 (C); m/z (ESI) 254.0784 (MNa^+). C_{11}H_{11}NO requires 254.0788, 227 (9%), 199 (9).

(2E)-7-(4'-Methoxyphenyl)hept-2-en-6-yn-1-ol (19)

(2E)-7-(4'-Methoxyphenyl)hept-2-en-6-yn-1-ol (19) was synthesised as described for (2E)-hept-2-en-6-yn-1-ol (15) using ethyl (2E)-7-(4'-methoxyphenyl)hept-2-en-6-ynoate (14) (0.44 g, 1.68 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 1:1) gave (2E)-7-(4'-methoxyphenyl)hept-2-en-6-yn-1-ol (19) (0.34 g, 94%) as a yellow oil. υ_{max}/cm^{-1} (neat) 3368 (OH), 2916 (CH), 1607 (C=C), 1508, 1424, 831; δ_H (400 MHz, CDCl_3) 1.43 (1H, br s, OH), 2.30-2.41 (2H, m, 4-H_2), 2.47 (2H, t, J 7.1 Hz, 5-H_2), 3.79 (3H, s, OCH_3), 4.12 (2H, d, J 4.5 Hz, 1-H_2), 5.69-5.85 (2H, m, 2-H and 3-H), 6.78-6.83 (2H, m, 3'-H and 5'-H), 7.29-7.34 (2H, m, 2'-H and 6'-H); δ_C (101 MHz, CDCl_3) 19.5 (CH_3), 31.6 (CH_2), 55.2 (CH_2), 63.2 (CH_3), 80.9 (C), 87.9 (C), 113.9 (2 × CH), 116.0 (C), 130.4 (CH), 130.7 (CH), 132.9 (2 × CH), 159.1 (C); m/z (EI) 216.1153 (M^+). C_{10}H_{12}O requires 216.1150, 172 (17), 145 (100), 130 (7), 105 (15).

3-(2',2',2'-Trichloromethylcarbonylamo)hept-1-en-6-yn-1-ol (20)\(^1\)

(2E)-Hept-2-en-6-yn-1-ol (15) (0.11 g, 1.00 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. To the solution was added 1.8-diabicyclo[5.4.0]undec-7-ene (0.03 mL, 0.20 mmol) and trichloroacetonitrile (0.15 mL, 1.50 mmol). The reaction mixture was allowed to warm to room temperature before stirring for 3 h. The reaction mixture was filtered through a short pad of silica gel and the filtrate concentrated except using (2 × CH), 130.5 (C), 128.0 (CH), 128.3 (2 × CH), 131.7 (2 × CH), 135.6 (CH), 161.2 (C); m/z (ESI) 289.9865 (MNa^+). C_{10}H_{12}Cl_3NNaO requires 289.9877.

7-Phenyl-3-(2',2',2'-trichloromethylcarbonylamo)hept-1-en-6-yn-1-ol (22)

7-Phenyl-3-(2',2',2'-trichloromethylcarbonylamo)hept-1-en-6-yn-1-ol (22) was synthesised as described for compound 20, except using (2E)-7-(4-nitrophenyl)hept-2-en-6-yn-1-ol (17) (0.08 g, 0.44 mmol) and a single portion of bis(acetonic)chloroform (0.012 g, 0.044 mmol). The reaction was performed at 20 °C for 12 h. Flash column chromatography using silica (petroleum ether/diethyl ether, 1:1) gave 7-phenyl-3-(2',2',2'-trichloromethylcarbonylamo)hept-1-en-6-yn-1-ol (22) (0.12 g, 81%) as a colourless oil. υ_{max}/cm^{-1} (neat) 3304 (NH), 2955 (CH), 2362, 1714 (C=O), 1511, 1265, 1175; δ_H (400 MHz, CDCl_3) 1.90-2.09 (2H, m, 4-H_2), 2.48-2.61 (2H, m, 5-H_2), 4.60-4.69 (1H, m, 3-H), 5.27 (1H, d, J 10.4 Hz, 1-H''), 5.32 (1H, d, J 17.2 Hz, 1-H'H), 5.85 (1H, ddd, J 17.2, 10.4, 5.6 Hz, 2-H'), 6.98 (1H, d, J 7.4 Hz, NH), 7.26-7.32 (3H, m, 3 × ArH), 7.37-7.44 (2H, m, 2 × ArH); δ_C (101 MHz, CDCl_3) 15.9 (CH_3), 32.8 (CH_2), 53.2 (CH), 82.0 (C), 88.4 (C), 92.7 (C), 116.9 (CH), 123.4 (C), 128.0 (CH), 128.3 (2 × CH), 131.7 (2 × CH), 135.6 (CH), 161.4 (C); m/z (ESI) 352.0019 (MNa^+). C_{12}H_{14}Cl_3NNaO requires 352.0033.

7-(4'-Nitrophenyl)-3-(2',2',2'-trichloromethylcarbonylamo)hept-1-en-6-yn-1-ol (23)

7-(4'-Nitrophenyl)-3-(2',2',2'-trichloromethylcarbonylamo)hept-1-en-6-yn-1-ol (23) was synthesised as described for compound 20, except using (2E)-7-(4'-nitrophenyl)hept-2-en-6-yn-1-ol (18) (0.06 g, 0.26 mmol) and a single portion of bis(acetonic)chloroform (0.008 g, 0.026 mmol). The reaction was performed at 20 °C for 12 h. Purification by flash column chromatography (petroleum ether/ethyle acetate, 8:2) gave 7-(4'-nitrophenyl)-3-(2',2',2'-trichloromethylcarbonylamo)hept-1-en-6-yn-1-ol (23) (0.07 g, 76%) as a yellow oil. υ_{max}/cm^{-1} (neat) 3339 (NH), 2932 (CH), 1697 (C=O), 1514 (C=C), 1341, 1107, 852, 820; δ_H (400 MHz, CDCl_3) 1.93-2.08 (2H, m, 4-H_2), 2.50-2.64 (2H, m, 5-H_2), 4.58-4.68 (1H, m, 3-H), 5.25-5.36 (2H, m, 1-H'), 5.85 (1H, ddd, J 17.2, 10.4, 5.7 Hz, 2-H), 6.80 (1H, d, J 7.9, NH), 7.50-7.55 (2H, m, 2′-H and 6″-H), 8.12-8.17 (2H, m, 3″-H and 5″-H); δ_C (101 MHz, CDCl_3) 16.2 (CH_2), 32.7 (CH_2), 53.0 (CH), 80.4 (C), 92.7 (C), 94.3 (C), 117.2 (CH_2), 123.5 (2 × CH), 130.5 (C), 132.4 (2 × CH), 135.5 (CH), 146.8 (C), 153.2 (C), 161.1 (C); m/z (ESI) 394.9813 (MNa^+). C_{12}H_{14}Cl_3NNaO requires 394.9825.
7-(4′-Methoxyphenyl)-3-(2′,2′,2′-trichloromethylcarbonyl)amino-hept-1-en-6-yn-1-ol (19) (0.11 g, 0.49 mmol) and a single portion of bis(acetonitrile) palladium chloride (0.014 g, 0.049 mmol). The reaction was performed at 20 °C for 12 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave 7-(4′-methylphenyl)-3-(2′,2′,2′-trichloromethylcarbonyl)amino-hept-1-en-6-yn-1-ol (20) (0.15 g, 83%) as a colourless oil. \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 3340 (NH), 2925 (CH), 1697 (C=O), 1509 (C=C), 1246, 1173, 831; \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 1.89–2.08 (2H, m, 4-H\(_2\)), 2.45–2.62 (2H, m, 5-H\(_2\)), 3.80 (3H, s, OCH\(_3\)), 4.59–4.69 (1H, m, 3-H), 5.24–5.35 (2H, m, 1-H\(_2\)), 5.85 (1H, dd, J 17.1, 10.4, 5.5 Hz, 2-H), 6.79–6.84 (2H, m, 3-H and 5-H), 7.02 (1H, d, J 8.0 Hz, NH), 7.30–7.36 (2H, m, 2″-H and 6″-H); \( \delta_{\text{C}} \) (126 MHz, CDCl\(_3\)) 15.8 (CH\(_2\)), 32.8 (CH\(_2\)), 53.2 (CH), 55.3 (CH\(_3\)), 81.9 (C), 86.8 (C), 92.7 (C), 113.9 (2 × CH), 115.4 (C), 116.7 (CH\(_3\)), 133.0 (2 × CH), 135.6 (CH\(_3\)), 159.3 (C), 161.4 (C); \( \text{m/z} \) (ESI) 382.0120 [M-\( \text{Na}^-\)]. \( \text{C}_{16}\text{H}_{15}\text{Cl}_{3}\text{N}_{2}\text{O}_{3} \) requires 382.0139.

\[ \text{(3aS,8R*,8aS*,8bR*)-2,5-Diphenyl-3a,4,6,7,8a,8b-hexahydro-1,2′-trichloromethylcarbonyl} \text{amino)cyclopen[t[e]isouonidole-1,3(2H,3aH)-dione (25)} \]

\[ \text{(2E)-7-Phenyleth-2-en-6-yn-1-ol (17) (0.12 g, 0.64 mmol) was dissolved in dichloromethane (16 mL) and cooled to 0 °C. To the solution, 1,8-diazabicyclo[5.4.0]undec-7-ene (0.02 mL, 0.013 mmol) and trichloroacetonitrile (0.10 L, 0.966 mmol) were added. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was filtered through a short pad of silica gel with diethyl ether (300 mL) and the filtrate concentrated to dryness. The crude product was purified by column chromatography (petroleum ether/diethyl ether, 7:3) to give compound 18 (0.39 mL, 2.58 mmol). The reaction mixture was stirred at room temperature for 12 h. Grubbs second generation catalyst (0.04 g, 0.05 mmol) was added with 1,7-octadiene (0.39 mL, 2.58 mmol) and the reaction mixture was stirred for 18 h at 90 °C. N-Phenyl maleimide (0.17 g, 0.96 mmol) was added with hydroquinone (0.008 g, 0.008 mmol). The reaction mixture was stirred for 18 h at 75 °C. The reaction mixture was then cooled and the solvent was evaporated. Flash column chromatography (petroleum ether/diethyl ether, 7:3) gave compound 20 (0.15 g, 51%) as a yellow solid. Mp 151–153 °C; spectroscopic data was consistent with the literature.}^{15} \]

\[ \text{7-(4′-Methoxyphenyl)-3-(2′,2′,2′-trichloromethylcarbonyl)amino-hept-1-en-6-yn-1-ol (19) (0.11 g, 0.49 mmol) and a single portion of bis(acetonitrile)palladium chloride (0.014 g, 0.049 mmol). The reaction was performed at 20 °C for 12 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 8:2) gave 7-(4′-methylphenyl)-3-(2′,2′,2′-trichloromethylcarbonyl)amino-hept-1-en-6-yn-1-ol (20) (0.15 g, 83%) as a colourless oil. \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 3340 (NH), 2925 (CH), 1697 (C=O), 1509 (C=C), 1246, 1173, 831; \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 1.89–2.08 (2H, m, 4-H\(_2\)), 2.45–2.62 (2H, m, 5-H\(_2\)), 3.80 (3H, s, OCH\(_3\)), 4.59–4.69 (1H, m, 3-H), 5.24–5.35 (2H, m, 1-H\(_2\)), 5.85 (1H, dd, J 17.1, 10.4, 5.5 Hz, 2-H), 6.79–6.84 (2H, m, 3-H and 5-H), 7.02 (1H, d, J 8.0 Hz, NH), 7.30–7.36 (2H, m, 2″-H and 6″-H); \( \delta_{\text{C}} \) (126 MHz, CDCl\(_3\)) 15.8 (CH\(_2\)), 32.8 (CH\(_2\)), 53.2 (CH), 55.3 (CH\(_3\)), 81.9 (C), 86.8 (C), 92.7 (C), 113.9 (2 × CH), 115.4 (C), 116.7 (CH\(_3\)), 133.0 (2 × CH), 135.6 (CH\(_3\)), 159.3 (C), 161.4 (C); \( \text{m/z} \) (ESI) 382.0120 [M-\( \text{Na}^-\)]. \( \text{C}_{16}\text{H}_{15}\text{Cl}_{3}\text{N}_{2}\text{O}_{3} \) requires 382.0139.

\[ \text{(3aS,8R*,8aS*,8bR*)-2,5-Diphenyl-3a,4,6,7,8a,8b-hexahydro-1,2′-trichloromethylcarbonyl} \text{amino)cyclopen[t[e]isouonidole-1,3(2H,3aH)-dione (25)} \]
Methyl (1R*,7S*,7aS*)-2,3,5,6,7,7a-hexahydro-4-phenyl-1-(2′,2′-trichloromethylcarbonylimino)inden-7-carboxylate (29)

Methyl (1R*,7S*,7aS*)-2,3,5,6,7,7a-hexahydro-4-phenyl-1-(2′,2′-trichloromethylcarbonylimino)inden-7-carboxylate (29) was synthesised as described for compound 25 using (2E)-7-phenyleth-2-en-6-yn-1-ol (17) (0.09 g, 0.48 mmol) and methyl acrylate (0.13 mL, 1.44 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 8 : 2) gave compound 29 (0.08 g, 56%) as a yellow solid. Mp 156–158 °C; \( \nu_{	ext{max}} \)/cm\(^{-1} \) (neat) 3398 (NH), 2925 (CH), 1720, 1191, 821, 753; \( \delta_{	ext{H}} \) (400 MHz, CDCl\(_3\)) 1.79 (1H, q, J 12.4, 8.0 Hz, 7-\( \text{H} \)), 2.16–2.26 (1H, m, 7-\( \text{H} \)), 2.50–2.70 (3H, m, 4-HH and 6-HH), 3.17 (1H, dd, J 9.5, 6.1 Hz, 8a-H), 3.33 (1H, dd, J 14.8, 1.0 Hz, 4-HH), 3.53–3.59 (2H, m, 3a-H and 8b-H), 4.90–5.02 (1H, m, 8-H), 7.02–7.08 (2H, m, 2′-\( \text{H} \) and 6′-\( \text{H} \)), 7.37–7.49 (5H, m, 5 × ArH), 8.16–8.27 (2H, m, 3′-\( \text{H} \) and 5′-\( \text{H} \)), 8.93 (1H, d, J 9.5 Hz, NH); \( \delta_{	ext{C}} \) (126 MHz, CDCl\(_3\)) 28.6 (CH\(_2\)), 31.3 (CH\(_3\)), 31.7 (CH\(_2\)), 40.2 (CH), 41.4 (CH), 44.2 (CH), 52.6 (CH), 92.8 (C), 123.8 (2 × CH), 126.4 (2 × CH), 128.2 (2 × CH), 128.9 (C), 129.4 (CH), 129.5 (2 × CH), 131.2 (C), 143.7 (C), 145.4 (C), 146.7 (C), 162.4 (C), 178.3 (C); \( m/z \) (ESI) 570.0347 (MNa\(^+\), C\(_{23}\)H\(_{29}\)_3Cl\(_2\)N\(_2\)O\(_5\) requires 570.0361).

\[ (1R*,7aR*)-2,3,5,6,7,7a-hexahydro-4-phenyl-6,6,7,7-tetraycano-1-(2′,2′-trichloromethylcarbonylimino)inden-1-carboxylic acid (30) \]

(3aS*,8R*,8aS*,8bR*)-3a,4,6,7,8a,8b-Hexahydro-5-(4′-nitrophenyl)-2-phenyl-8(2′,2′-trichloromethylcarbonylimino)cyclopent[e]-isoindole-1,3(2H,3aH)-dione (30)

(3aS*,8R*,8aS*,8bR*)-3a,4,6,7,8a,8b-Hexahydro-5-(4′-nitrophenyl)-2-phenyl-8(2′,2′-trichloromethylcarbonylimino)cyclopent[e]-isoindole-1,3(2H,3aH)-dione (30) was synthesised as described for compound 25 using (2E)-7-[4′-(nitrophenyl)hept-2-2-en-6-y1-1-ol (18) (0.05 g, 0.20 mmol). Flash column chromatography (petroleum ether/ethyl acetate, 7 : 3) gave compound 30 (0.08 g, 69%) as a yellow solid. Mp 160–162 °C; \( \nu_{	ext{max}} \)/cm\(^{-1} \) (neat) 3306 (NH), 2956 (CH), 1695 (C=O), 1513 (C=C), 1344, 1191, 821, 753; \( \delta_{	ext{H}} \) (400 MHz, CDCl\(_3\)) 1.79 (1H, q, J 12.4, 8.0 Hz, 7-\( \text{H} \)), 2.16–2.26 (1H, m, 7-\( \text{H} \)), 2.50–2.70 (3H, m, 4-HH and 6-HH), 3.17 (1H, dd, J 9.5, 6.1 Hz, 8a-H), 3.33 (1H, dd, J 14.8, 1.0 Hz, 4-HH), 3.53–3.59 (2H, m, 3a-H and 8b-H), 4.90–5.02 (1H, m, 8-H), 7.02–7.08 (2H, m, 2′-\( \text{H} \) and 6′-\( \text{H} \)), 7.37–7.49 (5H, m, 5 × ArH), 8.16–8.27 (2H, m, 3′-\( \text{H} \) and 5′-\( \text{H} \)), 8.93 (1H, d, J 9.5 Hz, NH); \( \delta_{	ext{C}} \) (126 MHz, CDCl\(_3\)) 28.6 (CH\(_2\)), 31.3 (CH\(_3\)), 31.7 (CH\(_2\)), 40.2 (CH), 41.4 (CH), 44.2 (CH), 52.6 (CH), 92.8 (C), 123.8 (2 × CH), 126.4 (2 × CH), 128.2 (2 × CH), 128.9 (C), 129.4 (CH), 129.5 (2 × CH), 131.2 (C), 143.7 (C), 145.4 (C), 146.7 (C), 162.4 (C), 178.3 (C); \( m/z \) (ESI) 570.0347 (MNa\(^+\), C\(_{23}\)H\(_{29}\)_3Cl\(_2\)N\(_2\)O\(_5\) requires 570.0361).
Methyl (1R*,7S*,7aS*)-2,3,5,6,7,7a-hexahydrop-4-(4'-nitrophenyl)-1-(2',2',2'-trichloromethylcarbonylamo)indene-7-carboxylate (33)

Methyl (1R*,7S*,7aS*)-2,3,5,6,7,7a-hexahydrop-4-(4'-nitrophenyl)-1-(2',2',2'-trichloromethylcarbonylamo)indene-7-carboxylate (33) was synthesised as described for compound 25 using (2E)-7-(4'-nitrophenyl)hept-2-en-6-yn-1-ol (18) (0.07 g, 0.29 mmol) and methyl acrylate (0.08 mL, 0.87 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 8:2) gave compound 33 (0.06 g, 46%) as a colourless oil; \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 3389 (NH), 2930 (CH), 1710 (C=O), 1464 (C), 1487 (C), 1618 (C), 1755 (C); \( \delta_{\text{F}} \) (EI) 460.0359 (M+, \( \text{C}_{24}\text{H}_{21}\text{Cl}_{3}\text{N}_{4}\text{O}_{4} \) requires 460.0360) 299 (100%), 240 (71).

\[ \text{(3S*,8R*,8aS*,8bR*)-3a,4,6,7a,8a,8b-Hexahydro-5-(4'-methoxyphenyl)-2-phenyl-7,8,9,9a-tetrahydro-1-(2H,3aH)-dione (34)} \]

7-(4'-Methoxyphenyl)-3-(2',2'-trichloromethylcarbonylamo)cyclopent[e]isoindole-1,3(2H,3aH)-dione (34) (0.04 g, 0.12 mmol) was dissolved in toluene (3 mL) and Grubbs second generation catalyst (0.007 g, 0.008 mmol) was added with 1,7-octadiene (0.07 mL, 0.48 mmol) and the reaction mixture was stirred for 20 h at 40 °C. N-Phenyl maleimide (0.03 g, 0.18 mmol) was added with hydroquinone (0.003 g, 0.003 mmol). The reaction mixture was stirred for 24 h at 75 °C. The reaction mixture was then cooled and the solvent was evaporated. Flash column chromatography (petroleum ether/diethyl ether, 8:2) gave (3S*,8R*,8aS*,8bR*)-3a,4,6,7,8a,8b-hexahydro-5-(4'-methoxyphenyl)-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamo)cyclopent[e]isoindole-1,3(2H,3aH)-dione (34) (0.042 g, 65%) as a yellow solid. \( \mu_{\text{max}}/\text{cm}^{-1} \) (neat) 3308 (NH), 2930 (CH), 1710 (C=O), 1464 (C), 1487 (C), 1618 (C), 1755 (C); \( \delta_{\text{F}} \) (EI) 460.0359 (M+, \( \text{C}_{24}\text{H}_{21}\text{Cl}_{3}\text{N}_{4}\text{O}_{4} \) requires 460.0360) 299 (100%), 240 (71).

\[ \text{(1R*,7aR*)-2,3,5,6,7,7a-Hexahydro-4-(4'-methoxyphenyl)-6,6,7,7-tetracyano-1-(2',2',2'-trichloromethylcarbonylamo)indene (36)} \]

(9R*,9aS*)-6-(4'-Methoxyphenyl)-2-phenyl-7,8,9,9a-tetrahydro-9-(2',2',2'-trichloromethylcarbonylamo)1H,5H-cyclopent[c]-[2,4,10]triazolo[1,2-a]pyridazine-1,3(2H)-dione (35)

\[ \text{(9R*,9aS*)-6-(4'-Methoxyphenyl)-2-phenyl-7,8,9,9a-tetrahydro-9-(2',2',2'-trichloromethylcarbonylamo)1H,5H-cyclopent[c]-[2,4,10]triazolo[1,2-a]pyridaze-1,3(2H)-dione (35)} \]

\[ \text{(9R*,9aS*)-6-(4'-Methoxyphenyl)-2-phenyl-7,8,9,9a-tetrahydro-9-(2',2',2'-trichloromethylcarbonylamo)1H,5H-cyclopent[c]-[2,4,10]triazolo[1,2-a]pyridaze-1,3(2H)-dione (35) was synthesised as described for compound 34 using 7-(4'-methoxyphenyl)-3-(2',2',2'-trichloromethylcarbonylamo)hept-1-en-6-yne (24) (0.03 g, 0.09 mmol) and 4-phenyl-1,2,4-triazole-3,5-dione (0.02 g, 0.11 mmol). The Diels-Alder reaction was stirred for 24 h at 75 °C. Purification by flash column chromatography (petroleum ether/ethyl acetate, 6:4) gave compound 35 (0.04 g, 76%) as a dark yellow solid. Mp 154–156 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 3406 (NH), 2932 (CH), 1774 (C=O), 1703 (C=O), 1510 (C=C), 1420, 1250, 821, 734; \( \delta_{\text{F}} \) (400 MHz, CDCl3) 2.12–2.30 (2H, m, 8-H2), 2.44–2.56 (1H, m, 7-HH), 2.61–2.71 (1H, m, 7-HH), 3.85 (3H, s, OCH3), 4.36 (1H, dd, J 16.0, 4.8, 2.6 Hz, 5-HH), 4.49–4.61 (2H, m, 5-HH and 9a-H), 4.92 (1H, q, J 5.8 Hz, 9-H), 6.70 (1H, d, J 5.8 Hz, NH), 6.93–6.99 (2H, m, 3-H and 5-HH), 7.22–7.56 (7H, m, 7 × ArH); \( \delta_{\text{F}} \) (100 MHz, CDCl3) 24.5 (CH2), 27.9 (CH2), 45.5 (CH2), 52.8 (CH), 92.7 (C), 123.5 (2 × CH), 127.8 (C), 128.4 (2 × CH), 139.5 (C), 146.4 (C), 148.7 (C), 1618 (C), 1755 (C); \( \delta_{\text{F}} \) (EI) 557.0510 (MNa+ C24H21Cl3N4O4 requires 557.0521).
Methyl (1R*,7S*,7aS*)-2,3,5,6,7,7a-hexahydro-4-(4'-methoxyphenyl)-1(2′,2′,2′-trichloromethylcarbonylamo)indene-7-carboxylate (37) was synthesised as described for compound 34 using 7-(4'-methoxyphenyl)-3(2′,2′,2′-trichloromethylcarbonylamo)hept-1-en-6-yne (24) (0.04 g, 0.11 mmol) and methyl acrylate (0.03 mL, 0.33 mmol). The Diels–Alder reaction was stirred for 5 days at 111 °C. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave compound 38 (0.08 g, 0.16 mmol) in ethyl acetate (4 mL) was added 10% palladium on charcoal (0.02 g). The mixture was stirred under an atmosphere of hydrogen at room temperature for 48 h. The reaction mixture was filtered through a short pad of Celite® with diethyl ether (80 mL) and the solvent was evaporated. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave compound 39 (0.04 g, 48%) as a white solid. Mp 164–166 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 3475 (NH/OH), 2931 (CH), 1698 (C=O), 1380, 1216, 818, 753; \( \delta_{\text{H}} \) (400 MHz, CDCl3) 3.15–3.84 (4H, m, 4 × ArH); \( \delta_{\text{C}} \) (126 MHz, CD3OD) 33.8 (CH3), 41.7 (CH), 42.4 (CH), 126.6 (CH2, 2 × CH), 127.2 (CH), 127.5 (2 × CH), 128.4 (2 × CH), 129.1 (CH), 129.4 (2 × CH), 130.1 (C), 131.5 (C), 139.0 (C), 139.9 (C), 164.6 (C), 178.6 (C), 179.7 (C); \( m/z \) (EI) 468.1012 (M+, C22H16 Cl3N2O4 requires 468.1007), 341 (100%), 194 (71), 167 (34), 152 (11), 77 (11).
X-ray procedure for 39

Single crystal diffraction data for 39 were collected by the EPSRC UK National Crystallography Service.38 Data reduction was carried out using CrystAlis PRO (Agilent Technologies, 2014). The structure was solved by charge-flipping methods using SuperFlip39 and refined against F2 using full-matrix least-squares refinement using SHELX201440 within OLEX2.41 Positional and anisotropic atomic displacement parameters (adps) were refined for all non-hydrogen atoms. Hydrogen atoms bound to carbon and nitrogen atoms were placed at calculated positions and refined as part of a riding model except for the MeOH methyl hydrogen and all hydroxyl hydrogen atoms which located in difference Fourier maps were refined as a rigid rotor. There are two independent molecules of both the compound and of MeOH in the asymmetric unit although the conformation of the two molecules is essentially the same.

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Notes and references

26 A preliminary study describing the synthesis of 25 has been previously published. See ref. 15 for details.
27 See ESI† for NOE experiments for all aminobicyclo[4.3.0]-nonanes.
30 Crystal data for 39. C_{25}H_{23}Cl_{3}N_{2}O_{5}·CH_{4}O, M_r = 569.84, Triclinic, a = 11.7084 (4) Å, b = 14.1127 (6) Å, c = 15.5928 (6) Å, α = 90.096 (3)°, β = 95.408 (3)°, γ = 91.971 (3)°, V = 2563.48 (17) Å³, T = 100 K, space group P1 (no. 2), Z = 4, 34139 reflections measured, 9008 unique (Rint = 0.073), which were used in all calculations. The final R_1 = 0.054 for 6437 observed data [F^2 > 2σ(F^2)] and wR_2(F^2) = 0.136 (all data).
31 Crystallographic data for compound 39 in this paper have been deposited with the Cambridge Crystallographic Data Centre with code CCDC 1429493.