Pergamon

Tetrahedron 58 (2002) 1361–1368

TETRAHEDRON

An efficient regioselective halogenation of 5-amino-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-ones

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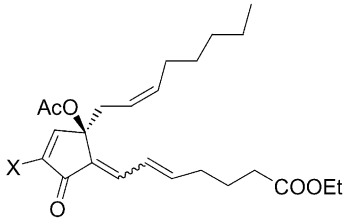
Received 13 July 2001; revised 6 November 2001; accepted 6 December 2001

Abstract—An effective regioselective halogenation of 5-amino-*endo*-tricyclo decenyl enaminones **6** using *N*-halosuccinimides is reported. The reaction is extremely fast and the yields are almost quantitative. Exclusive α,*N*-dihalo or α,γ-dihalo compounds can be obtained by tuning the reaction conditions. Facile transfer of bromine from α,*N*-dibromo enaminones **8** has been observed. A rationale for the formation of the various halogenated products is presented. The α,γ-dihalo enaminones allow further functionalisation of the tricyclodecadienone system and thus are promising precursors for pharmacologically interesting halo-cyclopentanoids. More importantly, the otherwise more reactive norbornene double bond remained intact under these halogenation conditions.

1. Introduction

Natural products containing halogen atoms and cyclopentenone substructure have been shown to exhibit interesting biological activity. Examples are naturally occurring marine prostanoids halovulones **1**[1] and related punaglandins **2**,[2] (Fig. 1) which show remarkable cytotoxicity.[3] Biological evaluation of these compounds and their analogues revealed that the presence of a halogen atom increases the biological activity significantly[4] and hence there is a great interest in these compounds.

Tricyclic structures **3** (Fig. 2), which serve as synthetic equivalents of cyclopentadienones, have been shown to be ideal substrates for the synthesis of a variety of substituted cyclopentenones e.g. **4**.[5] Since the tricyclodecadienone system is chiral and both the antipodes can be obtained in enantiopure form, either by enzymatic resolution[6] or by asymmetric synthesis,[7] it also allows efficient enantioselective approaches to cyclopentenoids. A typical application is the synthesis of (−)-kjellmanianone **5**,[8] (Fig. 2) a naturally occurring compound that shows antibiotic activity. A similar strategy can be envisaged for the synthesis of halo-cyclopentenoids and their analogues. An efficient route towards halo-cyclopentenoids however requires selective halogenation of the enone moiety of the tricyclodecadienone system, avoiding reaction at the more reactive C_8–C_9 norbornene double bond which is essential for the eventual [4+2]-cycloreversion. Recently, an efficient and diastereoselective synthesis of 5-amino-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-ones **6**[7] and their use in the synthesis of enantiopure 4-aminocyclopentene-2-ones **4**[5,9] have been reported by us. These tricyclic enaminones **6** may serve as ideal precursors for the selective halogenation of the enone moiety. The electron-rich enaminone might induce a regioselective electrophilic halogenation of



1 X=Cl, Br, I

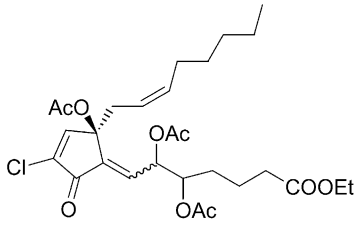


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Figure 1.

Keywords: aminotricyclodecadienone; selective halogenation; *N*-halosuccinimides; *N*-halogenation.

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PII: S0040-4020(01)01228-5

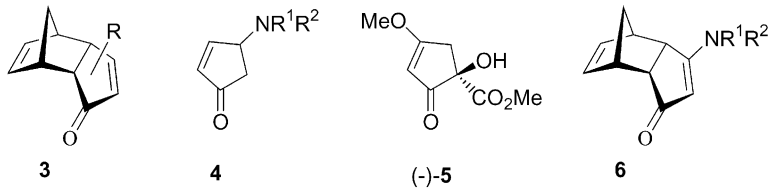


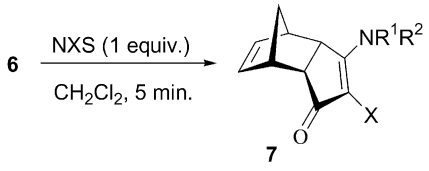
Figure 2.

the enone moiety leaving the norbornene double bond untouched. If so, this would provide a ready access to halo-cyclopentenoids and their analogues. In this paper, we report an efficient regioselective mono- and dihalogenation of tricyclic enaminones **6**, only involving the enaminone moiety. More importantly, the reaction conditions can be adjusted to direct the halogenation to occur at the specific positions.[10]

2. Results and discussion

2.1. Synthesis of α-halotricyclodecadienones

The required starting material, viz. 5-amino-tricyclo-[5.2.1.0^{2,6}]deca-4,8-dien-3-ones **6**, were prepared as reported recently.[7] Halogenation of enaminones to obtain α-halo enaminones has been carried out with a variety of reagents, viz. bromine,[11] iodine,[12] *N*-bromosuccinimide,[11] cyanogen bromide,[11] benzyltriethylammonium trichloroiodate[13,14] and bis-(trifluoroacetoxy)iodobenzene.[15] *N*-halosuccinimides (NXS) which are mild and easy to handle were chosen for the present study in order to minimise unwanted halogenation of the C_8–C_9-norbornene double bond. When the tricyclic enaminones **6** were treated with 1 equiv. of *N*-chloro (NCS) or *N*-bromosuccinimide (NBS) in CH_2Cl_2 at room temperature, the reaction was complete in 5 min to afford monohalogenated compounds in almost quantitative yield in most cases. Spectral analysis revealed that these products are the desired tricyclic α-halo enaminones **7** (Scheme 1, Table 1).

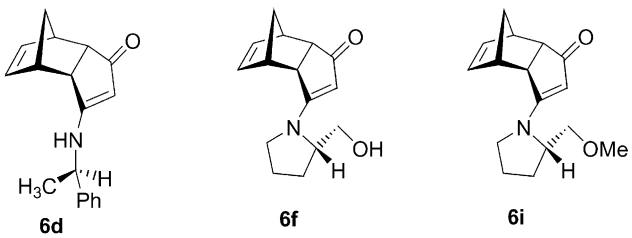


Scheme 1.

Table 1. Monohalogenation of enaminones **6** using NXS

Compound	R^1	R^2	Product	X	Yield (%)
6a	Benzyl	H	**7a**	Br	97
6b	Cyclohexyl	H	**7b**	Br	98
6c	*n*-Pentyl	H	**7c**	Br	97
6d[a]	*R*-(+)-α-Methylbenzyl	H	**7d**	Br	98
6e	$-CH_2-CH_2-CH_2-CH_2-$		**7e**	Br	98
6f[a]	See footnote		**7f**	Br	93
6a	Benzyl	H	**7g**	Cl	97
6e	$-CH_2-CH_2-CH_2-CH_2-$		**7h**	Cl	98
6i[a]	See footnote		**7i**	I	86

[a] The absolute configurations of the starting diastereomeric enaminones are as follows:

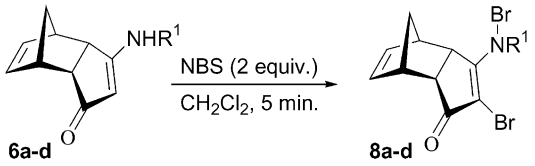


The reaction rate and the chemical yield of this halogenation reaction seem to be independent of the nature of the amino substituent. Both secondary and tertiary enaminones underwent this reaction with equal ease. No products arising from halogenation of the C_8–C_9 norbornene double bond were detected. In order to trap any conceivable transient C_8–C_9 halonium ion some of these reactions were tried in methanol as well. However, the results were the same thereby ruling out the possibility of initial formation of C_8–C_9 halonium ion. This observation seems typical for the tricyclic enaminones **6**, while normally the norbornene double bond is quite reactive towards NXS.[16] In contrast to a literature report,[14] polyhalogenation of **6** was not at all observed with 1 equiv. of NXS. However, a complex mixture of products was obtained, when elemental bromine was used instead of NBS.

2.2. Reaction of secondary enaminones with NBS: synthesis of α,*N*-dibromo enaminones

When enaminone **6a** was treated with a slight excess of NBS (1.1 equiv.), two products were formed, namely, the expected α-halo enaminone **7a** and a minor less polar compound identified as a dibrominated product **8a**. Interestingly, the second halogenation did not occur on the norbornene double bond, but on nitrogen instead. This is quite surprising, as once the monohalogenated product **7** is formed, the electron density on the nitrogen of the enaminone moiety will be considerably reduced due to the electron withdrawing nature of the bromine. Hence, the second bromination might be expected to take place on the norbornene double bond.

In order to have an in-depth look into this reaction, bromination of **6a** was carried out with 2 equiv. of NBS. The α,*N*-dibrominated compound **8a** was obtained as the sole product in almost quantitative yield (Scheme 2). Since a mono *N*-bromo compound, such as **9** (Fig. 3) was not isolated in any of these reactions, it is clear that the α-bromination precedes the formation of α,*N*-dibromo enaminones **8**. This was independently confirmed by treating **7a** with an additional equiv. of NBS. Again, compound **8a** was the only product. The introduction of a halogen at C_4



Scheme 2.

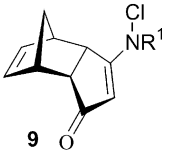


Figure 3.

deactivates this position in such a way that the second halogenation does not occur at the same α-position and reaction at other nucleophilic sites becomes competitive. In this case, a second bromine atom is introduced regioselectively at nitrogen. Dibromination was also successful with enaminones **6b**–**6d** affording the corresponding products **8b**–**8d**, respectively, in almost quantitative yields (Scheme 2, Table 2).

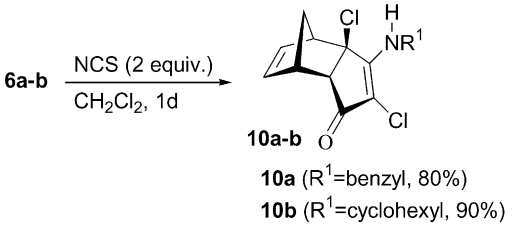
Table 2. α,*N*-Dibromination of secondary enaminones

Compound	R^1	Product	Yield (%)
6a	Benzyl	**8a**	97
6b	Cyclohexyl	**8b**	98
6c	*n*-Pentyl	**8c**	97
6d	*R*-(+)-α-methylbenzyl	**8d**	98

These α,*N*-dibromo enaminones **8**, being vinylogous halo amides, possess properties similar to that of NXS. They are capable of transferring a bromonium ion and thus can perform electrophilic bromination themselves. Thus, 2 equiv. of α-bromo enaminone **7a** were obtained upon mixing equimolar amounts of parent enaminone **6a** and dibromo enaminone **8a**. The fact that the α,*N*-dibromo enaminones **8a**–**8d** can be isolated suggests that the nitrogen–bromine bond in **8** is considerably more stable than that in NBS, which readily releases bromine, otherwise the α,*N*-dibromo enaminones **8a**–**8d** would not have been formed that quickly. Attempts were then made to accomplish an enantioselective bromine transfer with the optically active dibromo enaminone **8d**. Treatment of enaminone **8d** with an excess of cyclohexene in the presence of water under standard conditions[17] resulted in a facile transfer of bromine to afford *trans*-2-bromocyclohexan-1-ol in a moderate yield (42%, conditions not optimised), but without any optical activity (Scheme 3). The inertness of the norbornene double bond in this reaction is noteworthy.

2.3. Reaction of secondary enaminones with NCS: synthesis of α,γ-dichloro enaminones

Interestingly, the reaction of parent enaminones **6a**–**6b** with 2 equiv. of NCS, took a different course. Unlike the bromination, after the first α-chlorination, the second chlorination occurred at the γ-position instead of nitrogen, to give the α,γ-dichlorinated enaminone **10a**–**10b**, in high yield, but very slowly (Scheme 4). It was difficult to precisely determine the position (either α′ or γ) of the second chlorine atom in the products on the basis of spectral data alone (NMR as well as NOESY experiments). Fortunately, compound **10a** could be crystallised and its structure was determined by single crystal X-ray analysis (Fig. 4).[18]



Scheme 4.

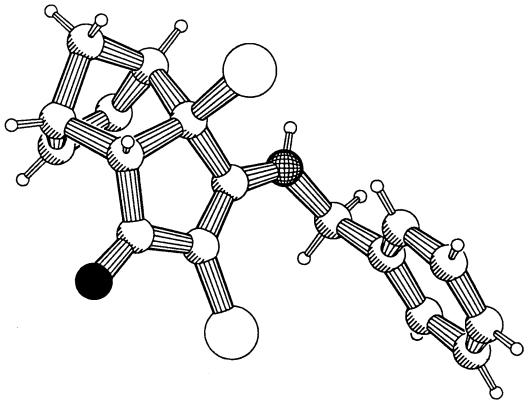
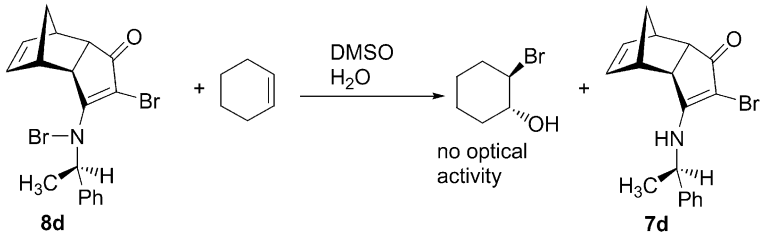


Figure 4. Pluton structure of **10a**.

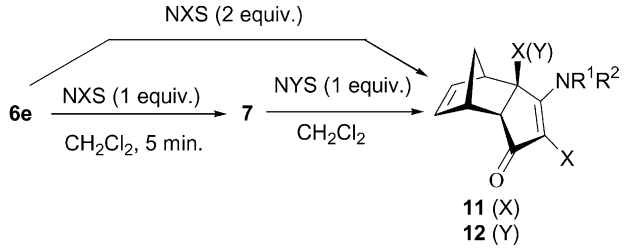
2.4. Reaction of tertiary enaminones with NXS: synthesis of α,γ-dihalo enaminones

Dibromination of tertiary enaminone **6e** was considered



Scheme 3.

next. Reaction of enaminone **6e** with 2 equiv. of NBS in CH_2Cl_2 proceeded smoothly to afford the α,γ-dibromo enaminone **11a**, within 10 min in almost quantitative yield. Thus, in the absence of a free NH, the second bromine can be regioselectively introduced on the γ-carbon. Dibromo enaminone **11a** was also obtained when the halogenation of **6e** was conducted in a stepwise manner by reacting monohalo compounds **7e** with an additional equiv. of NBS. Using this stepwise method, mixed α,γ-dihalotricyclo enaminones **12a** and **12b** were also synthesized in almost quantitative yields. On the other hand, reaction of tertiary enaminone **6e** with 2 equiv. of NCS in CH_2Cl_2 was found to be sluggish. After the initial instantaneous formation of α-chloro enaminone **7h** (monitored by TLC), introduction of the second chlorine atom was extremely slow. However, change of solvent from CH_2Cl_2 to methanol proved to be better and eventually the α,γ-dichloroenaminone **11b** was obtained in a good yield of 82% after 24 h (Scheme 5, Table 3).



Scheme 5.

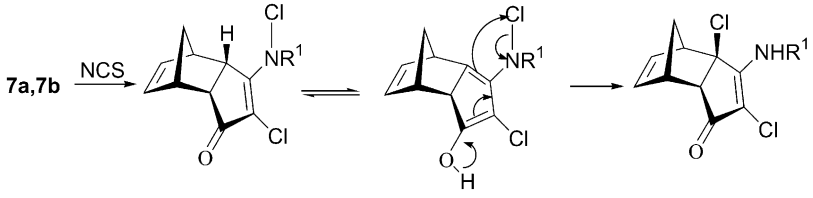
Table 3. α,γ-Dihalogenation of tertairy enaminone **6e**

X	Y	Solvent	Reaction time	Product	Yield (%)
Br		CH_2Cl_2	10 min	**11a**	99
Cl		MeOH	1 day	**11b**	82
Br	Cl	CH_2Cl_2	10 min	**12a**	99
Cl	Br	CH_2Cl_2	10 min	**12b**	98

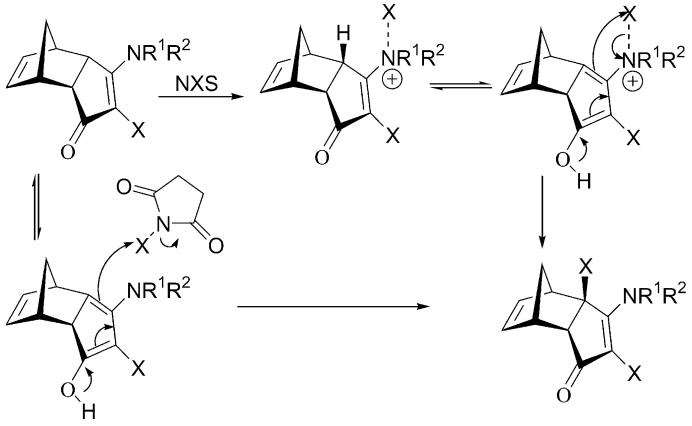
2.5. Mechanistic considerations

The mechanism of these halogenation reactions deserves some comments. While the monohalogenation of enaminones is independent of the amino substituent as well as the reagent and solvent, that is not the case for the dihalogenation. α-Halogenation of enaminones is well known and proceed through a direct enamine type addition followed by the release of a proton. Initial N-halogenation to a product such as **9** and subsequent rearrangement to the more stable **7** is also conceivable and could not be excluded. Once the monohalogenated products are formed, the electron-withdrawing ability of the halogens seems to play a decisive role in the subsequent halogenation. The halogen at the α-position deactivates this position for a second halogenation and reaction at other nucleophilic sites are favoured. As nitrogen being a more nucleophilic site, the initial step in the second halogenation of both the secondary and tertiary α-halo enaminones could be N-halogenation. In the case of secondary enaminones, a proton can be readily lost from the nitrogen to afford the α,*N*-dihalo enaminones. In the case of bromination, the α,*N*-dibromo compound is relatively stable and hence isolable. The outcome of the dichlorination is different, viz. exclusive formation of α,γ-dichlorides **10**. It is reasonable that the second halogenation step proceeds via the initial formation of an α,*N*-dichloro intermediate which in a subsequent step undergoes a chloride transfer reaction. A conceivable mechanism for this halide transfer involves the γ-enol as shown in Scheme 6. The enolization may be assisted by the succinimide anion as the base.

In the case of tertiary enaminone, the second halogenation step may take place directly via the enol (or enolate) or via an initial N-chlorination and subsequent halogen transfer as is predicted in Scheme 7. Again, the enolization may be



Scheme 6.



Scheme 7.

promoted by the succinimide anion. The regiochemical difference between the dichlorination and dibromination of the secondary enaminones can be attributed to the relatively low stability of N–Cl bond compared to that of a N–Br bond.

The complete inertness of the norbornene double bond towards this halogenation seems quite remarkable for this 5-amino-*endo*-tricyclodecadienone. It may be attributed to a strong orbital interaction between the two double bonds, which considerably reduces the nucleophilicity of the norbornene double bond. The observed complete regioselectivity for the electrophilic halogenation is a highly relevant finding as an intact C_8–C_9 double bond is a prerequisite in our synthetic approach to cyclopentenoids.

3. Conclusions

It has been demonstrated that 5-amino-*endo*-tricyclodecadienones can be regioselectively halogenated on the enaminone moiety without affecting the norbornene double bond. The reaction conditions can be tuned to obtain either α-halo, α,*N*-dihalo or α,γ-dihalo compounds. Mixed α,γ-dihalo compounds were also obtained. The reactions proceed with great ease and the yields are quantitative in most cases. The formation of γ-halogenated products is unprecedented. These γ-halogenated compounds are potential precursors for further functionalisation and thus may serve as suitable synthons for β-functionalised cyclopentenoids.[8] Research towards this is currently under progress.

4. Experimental

4.1. General

Melting points were measured with a Reichert Thermopan microscope and are uncorrected. IR spectra were recorded on a Perkin–Elmer 298 infrared spectrophotometer. FT-IR spectra were taken on a Biorad WIN-IR FTS-25 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-400, a Bruker AC-300 and a Bruker AC-100 at room temperature unless stated otherwise. Chemical shifts are reported in ppm relative to TMS. For mass spectra, a double focussing VG 7070E mass spectrometer was used. GC-MS spectra were run on a Varian Saturn 2 benchtop GC-MS ion-trap system. Elemental analyses were performed on a Carlo Erba Instruments CHNS-O 1108 Elemental Analyzer. Optical rotations were measured with a Perkin–Elmer 241 Polarimeter. GC analyses were conducted with a Hewlett-Packard HP5890II instrument. Flash chromatography was carried out using Merck Kieselgel 60H and column chromatography at atmospheric pressure was performed using Merck Kieselgel 60. Thin layer chromatography (TLC) was carried out on Merck precoated silicagel 60 F254 plates (0.25 mm) and spots were visualized with UV, iodine or a molybdate spray. Solvents used were of analytical grade and wherever necessary, were dried using the standard methods.

4.2. General procedure for the monohalogenation of 5-aminotricyclodecadienones 6

N-Halosuccinimide (1 equiv.) was added to a clear solution of **6** (1 equiv.) in CH_2Cl_2 at room temperature. When TLC indicated the absence of starting material (5 min), the reaction was stopped and the reaction mixture extracted with a 15 ml 0.1 M NaOH solution to remove the succinimide. The organic phase was dried over $MgSO_4$ and concentrated in vacuo to yield the α-halogenated product **7**.

4.2.1. 5-Benzylamino-4-bromo-*endo*-tricyclo[5.2.1.0^{2,6}]-deca-4,8-dien-3-one (7a). Compound **7a** was obtained in 97% yield from **6a** (0.310 g, 1.23 mmol) and NBS (0.220 g, 1.23 mmol) in CH_2Cl_2 (10 ml). Recrystallisation from 2-propanol provided an analytically pure sample of **7a** as white needles. Mp: 211°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 5H), 6.01 (dd, J=5.7 Hz, 2.9 Hz, 1H), 5.78 (dd, J=5.7, 2.9 Hz, 1H), 4.70 (d, J=6.2 Hz, 2H), 3.35 (dd, J=3.7, 1.7 Hz, 1H), 3.19 (br s, 1H), 3.07 (br s, 1H), 3.02 (dd, J=6.0, 4.4 Hz, 1H), 1.75 (dt, J=8.7, 1.8 Hz, 1H), 1.56 (br d, J=8.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 173.5, 136.8, 134.1, 130.9, 128.7, 127.7, 126.3, 92.0, 51.0, 49.2, 47.5, 44.1, 43.5, 42.8; IR (KBr, cm^{-1}) ν 3146, 1943, 1599, 1521, 1495, 1450; HRMS/EI: *m/z* calcd for $C_{17}H_{16}NO^{79}Br$: 329.04153 (M^+). Found: 329.04128 (M^+). Anal. calcd for $C_{17}H_{16}NOBr$: C, 61.88; H, 4.81; N, 4.24%. Found: C, 62.26; H, 4.72; N, 4.31%.

4.2.2. 4-Bromo-5-cyclohexylamino-*endo*-tricyclo[5.2.1.0^{2,6}]-deca-4,8-dien-3-one (7b). Compound **7b** was obtained in 97% yield (0.319 g) from **6b** (0.247 g, 1.02 mmol) and NBS (0.181 g, 1.02 mmol) in CH_2Cl_2 (10 ml). Recrystallisation from ethyl acetate provided an analytically pure sample of **7b** as yellow needles. Mp: 158°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (dd, J=5.5, 2.9 Hz, 1H), 5.82 (dd, J=5.5, 2.8 Hz, 1H), 5.18 (br d, J=9.7 Hz, 1H), 3.57 (m, 1H), 3.30 (m, 1H), 3.26 (br s, 1H), 3.07 (br s, 1H), 3.00 (m, 1H), 1.98–1.83 (m, 4H), 1.78 (br d, J=8.6 Hz, 1H), 1.70, 1.3 (m, 6H), 1.57 (br d, J=8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 170.4, 135.2, 130.9, 92.3, 53.6, 51.2, 49.4, 44.7, 43.5, 43.0, 34.8, 34.7, 25.0, 24.9; IR (KBr, cm^{-1}) ν 3250, 1670, 1587, 1449; HRMS/EI: *m/z* calcd for $C_{16}H_{20}NO^{79}Br$: 321.0728 (M^+). Found: 321.072 (M^+); Anal. calcd for $C_{16}H_{20}NOBr$: C, 59.64; H, 6.26; N, 4.35%. Found: C, 59.85; H, 6.32; N, 4.40%.

4.2.3. 4-Bromo-5-*n*-pentylamino-*endo*-tricyclo[5.2.1.0^{2,6}]-deca-4,8-dien-3-one (7c). Compound **7c** was obtained in 97% yield (0.324 g) from **6c** (0.248 g, 1.07 mmol) and NBS (0.191 g, 1.07 mmol) in CH_2Cl_2 (10 ml). Recrystallisation from ethyl acetate provided an analytically pure sample of **7c** as white needles. Mp: 120°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (dd, J=5.5, 2.9 Hz, 1H), 5.82 (dd, J=5.5, 2.8 Hz, 1H), 5.23 (br s, 1H), 3.45 (m, 2H), 3.29 (dd, J=5.6, 4.5 Hz, 1H), 3.26 (br s, 1H), 3.11 (br s, 1H), 3.01 (m, 1H), 1.78 (br d, J=8.6 Hz, 1H), 1.66 (m, 2H), 1.57 (br d, J=8.6 Hz, 1H), 1.39 (m, 4H), 0.95 (t, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 170.4, 135.0, 130.8, 92.6, 51.3, 49.4, 44.4, 44.3, 43.7, 43.0, 30.3, 28.7, 22.3, 13.8; IR (KBr, cm^{-1}): ν 3267, 1662, 1602, 1559, 1453; HRMS/EI: *m/z* calcd for $C_{15}H_{20}NO^{79}Br$: 309.07283 (M^+). Found: 309.07256 (M^+); Anal. calcd for

$C_{15}H_{20}NOBr$: C, 58.07; H, 6.50; N, 4.51%. Found: C, 58.31; H, 6.63; N, 4.57%.

4.2.4. 4-Bromo-5-(1*R*,2*S*,6*R*,7*S*,1′*R*)(1′-phenylethylamino)-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (7d). Compound **7d** was obtained in 98% yield (0.139 g) from **6d** (0.106 g, 0.4 mmol) and NBS (0.072 g, 0.4 mmol) in CH_2Cl_2 (2 ml) as a viscous oil. ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.50–7.26 (m, 5H), 5.95 (dd, J=5.6, 3.0 Hz, 1H), 5.62 (br d, 1H), 5.29 (m, 1H), 5.00 (quin, J=7.0 Hz, 1H), 3.35 (m, 1H), 3.16 (br s, 1H), 3.01 (m, 1H), 2.66 (br s, 1H), 1.66–1.41 (m, 5H).

4.2.5. 4-Bromo-5-pyrrolidino-*endo*-tricyclo[5.2.1.0^{2,6}]-deca-4,8-dien-3-one (7e). Compound **7e** was obtained in 98% yield (0.533 g) from **6e** (0.400 g, 1.86 mmol) and NBS (0.331 g, 1.86 mmol) in CH_2Cl_2 (15 ml). Recrystallisation from ethyl acetate provided an analytically pure sample of **7e** as white needles. Mp: 164°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (dd, J=5.6, 2.9 Hz, 1H), 5.86 (dd, J=5.6, 2.9 Hz, 1H), 4.06–3.64 (m, 4H), 3.27 (m, 2H), 3.14 (br s, 1H), 2.95 (dd, J=6.2, 4.5 Hz, 1H), 1.96 (m, 4H), 1.72 (br d, J=8.6 Hz, 1H), 1.52 (br d, J=8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 168.5, 134.9, 130.7, 90.5, 50.8, 50.5, 49.9, 48.2, 46.4, 44.5, 44.4, 25.5, 24.5; IR (KBr, cm^{-1}): ν 3318, 1663, 1563, 1454, HRMS/EI: m/z calcd for $C_{14}H_{16}NO^{79}Br$: 293.04153 (M^+). Found: 293.04164 (M^+). Anal. calcd for $C_{14}H_{16}NOBr$: C, 57.16; H, 5.48; N, 4.76%. Found: C, 57.17; H, 5.61; N, 4.78%.

4.2.6. 4-Bromo-(1*R*,2*S*,6*R*,7*S*,2′*R*)-5-(2′-hydroxymethylpyrrolidin-1′-yl)-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (7f). Compound **7f** was obtained in 93% yield (0.533 g) from **6f** (0.049 g, 0.2 mmol) and NBS (0.036 g, 0.2 mmol) in CH_2Cl_2 (2 ml) as a viscous liquid. ^{1}H NMR (100 MHz, $CDCl_3$) δ 6.06 (dd, J=5.4, 2.8 Hz, 1H); 5.69 (dd, J=5.4, 2.8 Hz, 1H), 4.00–2.09 (m, 9H), 2.03 (m, 4H), 1.74 (d, J=8.3 Hz, 1H), 1.55 (d, J=8.3 Hz, 1H); HRMS/EI: m/z calcd for $C_{15}H_{18}NO_2Br$: 323.05209 (M^+). Found 323.05197 (M^+).

4.2.7. 5-Benzylamino-4-chloro-*endo*-tricyclo[5.2.1.0^{2,6}]-deca-4,8-dien-3-one (7g). Compound **7g** was obtained in 97% yield (0.277 g) from **6a** (0.251 g, 1.00 mmol) and NCS (0.135 g, 1.01 mmol) in CH_2Cl_2 (10 ml) as a viscous liquid. Recrystallisation from ethyl acetate provided an analytically pure sample of **7g** as white needles. Mp: 210°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 5H), 6.09 (dd, J=5.7, 2.9 Hz, 1H), 5.82 (dd, J=5.7, 2.9 Hz, 1H), 5.46 (br s, 1H), 4.66 (m, 2H), 3.28 (m, 2H), 3.07 (br s, 1H), 2.99 (dd, J=6.1, 4.4 Hz, 1H), 1.77 (dt, J=8.7, 1.8 Hz, 1H), 1.56 (br d, J=8.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 169.6, 136.8, 135.0, 130.9, 129.1, 128.3, 126.9, 104.1, 51.5, 49.2, 48.0, 44.4, 43.7, 41.9; IR (KBr, cm^{-1}) ν 3153, 1657, 1603, 1521, 1452; HRMS/EI: m/z calcd for $C_{17}H_{16}NO^{35}Cl$: 285.09240 (M^+). Found: 285.0918 (M^+). Anal. calcd for $C_{17}H_{16}NOCl$: C, 71.45; H, 5.64; N, 4.90%. Found: C, 71.29; H, 5.56; N, 4.94%.

4.2.8. 4-Chloro-5-pyrrolidino-*endo*-tricyclo[5.2.1.0^{2,6}]-deca-4,8-dien-3-one (7h). Compound **7h** was obtained in 99% yield (0.494 g) from **6e** (0.430 g, 2.00 mmol) and NCS (0.271 g, 2.02 mmol) in CH_2Cl_2 (15 ml). Recrystallisation from ethyl acetate provided an analytically pure sample of **7h** as white needles. Mp: 134°C; ^{1}H NMR (400 MHz, $CDCl_3$, T=280 K) δ 6.08 (dd, J=5.7, 3.0 Hz, 1H), 5.87 (dd, J=5.7, 2.9 Hz, 1H), 4.02–3.62 (m, 4H), 3.26 (br s, 1H), 3.24 (dd, J=6.3, 4.0 Hz, 1H), 3.14 (br s, 1H), 2.95 (dd, J=6.0, 4.6 Hz, 1H), 1.94 (m, 4H), 1.74 (br d, J=8.6 Hz, 1H), 1.55 (br d, J=8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, T=280 K) δ 195.9, 166.7, 134.7, 130.6, 102.3, 50.9, 50.3, 49.3, 48.1, 44.8, 44.4, 44.3, 25.5, 24.5; IR (KBr, cm^{-1}): ν 3327, 1667, 1573, 1456; HRMS/EI: m/z calcd for $C_{14}H_{16}NO^{35}Cl$: 249.09204 (M^+). Found: 249.09213 (M^+); Anal. calcd for $C_{14}H_{16}NOCl$: C, 67.33; H, 6.46; N, 5.61%. Found: C, 67.28; H, 6.59; N, 5.61%.

4.2.9. 4-Bromo-(1*R*,2*S*,6*R*,7*S*,2′*R*)-5-(2′-methoxymethylpyrrolidin-1′-yl)-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (7i). Compound **7i** was obtained in 86% yield (0.248 g) from **6g** (0.193 g, 0.75 mmol) and NIS (0.203 g, 0.9 mmol of 95% purity) in CH_2Cl_2 (5 ml) as a viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06 (dd, J=5.6, 2.9 Hz, 1H), 5.80 (dd, J=5.6, 2.9 Hz, 1H), 5.35 (br s, 1H), 3.80 (br s, 2H), 3.44–3.34 (m, 6H with OMe), 3.25 (m, 1H), 3.12 (m, 1H), 2.96 (dd, J=6.5, 4.5 Hz, 1H), 2.04–1.89 (m, 4H), 1.70 (d, J=8.5 Hz, 1H), 1.52 (d, J=8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 134.9, 130.9, 73.9, 59.2, 56.7, 51.1, 50.8, 47.3, 45.0, 44.7, 27.0, 23.1; MS/EI: m/z 385 (M^+), 340, 312, 274, 192.

4.3. General procedure for the 4,*N*-dibromination of enaminones 6a–6d

NBS (2 equiv.) was added to a clear solution of **6a**–**6c** (1 equiv.) in CH_2Cl_2. After 5 min, the reaction mixture was extracted with 0.1 M NaOH solution (50 ml) to remove the succinimide. The organic phase was dried over $MgSO_4$ and then concentrated in vacuo to afford the 4,*N*-dibrominated enaminone **8a**–**8d**.

4.3.1. 5-Benzylamino-4,*N*-dibromo-*endo*-tricyclo[5.2.1.0^{2,6}]-deca-4,8-dien-3-one (8a). Compound **8a** was obtained in 97% yield (0.757 g) from **6a** (0.479 g, 1.91 mmol) and NBS (0.777 g, 4.37 mmol) in CH_2Cl_2 (20 ml) as a yellow solid. Recrystallisation from ethyl acetate provided an analytically pure sample of **8a** as yellow crystals. Mp: 124°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3 (m, 5H), 6.10 (dd, J=5.6, 2.8 Hz, 1H), 5.81 (dd, J=5.6, 2.9 Hz, 1H), 4.97 (dd, J=16.3, 16.3 Hz, 2H), 3.80 (dd, J=9.0, 4.4 Hz, 1H), 3.73 (dd, J=9.1, 3.8 Hz, 1H), 3.51 (br s, 1H), 3.45 (br s, 1H), 1.68 (d, J=8.9 Hz, 1H), 1.55 (d, J=8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 170.1, 138.6, 136.7, 134.5, 128.5, 127.1, 127.0, 63.8, 56.1, 50.6, 50.3, 46.4, 45.3, 43.9; IR (KBr, cm^{-1}) ν 3061, 1668, 1494, 1448, 1406; HRMS/EI: m/z calcd for $C_{17}H_{15}NO^{79}Br^{81}Br$: 408.9499 ($M^+$). Found: 408.9500 ($M^+$); Anal. calcd for $C_{17}H_{15}NOBr_2$: C, 49.91; H, 3.70; N, 3.42%. Found: C, 50.05, H, 3.75; N, 3.40%.

4.3.2. 5-Cyclohexylamino-4,*N*-dibromo-*endo*-tricyclo-[5.2.1.0^{2,6}]deca-4,8-dien-3-one (8b). Compound **8b** was obtained in 98% yield (0.824 g) from **6b** (0.500 g, 2.06 mmol) and NBS (0.801 g, 4.50 mmol) in CH_2Cl_2 (20 ml) as a yellow solid. Recrystallisation from ethyl acetate provided an analytically pure sample of **8b** as yellow

needles. Mp: 111°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (dd, J=5.7, 2.8 Hz, 1H), 5.95 (dd, J=5.7, 2.9 Hz, 1H), 3.71 (m, 3H), 3.44 (br s, 1H), 3.41 (br s, 1H), 1.88 (br t, 2H), 1.73–1.28 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 166.4, 137.1, 134.7, 63.7, 61.7, 50.6, 50.1, 47.2, 45.4, 43.3, 32.6, 32.4, 25.4, 24.5, 24.3; IR (KBr, cm^{-1}): ν 3489, 1668, 1446; HRMS/EI: m/z calcd for $C_{16}H_{19}NO^{79}Br^{81}Br$: 400.9813 ($M^+$). Found: 400.9814 ($M^+$); Anal. calcd for $C_{16}H_{19}NOBr_2$: C, 47.91; H, 4.77; N, 3.49%. Found: C, 48.06; H, 4.73; N, 3.53%.

4.3.3. 4,*N*-Dibromo-5-*n*-pentylamino-*endo*-tricyclo-[5.2.1.0^{2,6}]deca-4,8-dien-3-one (8c). Compound **8c** was obtained in 97% yield (0.385 g) from **6c** (0.234 g, 1.01 mmol) and NBS (0.370 g, 2.08 mmol) in CH_2Cl_2 (10 ml) as a viscous yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, T=305 K) δ 6.13 (dd, J=5.7, 2.8 Hz, 1H), 5.95 (dd, J=5.7, 2.9 Hz, 1H), 3.80–3.60 (m, 4H), 3.49 (br s, 1H), 3.44 (br s, 1H), 1.77 (m, 2H), 1.68 (d, J=8.9 Hz, 1H), 1.55 (d, J=8.9 Hz, 1H), 1.40 (m, 4H), 0.94 (t, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, T=305 K): δ 199.9, 168.3, 136.7, 134.5, 63.9, 53.4, 50.5, 50.1, 46.3, 45.3, 43.7, 29.9, 29.7, 22.5, 14.0; HRMS/EI: m/z calcd for $C_{15}H_{19}NO^{79}Br_2$: 386.9833 (M^+). Found: 386.9833 (M^+).

4.3.4. 4,*N*-Dibromo-5-(1*R*,2*S*,6*R*,7*S*,1′*R*)(1′-phenylethyl-amino)-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (8d). Compound **8d** was obtained in 98% yield (0.818 g) from **6d** (0.530 g, 2.0 mmol) and NBS (0.712 g, 4.0 mmol) in CH_2Cl_2 (10 ml) as a viscous yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.22 (m, 5H), 5.93 (dd, J=5.6, 2.8 Hz, 1H), 5.23 (dd, J=5.6, 2.8 Hz, 1H), 5.04 (q, J=6.3 Hz, 1H), 3.76 (d, J=2.2 Hz, 2H), 3.37 (br s, 1H), 3.31 (br s, 1H), 1.57–1.48 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 167.1, 144.7, 136.0, 134.8, 128.4, 126.8, 125.8, 64.2, 60.8, 50.3, 50.2, 47.1, 45.3, 43.3, 25.0.

4.3.5. 5-Benzylamino-4,6-dichloro-*endo*-tricyclo[5.2.1.0^{2,6}]-deca-4,8-dien-3-one (10a). NCS (0.124 g, 0.93 mmol) was added to a clear solution of **6a** (0.100 g, 0.40 mmol) in CH_2Cl_2 (10 ml). After 1 min, a white precipitate started to form. After one day the reaction mixture was extracted with 0.1 M NaOH (15 ml) solution. The organic phase was concentrated in vacuo and **10a** (0.102 g, 80%) was obtained by column chromatography (hexane–ethyl acetate=1:1). Recrystallisation from ethyl acetate provided an analytically pure sample of **10a** as white needles. Mp: 180°C; ^{1}H NMR (400 MHz, $CDCl_3$, T=315 K, ppm) δ 7.3 (m, 5H), 6.11 (dd, J=5.6, 2.9 Hz, 1H), 5.90 (dd, J=5.6, 3.1 Hz, 1H), 5.35 (br s, 1H), 4.96 (dd, J=14.7, 6.4 Hz, 1H), 4.78 (dd, J=14.7, 5.8 Hz, 1H), 3.33 (br s, 1H), 3.23 (d, J=4.3 Hz, 1H), 3.20 (br s, 1H), 2.26 (d, J=9.1 Hz, 1H), 2.00 (d, J=9.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 164.8, 137.3, 136.7, 132.3, 129.1, 128.4, 127.5, 105.1, 61.4, 53.6, 50.6, 48.2, 44.4; IR (KBr, cm^{-1}) ν 3260, 1674, 1573, 1550, 1494, 1440; HRMS/EI: m/z calcd for $C_{17}H_{15}NO^{35}Cl_2$: 319.05307 (M^+). Found: 319.05311 (M^+); Anal. calcd for $C_{17}H_{15}NOCl_2$: C, 63.77; H, 4.72; N, 4.37%. Found: C, 63.79; H, 4.76; N, 4.39%.

4.3.6. 5-Cyclohexylamino-4,6-dichloro-*endo*-tricyclo-[5.2.1.0^{2,6}]deca-4,8-dien-3-one (10b). NCS (0.294 g, 2.20 mmol) was added to a clear solution of **6b** (0.243 g, 1.00 mmol) in dichloromethane (20 ml). After one day, the reaction mixture was extracted with a 25 ml 0.1 M NaOH solution. The organic phase was concentrated in vacuo and **10b** (0.282 g, 90%) was obtained by column chromatography (hexane–ethyl acetate=1:1). Recrystallisation from ethyl acetate provided an analytically pure sample of **10b** as white needles. Mp: 177°C; ^{1}H NMR (400 MHz, $CDCl_3$, T=281 K, ppm) δ 6.13 (dd, J=5.4, 2.9 Hz, 1H), 5.97 (dd, J=5.4, 3.0 Hz, 1H), 5.15 (br d, J=10.9 Hz, 0.7H), 5.03 (br d, ^3J=8.3 Hz, 0.3H), 4.15 (m, 0.3H), 3.94 (m, 0.7H), 3.33 (br s, 1H), 3.23 (d, J=4.0 Hz, 1H), 3.15 (br s, 0.7H), 3.11 (br s, 0.3H), 2.28 (d, J=9.1 Hz, 1H), 2.2–1.1 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$, T=281 K, ppm) δ 189.5, 164.4, 137.4, 132.3, 103.4, 71.4, 61.3, 53.3, 50.3, 43.8, 34.4, 24.8; IR (KBr, cm^{-1}) ν 3242, 1674, 1569, 1447; HRMS/EI: m/z calcd for $C_{16}H_{19}NO^{35}Cl_2$: 311.0844 (M^+). Found: 311.0844 (M^+). Anal. calcd for $C_{16}H_{19}NOCl_2$: C, 61.55; H, 6.13; N, 4.49%. Found: C, 61.76; H, 6.17; N, 4.50%.

4.3.7. 4,6-Dibromo-5-pyrrolidino-*endo*-tricyclo[5.2.1.0^{2,6}]-deca-4,8-dien-3-one (11a). NBS (0.173 g, 0.97 mmol) was added to a clear solution of **6e** (0.101 g, 0.47 mmol) in CH_2Cl_2 (10 ml). After 10 min, the reaction mixture was extracted with a 15 ml 0.1 M NaOH solution. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. This yielded **11a** as a white solid (0.175 g, 99%). Recrystallisation from ethyl acetate provided an analytically pure sample of **11a** as white needles. Mp: 161°C (D); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (dd, J=5.6, 2.9 Hz, 1H), 5.98 (dd, J=5.5, 3.0 Hz, 1H), 4.25 (br s, 2H), 3.98 (br s, 2H), 3.45 (d, J=4.1 Hz, 1H), 3.37 (br s, 1H), 3.33 (br s, 1H), 2.26 (br d, J=9.1 Hz, 1H), 1.98 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, T=305 K, ppm) δ 192.0, 165.0, 137.0, 131.6, 94.0, 67.2, 61.3, 54.6, 50.8, 50.1, 45.4, 25.0; IR (KBr, cm^{-1}) ν 1669, 1552, 1477, 1456; HRMS/EI: m/z calcd for $C_{14}H_{15}NO^{79}Br^{81}Br$: 372.9500 ($M^+$). Found: 372.9494 ($M^+$); Anal. calcd for $C_{14}H_{15}NOBr_2$: C, 45.07; H, 4.05; N, 3.75%. Found: C, 45.40; H, 4.03; N, 3.80%.

4.3.8. 4,6-Dichloro-5-pyrrolidino-*endo*-tricyclo[5.2.1.0^{2,6}]-deca-4,8-dien-3-one (11b). NCS (0.133 g, 0.99 mmol) was added to a clear solution of **6e** (0.100 g, 0.46 mmol) in methanol (10 ml). After one day, the reaction mixture was concentrated in vacuo and dissolved in dichloromethane (10 ml). This mixture was extracted with a 20 ml 0.1 M NaOH solution. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. Purification with column chromatography (hexane–ethyl acetate=1:1) yielded **11b** as a white solid (0.108 g, 82%). Recrystallisation from ethyl acetate provided an analytically pure sample of **11b** as white needles. Mp: 143°C; ^{1}H NMR (400 MHz, $CDCl_3$, T=310 K) δ 6.13 (dd, J=5.6, 2.9 Hz, 1H), 5.98 (dd, J=5.6, 3.0 Hz, 1H), 4.16–3.76 (m, 4H), 3.32 (br s, 1H), 3.26 (br s, 1H), 3.23 (d, J=4.2 Hz, 1H), 2.21 (br d, J=9.1 Hz, 1H), 1.96 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, T=310 K) δ 191.6, 163.0, 137.4, 131.9, 105.2, 74.6, 60.9, 53.9, 50.3, 50.0, 49.8, 45.0, 25.0; IR (KBr, cm^{-1}) ν 1680, 1563, 1456; HRMS/EI: m/z calcd for $C_{14}H_{15}NO(^{35}Cl)_2$: 283.05307 ($M^+$). Found: 283.05318 ($M^+$); Anal. calcd for $C_{14}H_{15}NOCl_2$: C, 59.17; H, 5.32; N, 4.93%. Found: C, 59.45; H, 5.22; N, 5.01%.

4.3.9. 4-Bromo-6-chloro-5-pyrrolidino-*endo*-tricyclo-[5.2.1.0^{2,6}]deca-4,8-dien-3-one (12a). NCS (0.068 g, 0.50 mmol) was added to a clear solution of **7e** (0.100 g, 0.34 mmol) in CH_2Cl_2 (10 ml). After 15 min, the yellow reaction mixture was washed with 0.1 M NaOH solution (15 ml). The organic phase was dried over $MgSO_4$ and concentrated in vacuo. This yielded **12a** as a yellow solid (0.111 g, 99%). Recrystallisation from ethyl acetate provided an analytically pure sample of **12a** as yellow needles. Mp: 145°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (dd, J=5.4, 2.9 Hz, 1H), 5.98 (m, 1H), 4.22 (br s, 2H), 3.74 (br s, 2H), 3.42 (d, J=4.1 Hz, 1H), 3.36 (br s, 1H), 3.32 (br s, 1H), 2.27 (d, J=9.1 Hz, 1H), 1.97 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 164.0, 137.0, 131.6, 96.1, 66.1, 61.3, 54.5, 50.3, 50.2, 45.4, 25.0; IR (KBr, cm^{-1}) ν 1678, 1560, 1458; HRMS/EI: m/z calcd for $C_{14}H_{15}NO^{35}Cl^{79}Br$: 327.0026 ($M^+$). Found: 327.0026 ($M^+$); Anal. calcd for $C_{14}H_{15}NOClBr$: C, 51.17; H, 4.60; N, 4.26%. Found: C, 51.27; H, 4.63; N, 4.31%.

4.3.10. 6-Bromo-4-chloro-5-pyrrolidino-*endo*-tricyclo-[5.2.1.0^{2,6}]deca-4,8-dien-3-one (12b). NBS (0.200 g, 1.12 mmol) was added to a clear solution of **7h** (0.254 g, 1.02 mmol) in CH_2Cl_2 (10 ml). After approximately 15 min when the reaction was complete (TLC), solvent was evaporated and purification by column chromatography (hexane–ethyl acetate=1:1) yielded **12b** as a yellow solid (0.327 g, 98%). Recrystallisation from ethyl acetate provided an analytically pure sample of **12b** as yellow needles. Mp: 148°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (dd, J=5.6, 2.9 Hz, 1H), 5.98 (dd, J=5.4, 3.0 Hz, 1H), 4.21 (br s, 2H) 3.74 (br s, 2H), 3.42 (d, J=4.1 Hz, 1H), 3.36 (br s, 1H), 3.32 (br s, 1H), 2.27 (d, J=9.1 Hz, 1H), 1.97 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 164.1, 136.9, 131.6, 105.2, 66.1, 61.3, 54.5, 50.3, 50.2, 45.4, 25.0; IR (KBr, cm^{-1}) ν 1678, 1558, 1479, 1456; HRMS/EI: m/z calcd for $C_{14}H_{15}NO^{35}Cl^{79}Br$: 327.0026 ($M^+$). Found: 327.0025 ($M^+$); Anal. calcd for $C_{14}H_{15}NOClBr$: C, 51.17; H, 4.60; N, 4.26%. Found: C, 51.17; H, 4.47; N, 4.19%.

References

1. Iguchi, K.; Kaneta, S.; Mori, K.; Yamada, Y.; Honda, A.; Mori, Y. *Tetrahedron Lett.* **1985**, 5787. Nagaoka, H.; Iguchi, K.; Miyakoshi, T.; Yamada, N.; Yamada, Y. *Tetrahedron Lett.* **1986**, 223. Iguchi, K.; Kaneta, S.; Mori, K.; Yamada, Y.; Honda, A.; Mori, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 981.
2. Baker, B. J.; Okuda, R. K.; Yu, P. T. K.; Scheuer, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 2976. Nagaoka, M. Y.; Miyakoshi, Y.; Yamada, Y. *J. Am. Chem. Soc.* **1986**, 5019.
3. Fukushima, M.; Kato, T.; Yamada, Y.; Kitagawa, I.; Kurozumi, S.; Scheuer, P. J. *Proc. Am. Assoc. Cancer Res.* **1985**, *26*, 249.
4. Honda, A.; Mori, Y.; Iguchi, K.; Yamada, Y. *Mol. Pharmacol.* **1987**, *32*, 530. Fukushima, M.; Kato, T. *Adv. Prostaglandin Thromboxane Leukot. Res.* **1985**, *15*, 415. Honda, A.; Mori, Y.; Iguchi, K.; Yamada, Y. *Prostaglandins* **1988**, *36*, 621.
5. Ramesh, N. G.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron Lett.* **1998**, *39*, 1429.
6. Zhu, J.; Yang, J.-Y.; Klunder, A. J. H.; Liu, Z.-Y.; Zwanenburg, B. *Tetrahedron* **1995**, *51*, 5847.
7. Bakkeren, F. J. A. D.; Ramesh, N. G.; de Groot, D.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron Lett.* **1996**, *52*, 8003.
8. Zhu, J.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron Lett.* **1994**, *35*, 2787. Zhu, J.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1994**, *50*, 10597.
9. Ramesh, N. G.; Klunder, A. J. H.; Zwanenburg, B. *J. Org. Chem.* **1999**, *64*, 3635.
10. Ramesh, N. G.; Heijne, E. H.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron Lett.* **1998**, *39*, 3295.
11. Jirkovsky, I. *Can. J. Chem.* **1974**, *52*, 55.
12. Habermehl, G. G.; Wippermann, I.; Krebs, H. C.; Dieck, S. T. *Z. Naturforsch.* **1991**, 1415. Bovonsombat, P.; Angara, G. J.; McNelis, E. *Tetrahedron Lett.* **1994**, *35*, 6787. Johnson, C.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 917.
13. Matsuo, K.; Ishida, S.; Takuno, Y. *Chem. Pharm. Bull.* **1994**, *42* (5), 1149.
14. Kordik, C.; Reitz, A. B. *J. Org. Chem.* **1996**, *61*, 5644.
15. Benhida, R.; Blanchard, P.; Fourrey, J-L. *Tetrahedron Lett.* **1998**, *39*, 6849.
16. Dalton, D. R.; Rodebaugh, R. K.; Jefford, C. W. *J. Org. Chem.* **1972**, *37*, 362. Dols, P. P. M. A.; Verstappen, M. M. H.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1993**, *49*, 11353.
17. Dalton, D. R.; Hendrickson, J. B.; Jones, D. *J. Chem. Soc., Chem. Commun.* **1966**, 591.
18. de Gelder, R.; Smits, J. M. M.; Ramesh, N. G.; Heijne, E. H.; Klunder, A. J. H. X-ray crystallographic data will be published elsewhere. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Centre as supplementary publication numbers CCDC 167161. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033 or email: deposit@ccdc.cam.ac.uk).