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A short synthesis of (−)-dendrobine. Some observations on the nickel mediated radical cyclisation and on the Pauson–Khand reaction

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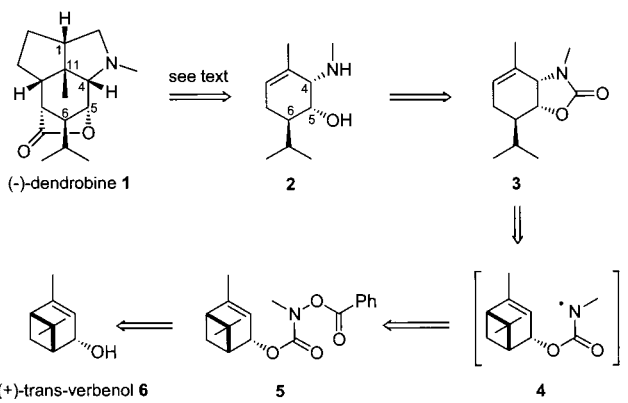
Abstract

The total synthesis of (−)-dendrobine was accomplished in 13 steps starting from (+)-verbenol. The key step is a radical cascade starting with a carbamyl radical generated by reaction of the *N*-benzoyloxy–carbamyl derivative of *trans*-verbenol with tributylstannane. This allows the one step establishment of three contiguous stereogenic centres, including the difficult *cis*-vicinal amino alcohol motif, and ultimately the control of the configuration of the remaining four asymmetric carbons. The synthesis also features the use of the Pauson–Khand reaction where an interesting solvent effect was observed. Thus, the use of a coordinating solvent such as acetonitrile was found necessary to suppress the formation of a ring-opened by-product resulting from scission of a C–N bond. In an ancillary model study, we observed an unusual but interesting 1,4-hydrogen atom abstraction which, however, thwarted our initial synthetic plan. © 2001 Published by Elsevier Science B.V.

Keywords: (−)-Dendrobine; Total synthesis; Radical cyclisation; Nitrogen centred radical; Nickel metal; Pauson–Khand reaction

1. Introduction

(−)-Dendrobine (**1**), the major alkaloid constituent isolated from the Chinese ornamental orchid *Dendrobium Nobile* [1], exhibits interesting antipyretic and hypotensive activity [2]. Since the elucidation of its structure in 1964 [3], dendrobine has been the subject of extensive synthetic investigations, stimulated by its physiological properties similar to those of picrotoxinine, but above all, by its unique and challenging molecular structure, including a compact tetracyclic skeleton bearing seven stereocentres, among which a quaternary centre at C(11). First, total syntheses of **1** thus appeared in the 1970s [4], but efficient and stereoselective routes to this molecule were only reported during the last decade [5], culminating in two formal [5b,d] and one total [5e] enantioselective syntheses.



Scheme 1.

We have been interested for a long time in developing new radical processes for organic synthesis. We hoped that some of the methodologies recently discovered in our laboratory could be exemplified and validated through an enantioselective and particularly short synthesis of (−)-dendrobine. Herein we describe the full details of this synthesis, a preliminary account of which has been published previously [6].

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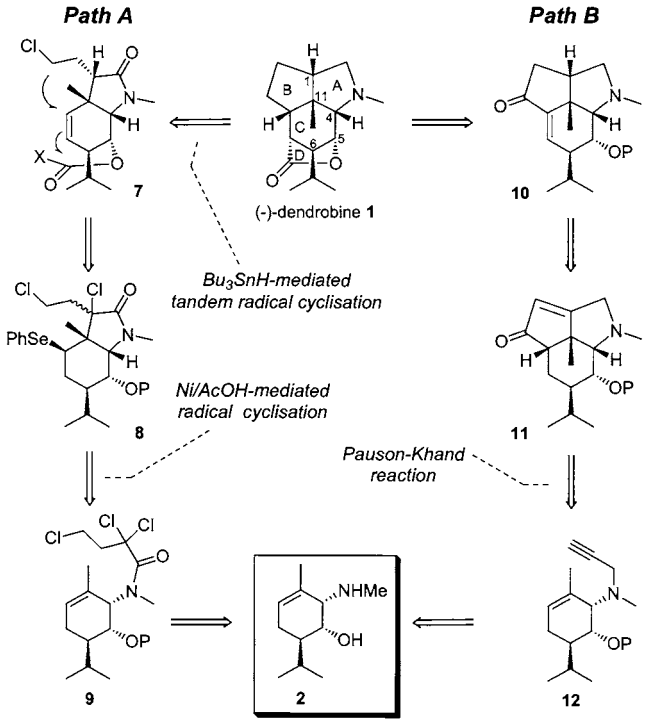
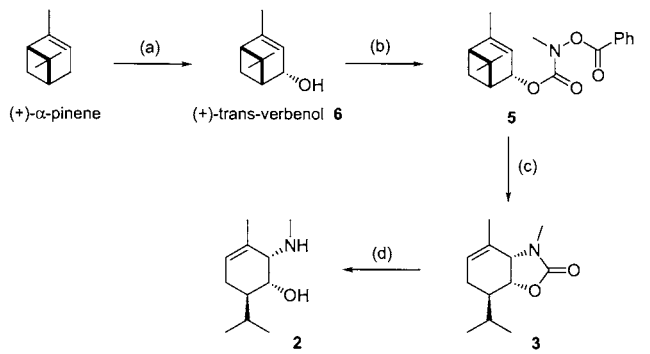


Scheme 2.



Scheme 3. (a) (i) $Pb(OAc)_4$, toluene, 70°C; (ii) AcOH, 20°C; (iii) aq. KOH 20%, MeOH (49%); (b) (i) Im_2CO, THF 20°C; (ii) MeNHOH·HCl, Et_3N, THF 20°C; (iii) BzCl, Et_3N, THF, 0°C (49%, (i)–(iii)); (c) Bu_3SnH, ACCN, toluene, 110°C (71%); (d) KOH/H_2O/EtOH, 20°C (68% from **5**).

2. Synthetic strategy

Our synthetic strategy to (−)-dendrobine (**1**) was based on the early introduction of the three main stereogenic centres at C(4), C(5), and C(6), thus simplifying stereochemical problems for the continuation of the synthesis. Recognising within dendrobine a *cis* vicinal relationship between the amino function and the masked hydroxy group of the lactone, we considered that an amino alcohol such as **2** would constitute an attractive intermediate. Indeed, the allylic methylamino group at C(4) could then serve as a template for the stereoselective construction of the azatricyclo[6.2.1.0]undecane ring system, whereas the hydroxy group at C(5) would control the stereochemistry of the bridged lactone (Scheme 1). Moreover, we presumed that the key intermediate **2** would be readily obtained from (+)-*trans*-verbenol (**6**), after a radical cascade involving cyclisation–fragmentation of a carbamyl radical **4**, to give the oxazolidinone **3** with the desired stereochemistry.

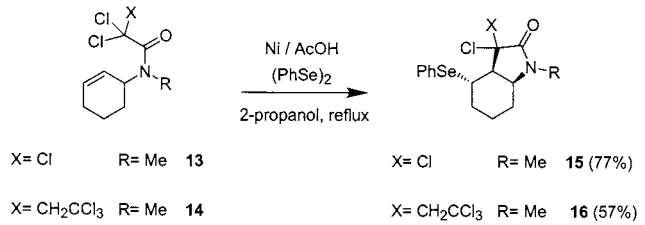
Two different strategies were then devised to convert **2** into dendrobine **1**, both of which are depicted in Scheme 2. In an attempt to take advantage of some of our radical reactions, we envisaged the possibility of assembling the three rings A, B and C of dendrobine by two successive radical sequences (path A). We thus envisaged that **1** might result from Bu_3SnH-mediated tandem radical cyclisation of **7** using an acyl acceptor [7] as the final internal radical trap. On the other hand, lactam **8**, a reasonable precursor of **7**, would result from 5-*exo*-trig radical cyclisation of the dichloroacetamide **9** induced by the Ni–AcOH combination, a new system recently developed in our laboratory. As an alternative strategy, and because of the failure of the initial approach, we also went into studying intramolecular Pauson–Khand cycloaddition of **12** into **11** for the direct and stereoselective construction of the tricyclic core of dendrobine (path B).

3. Results and discussion

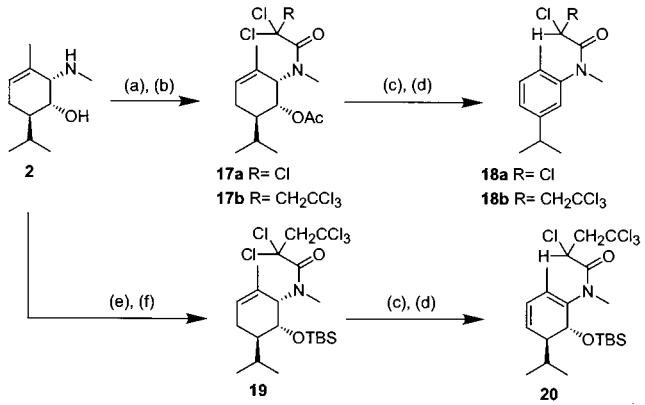
3.1. Synthesis of the key intermediate 2

The first key step of this synthesis was based on the assumption that a carbamyl radical such as **4**, would undergo 5-*exo*-trig cyclisation followed by fragmentation to give the oxazolidinone **3** in a stereoselective manner. We have recently developed new and reliable methods for the generation and cyclisation of various nitrogen-centred radicals [8]; we therefore selected the *O*-benzoyl-*N*-hydroxyurethane **5** as a suitable precursor for this crucial cyclisation, since attack of a tributylstannyl radical on the carbonyl oxygen of the benzoate would induce cleavage of the weak N–O bond, and formation of the desired radical **4**.

Thus our synthesis started from (+)-*trans*-verbenol (**6**), prepared by allylic oxidation of (+)-α-pinene, according to a literature procedure [9]. Upon successive treatment with 1,1′-carbonyldiimidazole, *N*-methylhydroxylamine and finally benzoyl chloride, **6** was converted into **5** in 49% overall yield without isolation of the intermediates (Scheme 3). To our delight, slow addition of tributyltin hydride and 1,1′-azobis(cyclohexanecarbonitrile) (ACCN) to a refluxing solution of **5** in toluene produced the desired oxazolidinone **3** in 71% yield. The amino-alcohol **2** was then obtained by hydrolysis of **3** with aqueous ethanolic potassium hydrox-



Scheme 4.



Scheme 5. (a) $RCCl_2COCl$, MeOH, Et_3N, ether, 0°C; (b) Ac_2O, Et_3N, DMAP, ether, r.t.; (c) Ni powder, AcOH, $(PhSe)_2$, 2-propanol, 80°C; (d) H_2O_2, THF, 0°C to r.t.; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C; (f) $Cl_3CCH_2CCl_2COCl$, Et_3N, ether, 0°C.

ide. It is noteworthy that this two-step process was best carried out without the isolation of **3**, allowing a simple purification of **2** and a particularly convenient separation of the tin residues by an acid–base extraction (68% yield from **5**, see Section 5).

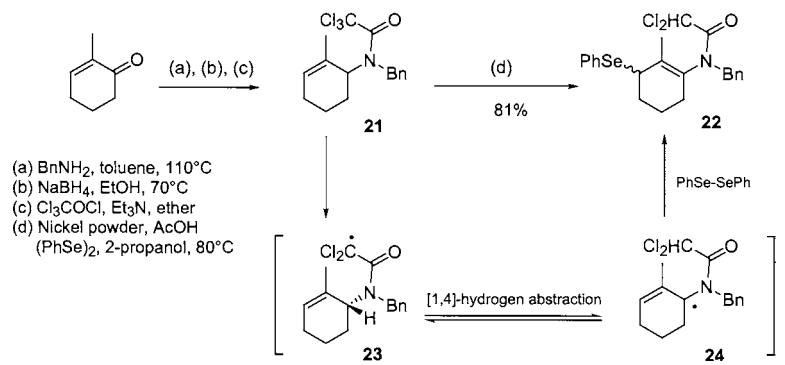
This efficient and straightforward sequence not only allowed the preparation of multigram quantities of intermediate **2**, but also represents one of the first examples of a successful cyclisation of a carbamyl radical, laying the basis of a new method for the synthesis of cyclic *cis*-vicinal amino alcohols [10].

3.2. First approach: studies on the Ni–AcOH-mediated radical cyclisations

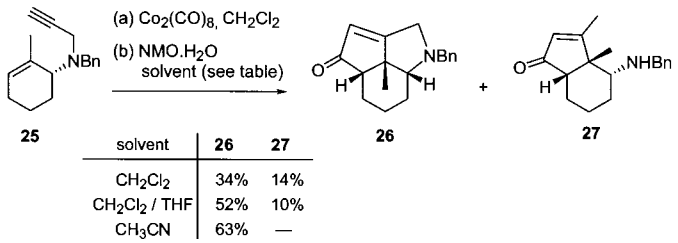
Having the new intermediate **2** in hand, we then investigated the formation of the crucial C(1)–C(11) central bond. We recently reported a new method for the synthesis of functionalised γ-lactams via 5-*exo* or 5-*endo* cyclisations of carbamoylmethyl radicals, generated by one-electron reduction of α-haloacetamides using nickel powder as the promoter [11]. Following several successful applications in alkaloid synthesis [12], we believed that this methodology would also be useful for the preparation of advanced intermediate **8** (see Scheme 2). The typical examples presented in Scheme 4 demonstrated the feasibility of this approach, and its compatibility with a halogenated lateral side-chain. It should be noted that this system allows the final introduction of a valuable functionality, in this case a phenylseleno group, which can serve to regenerate a double bond [13].

We next prepared the required tri- and dichloroacetamides **17a** and **17b** from **2**, after protecting the hydroxy group as an acetate (Scheme 5). Upon treatment with nickel and acetic acid in refluxing 2-propanol in the presence of diphenyl diselenide, both **17a** and **17b** were converted into a complex mixture of diastereoisomers, the mass spectrum of which was apparently consistent with the expected bicyclic lactam (Scheme 2). However, when subjected to selenide oxidative elimination, these intermediates afforded the aromatized compounds **18a–b**. The same sequence was repeated starting from the silyl ether **19**, giving similarly the dienamide **20** in 55% yield. Despite careful examination of the NMR spectrum, we were unable, at this stage, to identify the intermediate product, and therefore decided to carry out additional experiments on a simpler model.

We thus selected the trichloroacetamide **21** as a suitable model substrate, since we rapidly suspected the nefarious role of the methyl substituent on the double bond in the failure of the radical cyclisation. In fact, in sharp contrast to substrate **13**, which gave the bicyclic lactam **15** in 77% yield (see Scheme 4), reaction of **21**



Scheme 6.



solvent	26	27
CH_2Cl_2	34%	14%
CH_2Cl_2 / THF	52%	10%
CH_3CN	63%	—

Scheme 7.

under identical conditions afforded the enamide **22** as the sole product in 81% yield (Scheme 6). This was therefore fully consistent with the results presented on Scheme 5, since oxidative elimination of the selenide within **22** would effectively afford a dienamide similar to **20**, whereas **18a–b** were formed after final elimination of acetic acid. A reasonable mechanism for this unexpected but nevertheless interesting transformation is shown in Scheme 6: we assume that a rare [1,4]-hydrogen abstraction [14] from the initially formed radical **23** gives the stabilised allylic radical **24** which finally reacts with diphenyldiselenide at the less hindered position to give **22**. We believe that this hydrogen transfer is not specially favoured, but is faster in this case than any of the other competing pathways: 5-*exo* cyclisation at a hindered sp^2 carbon or over-reduction of radical **23** are apparently slower processes under these conditions. This also demonstrates the specificity of this system, allowing the generation of relatively long-lived radicals, which can undergo kinetically disfavoured radical transformations.

At this point of our studies, it became evident that the creation of the crucial C(11) quaternary centre of dendrobine was not feasible using the Ni-induced radical cyclisation. However, still desirous of taking advantage of intermediate **2**, we decided to devise an alternative synthetic approach.

3.3. Second approach: total synthesis of (−)-dendrobine

As mentioned in the retrosynthetic analysis presented in Scheme 2, our second approach to dendrobine rested on the idea that the allylic methylamino function within **2** could serve as a directing group for the stereoselective construction of the AB ring system of dendrobine via an intmmolecular Pauson–Khand reaction (**12**→**11**) [15]. Although this reaction has been known since 1973 [16], it has found effective applications in organic synthesis only for the past decade, with the emergence of reliable procedures for carrying out the transformation under very mild conditions, and more recently with the development of catalytic and asymmetric versions [17]. The application of the intmmolecular Pauson–Khand reaction (PKR) to the synthesis of nitrogen-containing bicycles or polycycles has also been well studied but surprisingly very little is known about the influence of an *unprotected* basic nitrogen atom as would be the case for **12** [18]. We therefore started our investigations with the simple but realistic model substrate **25** (Scheme 7).

Treatment of the alkyne cobalt complex derived from **25** with an excess of *N*-methylmorpholine oxide [19] in dichloromethane at room temperature afforded the desired tricyclic cyclopentenone **26**, but in low yield and along with an unexpected ring-opened product **27** (ratio 2.5:1). We then found that the formation of this side-product could be reduced by using THF as a co-solvent, and finally completely suppressed when the reaction was carried out in acetonitrile. Even if the mechanism for the formation of **27** is not clear, we reasoned that the basic β-nitrogen atom could coordinate a cobalt atom and induce a β-elimination within one of the intermediate complex to give **27** after protonation [20]. More coordinating solvents, such as acetonitrile, would not only accelerate the different steps of the Pauson–Khand process [21], but also limit this side reaction by acting as competitive ligands.

Having demonstrated the viability of this strategy, we next turned to its application to the synthesis of the tricyclic core of dendrobine, as depicted on Scheme 8. Thus, the *N*-propargylated derivative **28**, readily obtained from **2** by treatment with propargyl bromide and subsequent acetylation of the hydroxy group [22], was subjected to the Pauson–Khand and cyclisation in acetonitrile, affording the desired cyclopentenone **29** in 68% yield as a single diastereoisomer (acetonitrile was also essential here to avoid formation of undesirable ring-opened products). This strained and somewhat unstable enone was directly converted into the tricyclic ketone **30** by catalytic hydrogenation.

The construction of the final bridged γ-lactone then required functionalisation at C(7). This was achieved by regioselective α-dehydrogenation of **30**, using iodotrimethylsilane [23] for the exclusive formation of the more substituted enol silyl ether. The α,β-unsaturated ketone **31** was then obtained by sequential treatment with phenylselenenyl bromide and MCPBA. In order to install the last carbon atom of the final target, we then considered the conjugated addition of a carboxylate anion equivalent onto the enone **31**. After several failed attempts using various nucleophiles and experimental conditions, we found that treatment of **31** with diethylaluminium cyanide [24] in toluene at 70°C resulted in the formation of the keto-nitrile **32** in 77% yield as a single diastereoisomer. We presume that the stereochemical outcome of this addition ensued from a specific chelation of the aluminium reagent from the less hindered *exo* face of the molecule and subsequent internal delivery of nitrile from the same face. Stereoselective reduction of **32** followed by Barton–McCombie deoxygenation of the resulting secondary alcohol af-

forded the nitrile **33**. Surprisingly, the required isomerisation of the axial cyano group at C(7) proved particularly difficult, and was eventually accomplished, but only partially, by prolonged treatment of **33** with sodium methoxide in methanol at 100°C (sealed tube, 24 h), which caused concomitant hydrolysis of the acetate group at C(5). The resulting 1:1 mixture of epimers **34a** and **34b** was directly subjected to acid-catalysed hydrolysis to give (−)-dendrobine in 44% yield from **33**, along with unreacted **34b**, which surprisingly was not hydrolysed under these conditions. This unexpected chemoselectivity may be explained by considering the initial acid-catalysed cyclisation of **34a** to the imino-lactone **35** to be hydrolysed faster than the more robust nitrile **34b**. This hypothesis was ultimately confirmed by subjecting **34a**–**b** to anhydrous acid (PTSA, toluene, 110°C), providing the imino-lactone **35** in 50% yield along with unreacted nitrile **34b**.

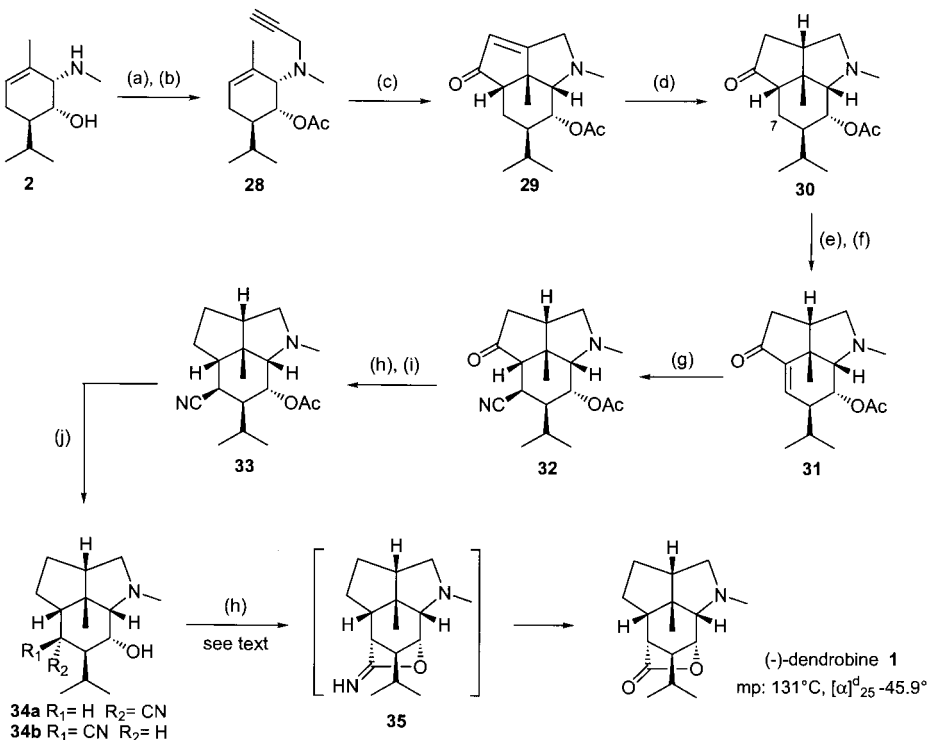
4. Conclusion

In summary, we have exploited, in this relatively short and efficient synthesis of (−)-dendrobine, some new methodologies, especially radical reactions, and have demonstrated their utility for the synthesis of complex organic molecules. In particular, the cascade radical sequence involving the cyclisation of the carbamyl radical **4** allowed the straightforward synthesis of the useful intermediate **2**, thus illustrating the potential of these unusual radicals. Other important features of this work include the unexpected [1,4]-hydrogen abstraction observed during the course of our studies on nickel-promoted radical cyclisations, and the Pauson–Khand cycloaddition of **28**, which was found to be strongly dependent on the solvent used.

5. Experimental

*5.1. (+)-(1R,2R,5S)-N-Benzoyloxy-N-methyl-carbamic acid-4,6,6-trimethyl-bicyclo[3.1.1]hept-3-en-2-yl-ester (**5**)*

To a solution of (+)-*trans*-verbenol **6** (24.3 g, 0.16 mol) in dry THF (160 ml) was added 1,1′-carbonyldiimidazole (32.4 g, 0.2 mol). The reaction mixture was stirred at room temperature (r.t.) for 2 h. Et_3N (27 ml, 0.19 mol) and *N*-methylhydroxylamine hydrochloride (16 g, 0.19 mol) were successively added and the mixture stirred at r.t. for 12 h. After cooling to 0°C, the



Scheme 8. (a) Propargyl bromide, K_2CO_3, CH_3CN; (b) Ac_2O, pyridine, CH_2Cl_2 (88% from **3**); (c) (i) $Co_2(CO)_8$, CH_2Cl_2; (ii) NMO·H_2O, CH_3CN, 25°C; (d) H_2, Pd/C, MeOH (51% from **28**); (e) (i) TMSI, HMDS, pentane, −20°C; (ii) PhSeBr, THF, −78°C (72%); (f) MCPBA, THF, −40 to 25°C (60%); (g) Et_2AlCN, toluene, 70°C (77%); (h) (i) $NaBH_4$, EtOH, 25°C; (ii) PhOC(S)Cl, 4-DMAP, CH_2Cl_2, 25°C (60%); (i) Bu_3SnH, ACCN, toluene, 110°C (80%); (j) MeONa, MeOH, sealed tube, 100°C; (h) PTSA, dioxane/water, sealed tube, 100°C (44%, 2 steps, 75% based on recovered **34a**).

mixture was treated with Et_3N (27 ml, 0.19 mol) and benzoyl chloride (27.9 ml, 0.19 mol), and stirred at r.t. for 2 h. It was then filtered, dried over magnesium sulphate, and the solvent removed under reduce pressure. The residue was purified by column chromatography (silica gel, heptane–AcOEt, 95:5) to give **5** (24.5 g, 49%) as a colourless oil. $[\alpha]_D^{25}$ +96.0° (*c* 0.43, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.30 (m, 1H), 1.32 (s, 3H), 1.71 (s, 3H), 2.00 (t, $J = 5.5$ Hz, 1H), 2.21 (dt, $J = 8.8$, 5.5 Hz, 1H), 2.28 (m, 1H), 3.37 (s, 3H), 5.32–5.39 (m, 2H), 7.47 (m, 2H), 7.62 (m, 1H), 8.05 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 20.7, 22.8, 26.5, 29.4, 38.1, 44.5, 46.6, 47.6, 76.6, 115.1, 127.5, 128.7, 130.0, 134.0, 150.9, 156.4, 164.7. IR (neat) 1767, 1720 cm^{-1}. Anal. Calc. for $C_{19}H_{23}NO_4$: C, 69.27; H, 6.81. Found: C, 69.36; H, 7.04%.

5.2. (+)-(3aS,7R,7aR)-7-Isopropyl-3,4-dimethyl-3a,6,7,7a-tetrahydro-3H-benzooxazol-2-one (3)

To a solution of **5** (520 mg, 1.58 mmol) in refluxing toluene (8 ml) was added a solution of Bu_3SnH (0.53 ml, 1.98 mmol) and 1,1′-azobis(cyclohexanecarbonitrile) (77 mg, 0.32 mmol) in toluene (8 ml) over 6 h. After the addition, the reaction mixture was refluxed for 3 h, then cooled to r.t., and concentrated. The residue was purified by column chromatography (silica gel, heptane–AcOEt, 95:5) to afford **3** (234 mg, 71%) as colourless needles (m.p. 52–53°C, pentane). $[\alpha]_D^{25}$ +54.9° (*c* 0.57, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.87 (d, $J = 6.9$ Hz, 3H), 0.95 (d, $J = 6.9$ Hz, 3H), 1.62–2.15 (m, 4H), 1.87 (s, 3H), 2.97 (s, 3H), 3.87 (d, $J = 7.6$ Hz, 1H), 4.48 (t, $J = 7.6$ Hz, 1H), 5.77 (m, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 17.8, 20.9, 22.4, 22.6, 26.3, 31.9, 40.7, 59.6, 75.2, 128.1, 128.9, 158.7. IR (neat) 1725 cm^{-1}. Anal. Calc. for $C_{12}H_{19}NO_2$: C, 68.85; H, 9.16. Found: C, 69.01; H, 9.17%.

5.3. (+)-(1R,2S,6R)-6-Isopropyl-3-methyl-2-methylamino-cyclohex-3-enol (2)

To a degassed solution of crude product **3** (from **5**, 1.5 g, 4.6 mmol) in EtOH (20 ml) and water (5 ml) was added KOH (5,3 g) and the resulting mixture was heated at reflux for 2 h, then cooled to r.t. Water was added and the mixture was extracted with CH_2Cl_2 (3×100 ml). The combined organic layers were dried over magnesium sulphate, filtered and concentrated. The residue was taken up in ether (100 ml) and water (50 ml). Aq. 1 M H_2SO_4 was added until pH 1 and the aqueous layer was separated. The operation was repeated twice. The combined aqueous layer was made alkaline with 1 M NaOH until pH 9 and extracted with ether (4×50 ml). The combined organic layer was dried over magnesium sulphate, filtered, and concentrated to give **2** (570 mg, 68% from **5**) as an oil, which was used without further purification for the next step. Data for crude **2**: ^{1}H-NMR (300 MHz, $CDCl_3$) 60.85 (d, $J = 6.9$ Hz, 3H), 0.90 (d, $J = 6.9$ Hz, 3H), 1.33 (dddd, $J = 10.9$, 5.5, 3.8, 2.5 Hz, 1H), 1.72 (ddd, $J = 17.4$, 4.0, 2.5 Hz, 1H), 1.80 (s, 3H), 1.91 (ddd, $J = 17.4$, 5.5, 5.5 Hz, 1H), 2.19 (dsep, $J = 3.8$, 6.9 Hz, 1H), 2.61 (s, 3H), 2.81 (d, $J = 5.1$ Hz, 1H), 3.43 (dd, $J = 10.9$, 5.1 Hz, 1H), 5.44 (m, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 16.4, 20.9, 22.3, 24.1, 25.9, 37.6, 41.2, 62.4, 69.4, 124.4, 134.1. IR (neat) 3394, 3332 cm^{-1}.

5.4. (+)-(3R,4R,5R)-4-Acetoxy-5-isopropyl-2-methyl-3-(N-methyl-N-trichloroacetylamino)-cyclohex-1-ene (17a)

To a stirred solution of **2** (366 mg, 2 mmol) in 5 ml of Et_2O at 0°C were successively added triethylamine (0.28 ml, 2 mmol), MeOH (0.24 ml, 6 mmol), and trichloroacetyl chloride (0.67 ml, 6 mmol). The solution was stirred for 1 h at r.t., then triethylamine (0.56 ml, 4 mmol) was added followed by Ac_2O (0.95 ml, 10 mmol). The solution was stirred for 1 h at r.t., then subjected to an aqueous work-up. The residue was purified by column chromatography (silica gel, heptane–AcOEt, 95:5) to afford **17a** (482 mg, 65%). $[\alpha]_D^{25}$ +90.6° (*c* 1.0 $CHCl_3$). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 0.77 (d, $J = 6.7$ Hz, 3H), 0.93 (d, $J = 6.7$ Hz, 3H), 1.63 (s, 3H), 1.83–2.23 (m, 4H), 2.02 (s, 3H), 3.29 (s, 3H), 5.17 (dd, $J = 11.2$, 6.1 Hz, 1H), 5.26 (d, $J = 6.1$ Hz, 1H), 5.84 (dd, $J = 3.0$, 0.9 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 62.5 MHz) δ 16.0, 20.5, 20.6, 20.9, 23.8, 26.2, 35.0, 38.4, 57.1, 70.9, 128.8, 128.9, 161.7, 170.1. IR (neat) 1751, 1677 cm^{-1}. Anal. Calc. for $C_{15}H_{22}NO_3Cl_3$: C, 48.77; H, 6.01. Found: C, 48.91; H, 6.18%.

5.5. (+)-(3R,4R,5R)-4-Acetoxy-5-isopropyl-2-methyl-3-[(N-methyl-N-pentachlorobutyryl)-amino]-cyclohex-1-ene (17b)

According to the same procedure as for the preparation of **17a**, **2** (91.5 mg, 0.5 mmol) was converted into **17b** (222 mg, 95%), using 2,2,4,4,4-pentachlorobutyryl chloride as the first acylating agent. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.77 (d, $J = 6.6$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H), 1.60 (s, 3H), 1.84–1.99 (m, 3H), 2.00 (s, 3H), 2.11–2.21 (m, 1H), 3.36 (s, 3H), 4.10 (d, $J = 16.1$ Hz, 1H), 4.26 (d, $J = 16.1$ Hz, 1H), 5.15 (dd, $J = 11.0$, 6.4 Hz, 1H), 5.25 (d, $J = 6.4$ Hz, 1H), 5.83 (m, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 16.2, 20.5, 20.6, 21.0, 23.7, 26.3, 34.8, 38.8, 55.8, 64.1, 71.0, 79.0, 94.4, 128.2, 129.3, 165.0, 170.0. IR (neat) 1751, 1656 cm^{-1}.

5.6. (+)-(1R,2R,6R)-2,2,4,4,4-Pentachloro-N-[(6-(tert-butyl-dimethylsiloxy)-5-isopropyl-2-methyl-cyclohex-2-enyl)]-N-methyl-butyramide (**19**)

To a stirred solution of **2** (346 mg, 1.9 mmol) and 2,6-lutidine (0.55 ml, 4 mmol) in 16 ml of CH_2Cl_2 at 0°C, was added dropwise *t*-butyldimethylsilyl triflate (0.48 ml, 2.1 mmol). After stirring for 30 min at 0°C, the reaction was poured into cold water and extracted with EtOAc. The combined organic layer was washed with 5% $KHSO_4$, water, and brine, and was dried and concentrated. The residue was dissolved in Et_2O (15 ml), then triethylamine (0.21 ml, 1.9 mmol) and 2,2,4,4,4-pentachlorobutyryl chloride (583 mg, 2.1 mmol) were successively added at 0°C, and the reaction mixture was stirred for 30 min at r.t. Aqueous work-up and column chromatography (silica gel, heptane–AcOEt, 99:1) afforded **19** (462 mg, 52%), as a mixture of two rotamers (ratio 85:15). $[\alpha]_D^{25}$ +14.2° (*c* 1.2 $CHCl_3$). Data for the major rotamer: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.87 (d, $J = 6.5$ Hz, 3H), 0.91 (s, 9H), 1.02 (d, $J = 6.5$ Hz, 3H), 1.50 (m, 1H), 1.58 (d, $J = 1.1$ Hz, 3H), 1.65 (m, 1H), 1.90 (m, 1H), 2.39 (m, 1H), 3.39 (s, 3H), 4.14 (d, $J = 16.1$ Hz, 1H), 4.24 (t, $J = 4.9$ Hz, 1H), 4.32 (d, $J = 16.1$ Hz, 1H), 4.97 (m, 1H), 5.68 (m, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ −4.3, −4.0, 18.1, 20.2, 21.2, 21.3, 22.7, 26.2, 26.6, 36.5, 47.5, 58.3, 64.4, 70.2, 79.2, 94.6, 127.0, 129.9, 164.8. IR (neat) 1655 cm^{-1}. Anal. Calc. for $C_{31}H_{36}Cl_5NO_2Si$: C, 46.92; H, 6.76. Found: C, 47.53; H, 6.85%.

5.7. 3,3-Dichloro-4-phenyselenyl-3a-methyl-octahydroindol-2-one (**15**)

To a solution of **13** (237 mg, 0.92 mmol) in 2-propanol (10 mmol) were added diphenyldiselenide (900 mg, 3 mmol), AcOH (1.1 ml, 20 mmol) and nickel powder (1.7 g, 30 mmol). The resulting mixture was stirred under reflux in an inert atmosphere for 2 h, then cooled to r.t., diluted with ether and filtered through Celite. Water was added to the filtrate, which was subsequently neutralised with saturated $NaHCO_3$, washed with water, brine, dried over magnesium sulphate and concentrated. The residue was purified by column chromatography (silica gel, heptane–AcOEt, 9:1) to afford **15** (265 mg, 77%) as a colourless oil. This compound consisted of an 88:12 mixture of epimeric selenides, the major isomer (structure shown as **15**) having the following data: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.40–2.42 (m, 6H), 2.93 (s, 3H), 3.00 (d, $J = 7.2$ Hz, 1H), 3.75 (ddd, $J = 11.3$, 7.2, 5.2 Hz, 1H), 4.14 (m, 1H), 7.26–7.62 (m, 5H). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 19.2, 26.4, 29.1, 38.0, 52.2, 55.3, 84.8, 128.4, 129.4, 135.1, 137.8, 165.8.

5.8. 3-Chloro-3a-methyl-3-(2′,2′,2′-trichloroethyl)-4-phenyselenyl-octahydroindo1-2-one (**16**)

Following the same procedure as above starting with amide **14** (132 mg, 0.37 mmol), compound **16** was obtained as a colourless oil (100 mg, 57%) after purification by column chromatography (silica gel, heptane–AcOEt, 9:1): ^{1}H-NMR (200 MHz, $CDCl_3$) 61.52–2.37 (m, 6H); 2.97 (s, 3H); 3.37 (dd, $J = 1.2$, 7.4 Hz, 1H); 3.52 (d, $J = 15.5$ Hz, 1H); 3.72 (ddd, $J = 11.9$, 7.4, 5.9 Hz, 1H); 4.00 (d, $J = 15.5$ Hz, 1H); 4.04 (m, 1H); 7.29–7.57 (m, SH). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 18.2; 26.9; 27.7 (CH_2); 28.9; 40.9; 41.0; 56.1; 58.6; 70.4; 94.0 (CCl_3); 128.2; 129.4, 135 1, 135.4; 168.9.

5.9. 2,2-Dichloro-N-(5-isopropyl-2-methyl-phenyl)-N-methyl-acetaminde (**18a**)

General procedure: To a solution of **17a** (361 mg, 0.97 mmol) in 2-propanol (10 mmol) were added diphenyldiselenide (900 mg, 3 mmol), AcOH (1.1 ml, 20 mmol) and nickel powder (1.7 g, 30 mmol). The resulting mixture was stirred under reflux in an inert atmosphere for 3 h, then cooled to r.t., diluted with ether and filtered through Celite. Water was added to the filtrate, which was subsequently neutralised with saturated $NaHCO_3$, washed with water, brine, dried over magnesium sulphate and concentrated. The residue was purified by column chromatography (silica gel, heptane–AcOEt, 95:5) to afford 324 mg of a mixture of isomers (68%), which was directly oxidised by hydrogen peroxide (30% in water, 0.45 ml, 4 mmol) in THF (10 ml) at r.t. for 30 min. Aqueous work-up and column chromatography (silica gel, heptane–AcOEt, 4:1) afforded **18a** (95 mg, 36%, two steps) as a colourless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.25 (d, $J = 6.9$ Hz, 6H), 2.23 (s, 3H), 2.91 (sep, $J = 6.9$ Hz, 1H), 3.27 (s, 3H), 5.74 (s, 1H), 7.04 (d, $J = 1.5$ Hz), 7.21 (dd, $J = 7.9$, 1.5 Hz, 1H), 7.26 (d, $J = 7.9$ Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 17.0, 23.7, 24.1, 33.6, 37.1, 63.5, 125.8, 127.8, 131.9, 132.5, 149.2. IR (neat) 1692 cm^{-1}. Anal. Calc. for $C_{13}H_{17}Cl_2NO$: C, 57.13; H, 6.27. Found: C, 57.93; H, 6.41%.

5.10. 2,4,4,4-Tetrachloro-N-(5-isopropyl-2-methyl-phenyl)-N-methyl-butyramide (**18b**)

According to the general procedure, 1**7b** (197 mg, 0.42 mmol) was converted into **18b** (29 mg, 55%), which was obtained as a mixture of two rotamers (ratio 65:35). ^{1}H-NMR (200 MHz, $CDCl_3$) major rotamer δ 1.22 (d, $J = 6.9$ Hz, 3H), 1.24 (d, $J = 6.9$ Hz, 3H), 2.31 (s, 3H), 2.89 (sep, $J = 6.9$ Hz, 1H), 3.08 (dd, $J = 14.9$, 3.2 Hz, 1H), 3.26 (s, 3H), 4.04 (dd, $J = 14.9$, 8.6 Hz, 1H), 4.54 (dd, $J = 8.6$, 3.2 Hz, 1H), 7.19–7.28 (m, 3H); minor rotamer δ 1.24 (d, $J = 6.8$ Hz, 3H), 1.25 (d, $J = 6.8$ Hz, 3H), 2.24 (s, 3H), 2.89 (sep, $J = 6.8$ Hz,

1H), 3.17 (dd, $J = 15.4$, 3.6 Hz, 1H), 3.25 (s, 3H), 3.91 (dd, $J = 15.4$, 7.7 Hz, 1H), 4.28 (dd, $J = 7.7$, 3.2 Hz, 1H), 7.05–7.28 (m, 3H). ^{13}C-NMR ($CDCl_3$, 50 MHz) major rotamer δ 17.4, 23.9, 24.0, 33.7, 37.1, 48.8, 58.5, 96.0, 126.2, 127.6, 132.0, 133.4, 140.5, 148.5, 167.6; minor rotamer δ 17.4, 23.5, 24.2, 33.6, 37.1, 49.7, 58.4, 96.0, 126.7, 127.5, 131.5, 133.4, 140.5, 148.5, 167.6. MS (IC) m/z 389 (MNH_4^+), 372 (MH^+), 356, 336, 300, 253, 190.

5.11. (5R,6S)-2,4,4,4-Tetrachloro-N-(5-isopropyl-6-tert-butyldimethylsiloxy-2-methyl-1,3-cyclohexadienyl)-N-methyl-butyramide (**20**)

According to the general procedure, **19** (373 mg, 0.69 mmol) afforded diene **20** (173 mg, 54%) as a 85:15 mixture of diastereoisomers. Data for the major isomer: ^{1}H-NMR (300 MHz, $CDCl_3$) 0.08 (s, 3H), 0.10 (s, 3H), 0.86 (s, 9H), 0.93 (d, $J = 6.7$ Hz, 1H), 1.10 (d, $J = 6.7$ Hz, 1H), 1.72 (m, 1H), 1.74 (s, 3H), 2.27 (ddd, $J = 7.3$, 5.0, 1.6 Hz, 1H), 3.19 (s, 3H), 3.28 (dd, $J = 15.6$, 4.7 Hz, 1H), 3.72 (dd, $J = 15.6$, 6.2 Hz, 1H), 4.49 (m, 1H), 4.77 (dd, $J = 6.2$, 4.7 Hz, 1H); 5.88 (d, $J = 9.8$ Hz, 1H), 5.92 (dd, $J = 9.8$, 4.7 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ −4.1, −3.8, 17.9, 18.0, 20.2, 22.1, 26.0, 31.6, 39.0, 49.9, 52.5, 58.9, 72.1, 95.9, 125.5, 130.2, 131.9, 133.5, 167.7. IR (neat) 1670 cm^{-1}.

5.12. N-Benzyl-2,2-dichloro-N-(2-methyl-3-phenylseleno-cyclohex-1-enyl)-acetamide (**22**)

To a solution of **21** (693 mg, 2 mmol) in 2-propanol (20 mmol) were added diphenyldiselenide (1.8 g, 6 mmol), AcOH (2.2 ml, 40 mmol) and nickel powder (3.4 g, 60 mmol). The resulting mixture was stirred under reflux in an inert atmosphere for 3 h, then cooled to r.t., diluted with ether and filtered through Celite. Water was added to the filtrate, which was subsequently neutralised with saturated $NaHCO_3$, washed with water, brine, dried over magnesium sulphate and concentrated. The residue was purified by column chromatography (silica gel, heptane–AcOEt, 4:1) to afford **22** (757 mg, 81%) as an inseparable mixture of two isomers (ratio 55:45). ^{1}H-NMR (300 MHz, $CDCl_3$) major isomer δ 1.49 (s, 3H), 1.73–2.06 (m, 6H), 3.69 (m, 1H), 4.49 (d, $J = 13.8$ Hz, 1H), 4.77 (d, $J = 13.8$ Hz, 1H), 6.20 (s, 1H), 7.25–7.59 (m, 10H); minor isomer δ 1.52 (s, 3H), 1.73–2.06 (m, 6H), 3.74 (m, 1H), 4.65 (s, 2H), 6.22 (s, 1H), 7.25–7.59 (m, 10H). ^{13}C-NMR ($CDCl_3$, 75 MHz) major isomer δ 18.0, 19.0, 28.5, 29.2, 47.9, 50.3, 64.1, 127.8, 128.0, 128.5, 129.3, 129.8, 130.5, 133.2, 134.6, 135.5, 136.4, 163.5; minor isomer δ 18.1, 19.4, 29.2, 29.5, 48.1, 50.4, 63.6, 128.0, 128.1, 128.7, 129.3, 129.4, 130.1, 132.7, 134.4, 135.9, 136.5, 163.9. IR (neat) 1682 cm^{-1}. MS (IC) m/z 485 (MNH_4^+), 468 (MH^+), 391, 310, 293, 276.

5.13. (4β,8β,11β)-3-Benzyl-11-methyl-3-azatricyclo-[6.2.1.0^{4,11}]undec-1(10)-en-9-one (**26**) and (1β,2β,6β)-2-benzylamino-1,9-dimethyl-8-bicyclo-[4.3.0]nonen-7-one (**27**)

To a solution of propargylic amine **25** (239 mg, 1 mmol) in CH_2Cl_2 (5 ml) was added dicobalt octacarbonyl complex (376 mg, 1.1 mmol), and the resulting mixture was stirred for 30 min at r.t. After concentration, the black residue was dissolved in 20 ml of the given solvent (see Scheme 7), and N-methylmorpholine oxide (1.3 g, 10 mmol) was added in one portion. The mixture was stirred at r.t. (1–20 h), then filtered through silica, and concentrated. Column chromatography (silica gel, heptane–AcOEt, 9:1) afforded **26** and **27** in the proportions indicated in Scheme 7. Data for **26**: ^{1}H-NMR (300 MHz, $CDCl_3$) 60.91–1.15 (m, 3H), 1.36 (s, 3H), 1.56–1.72 (m, 2H), 1.96 (m, 1H), 2.41 (t, $J = 8.8$ Hz, 1H), 2.94 (dd, $J = 9.8$, 6.2 Hz, 1H), 3.41 (d, $J = 17.4$ Hz, 1H), 3.80 (d, $J = 13.4$ Hz, 1H), 3.83 (d, $J = 17.4$ Hz, 1H), 3.93 (d, $J = 13.4$ Hz, 1H), 5.69 (s, 1H), 7.22–7.37 (m, 5H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 21.4, 25.4, 26.8, 30.4, 50.5, 52.2, 55.0, 55.9, 64.9, 120.2, 127.1, 128.3, 128.4, 139.4, 188.1, 213.7. IR (neat) 1704, 1641 cm^{-1}. Data for **27**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.91 (m, 1H), 1.29 (s, 3H), 1.33–1.69 (m, 6H), 2.00 (s, 3H), 2.02–2.15 (m, 1H), 2.71 (m, 1H), 3.49 (d, $J = 13.4$ Hz, 1H), 3.78 (d, $J = 13.4$ Hz, 1H), 6.00 (s, 1H), 7.21–7.33 (m, SH). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 15.7, 16.4, 20.2, 23.0, 23.1, 49.9, 51.6, 53.5, 57.7, 126.9, 127.9, 128.4, 130.9, 140.6, 179.4, 208.2. IR (neat) 3350, 1704, 1609 cm^{-1}.

5.14. (+)-(1S,5R,6S)-N-(6-acetoxy-5-isopropyl-2-methyl-cyclohex-2-enyl)-N-methyl-N-(prop-2-ynyl)-amine (**28**)

To a solution of amino-alcohol **2** (1.06 g, 5.8 mmol) and potassium carbonate (1.6 g, 11.6 mmol) in MeCN (60 ml) at 0°C, was added propargyl bromide (80% in toluene, 1.14 ml, 8.7 mmol) and the reaction mixture was stirred at r.t. for 18 h. Water was added and the mixture was extracted with EtOAc (3 × 50 ml). The combined organic layer was washed with brine, dried over magnesium sulphate, filtered, and concentrated. To a solution of the residue in CH_2Cl_2 (25 ml) at 0°C was added pyridine (1.17 ml, 14.5 mmol), Ac_2O (5 ml, 53 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred at r.t. for 3 h, and satd. aq. $NaHCO_3$ was added. The mixture was extracted with CH_2Cl_2 (3 × 50 ml). The combined organic layer was washed with brine, dried over magnesium sulphate and concentrated. The residue was purified by column chromatography (silica gel, heptane–AcOEt, 95:5) to give **28** (1.34 g, 88%) as a colourless oil. $[\alpha]_D^{25}$ +137.0° (c 0.98, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) 60.74 (d,

$J = 6.7$ Hz, 3H), 0.91 (d, $J = 6.7$ Hz, 3H), 1.72 (d, $J = 1.8$ Hz, 3H), 1.82–2.06 (m, 4H), 2.11 (s, 3H), 2.20 (t, $J = 2.4$ Hz, 1H), 2.49 (s, 3H), 3.41 (d, $J = 4.4$ Hz, 1H), 3.47 (d, $J = 2.4$ Hz, 1H), 3.49 (d, $J = 2.4$ Hz, 1H), 4.94 (dd, $J = 10.4$, 4.4 Hz, 1H), 5.56 (m, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 16.5, 20.5, 21.6, 22.9, 24.3, 26.2, 37.4, 39.3, 45.6, 61.4, 71.9, 75.5, 81.5, 125.2, 132.1, 170.8. IR (neat) 3438, 1730, 1643 cm^{-1}. Anal. Calc. for $C_{16}H_{25}NO_2$: C, 72.95; H, 9.57. Found: C, 73.11; H, 9.61%.

5.15. (+)-(1S,4S,5R,6R,8S,11R)-5-Acetoxy-6-isopropyl-3,11-dimethyl-3-azatricyclo[6.2.1.0^{4,11}]undecan-9-one (**30**)

To a solution of **28** (955 mg, 3.63 mmol) in CH_2Cl_2 (30 ml) was added dicobalt octacarbonyl (1.49 g, 4.36 mmol) and the black reaction mixture was stirred at r.t. for 1 h. The solvent was evaporated under reduce pressure and the residue dissolved in MeCN (60 ml). 4-Methylmorpholine *N*-oxide monohydrate (4.90 g, 36.3 mmol) was added, and the solution was stirred at r.t. for 4 h, by which time the mixture had turned purple and no cobalt complex was visible by TLC. Filtration through silice (eluent ether) and concentration gave cyclopentenone **29**. The unstable crude product **9** was used for the next step without purification. Data for crude **29**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.90 (d, $J = 6.1$ Hz, 3H), 0.96 (d, $J = 6.1$ Hz, 3H), 1.30 (s, 3H), 1.53–1.61 (m, 3H); 1.85 (m, 1H), 2.00 (s, 3H), 2.38 (t, $J = 8.8$ Hz, 1H), 2.55 (s, 3H), 2.92 (d, $J = 5.1$ Hz, 1H), 3.76 (d, $J = 1.4$ Hz, 2H), 5.18 (t, $J = 5.1$ Hz, 1H), 5.60 (t, $J = 1.4$ Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 19.9, 20.7, 21.5, 22.9, 26.2, 30.7, 40.5, 42.3, 51.3, 51.8, 54.0, 65.6, 71.9, 120.0, 170.0, 188.6, 213.3. IR (neat) 1738, 1708, 1648 cm^{-1}. To a solution of **29** in MeOH (25 ml) was added 10% Pd/C (0.8 g) and the solution was stirred under H_2 (1 atm) for 1 h. Filtration through Celite, concentration, and column chromatography (silica gel, heptane–AcOEt, 9:1) afforded **30** (542 mg, 51%) as a white solid (m.p. 95–96°C, pentane). $[\alpha]_D^{25}$ +69.4° (*c* 0.85 $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.74 (d, $J = 6.9$ Hz, 3H), 0.95 (d, $J = 6.9$ Hz, 3H), 1.27 (ddd, $J = 13.6$, 12.1, 6.6 Hz, 1H), 1.41 (s, 3H), 1.80–2.14 (m, 5H), 2.03 (s, 3H), 2.08 (d, $J = 3.0$ Hz, 1H), 2.22 (ddd, $J = 13.5$, 3.3, 1.9 Hz, 1H), 2.19 (s, 3H), 2.41 (dd, $J = 9.3$, 6.3 Hz, 1H), 2.59 (d, $J = 9.3$ Hz, 1H), 2.71 (ddd, $J = 17.2$, 10.4, 2.6 Hz, 1H), 4.90 (dd, $J =$ 11.7, 3.0 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 16.1, 20.2, 20.6, 21.2, 26.1, 26.3, 35.4, 41.0, 41.7, 45.0, 50.2, 52.1, 66.8, 73.7, 74.9, 170.1, 214.1. IR (neat) 1744, 1736.cm^{-1}. Anal. Calc. for $C_{17}H_{27}NO_3$: C, 69.58; H, 9.28. Found: C, 69.76; H, 9.26%.

5.16. (+)-(1S,4S,5R,6S,11R)-(5-Acetoxy-6-isopropyl-3,11-dimethyl-3-azatricyclo-[6.2.1.0^{4,11}]undec-7-en-9-one (**31**)

To a solution of **30** (707 mg, 2.41 mmol) and HMDS (1.26 ml, 5.97 mmol) in CH_2Cl_2 (25 ml) at −20°C, was added iodotrimethylsilane (0.68 ml, 4.82 mmol) and the solution was stirred 15 min at −20°C and 1 h at r.t. The reaction mixture was diluted with pentane (75 ml), and washed with saturated aq. $NaHCO_3$. The organic layer was dried over sodium sulphate, and solvents were removed under reduce pressure. To the residue in THF (30 ml) at −78°C, was added phenylselenenyl bromide (569 mg, 2.41 mmol), and the reaction mixture was stirred at r.t. for 4 h. Water (2 ml) was added at 0°C, and the mixture was extracted with EtOAc (2 × 50 ml). The combined organic layer was washed with brine, dried over magnesium sulphate, and concentrated. Column chromatography (silica gel, heptane–AcOEt, 9:1) afforded the selenide (779 mg, 72%) as an unstable white solid. The selenide (779 mg, 1.74 mmol) was dissolved in THF (15 ml), and the solution was cooled to −40°C. mCPBA (70%, 480 mg, 1.95 mmol) was added in one portion, and the mixture was stirred at −40°C for 1 h. The mixture was slowly warmed to r.t. and stirred for 30 min. Satd. aq. $NaHCO_3$ was added, and the mixture was extracted with EtOAc (3 × 50 ml). The combined organic layer was dried over magnesium sulphate, and solvents were removed under reduce pressure. The residue was purified by column chromatography (silica gel, heptane–AcOEt, 7:3) to give **31** (303 mg, 60%) as a pale yellow oil. $[\alpha]_D^{25}$ +12.9° (*c* 0.45 $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.83 (d, $J = 6.9$ Hz, 3H), 1.08 (d, $J = 6.9$ Hz, 3H), 1.25 (s, 3H), 1.92 (dsep, $J = 3.0$, 6.9 Hz, 1H), 2.11 (s, 3H), 2.17 (d, $J = 19.0$ Hz, 1H), 2.40 (s, 3H), 2.46 (m, 1H), 2.60 (dd, $J = 19.0$, 8.3 Hz, 1H), 2.62 (ddd, $J = 9.7$, 3.6, 3.0 Hz, 1H), 2.71 (d, $J = 10.4$ Hz, 1H), 2.72 (d, $J = 2.4$ Hz, 1H), 2.78 (dd, $J = 10.4$, 5.2 Hz, 1H), 5.29 (dd, $J = 9.7$, 2.4 Hz, 1H), 6.47(d, $J = 3.6$ Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 18.2, 20.8, 21.3, 22.9, 27.1, 40.8, 41.5, 42.9, 44.8, 51.9, 63.2, 71.3, 72.4, 131.2, 144.6, 170.6, 205.3. IR (neat) 1740, 1723, 1653.cm^{-1}. MS (IC) m/z 292 (MH^+), 276, 262, 248, 232.

5.17. (+)-(1S,4S,5R,6S,7R,8S,11R)-5-Acetoxy-7-cyano-6-isopropyl-3,11-dimethyl-3-azatricyclo-[6.2.10^{4,11}] undecan-9-one (**32**)

To a solution of **31** (51 mg, 0.175 mmol) in toluene (4 ml) at 0°C, was added diethylaluminium cyanide (1 M in toluene, 0.7 ml, 0.7 mmol) and the reaction mixture was heated at 70°C for 1 h. The solution was cooled to r.t., satd. aq. $NaHCO_3$ (5 ml) was added, and the mixture was extracted with EtOAc (3 × 15 ml). The combined organic layer was dried over magnesium

sulphate, and the solvents were removed under reduce pressure. Column chromatography (silica gel, heptane–AcOEt, 4:1) afforded **32** (43 mg, 77%) as a colourless oil. $[\alpha]_D^{25}$ +94.1° (*c* 1.1 $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.05 (d, $J=6.9$ Hz, 3H), 1.10 (d, $J=6.9$ Hz, 3H), 1.62 (s, 3H), 1.98 (m, 1H), 2.07 (s, 3H), 2.02–2.25 (m, 3H), 2.21 (s, 3H), 2.24 (d, $J=2.9$ Hz, 1H), 2.38 (dd, $J=2.1$, 1.8 Hz, 1H), 2.49 (dd, $J=9.5$, 5.9 Hz, 1H), 2.61 (d, $J=9.5$ Hz, 1H), 2.76 (ddd, $J=17.3$, 10.4, 2.1 Hz, 1H), 3.66 (dd, $J=4.0$, 1.8 Hz, 1H), 5.40 (dd, $J=11.9$, 2.9 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 18.8, 21.1, 21.3, 26.8, 27.1, 27.3, 36.7, 41.5, 41.6, 43.9, 50.1, 55.2, 66.5, 72.5, 73.4, 121.5, 169.7, 209.3. IR (neat) 2238, 1745, 1743 cm^{-1}.

5.18. (+)-(1S,4S,5R,6S,7R,8S,11R)-5-Acetoxy-7-cyano-6-isopropyl-3,11-dimethyl-3-azatricyclo-[6.2.1.0^{4,11}] undecane (**33**)

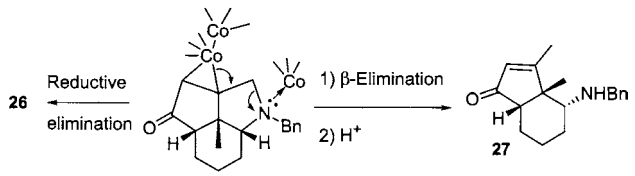
To a solution of **32** (90 mg, 0.28 mmol) in EtOH (4 ml) at 0°C, was added $NaBH_4$ (32 mg, 0.84 mmol) and the mixture was stirred at r.t. for 5 h. The reaction was quenched by addition of satd. aq. ammonium chloride (0.3 ml). The solution was diluted with EtOAc (25 ml), washed with satd. aq. $NaHCO_3$ and brine, dried over magnesium sulphate, and concentrated to afford the crude alcohol. To the residue in CH_2Cl_2 (5 ml) and DMAP (102 mg, 0.84 mmol) at 0°C, was added *O*-phenyl chlorothionoformate (60 μl, 0.42 mmol) and the mixture was stirred at r.t. for 2 h. Concentration and column chromatography (silica gel, heptane–AcOEt, 4:1) afforded the thiocarbonate (77 mg, 60%) as a white solid: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.97 (d, $J=6.9$ Hz, 3H), 1.06 (d, $J=6.9$ Hz, 3H), 1.26 (s, 3H), 1.96–2.01 (m, 1H), 2.05 (s, 3H), 2.07 (d, $J=2.4$ Hz, 1H), 2.21–2.27 (m, 2H), 2.32 (s, 3H), 2.40–2.51 (m, 3H), 2.67–2.74 (m, 2H), 4.20 (dd, $J=12.3$, 8.1 Hz, 1H), 5.15 (dd, $J=9.4$, 2.4 Hz, 1H), 5.50 (m, 1H), 7.09–7.46 (m, SH). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 18.5, 21.3, 21.5, 26.0, 26.8, 29.8, 35.9, 39.0, 42.0, 43.5, 44.4, 51.8, 62.7, 69.9, 73.0, 83.4, 120.3, 122.3, 126.6, 129.5, 153.8, 170.2, 195.1. IR (neat) 2245, 1740 cm^{-1}. To a solution of the thiocarbonate (77 mg, 0.17 mmol) in toluene (5 ml) was added tributyltin hydride (0.11 ml, 0.41 mmol) and 1,1′-azobis(cyclohexanecarbonitrile) (11 mg, 0.045 mmol), and the reaction mixture was refluxed for 2 h. Concentration and column chromatography (silica gel, heptane–AcOEt, 9:1) afforded **33** (43 mg, 83%) as a colourless oil. $[\alpha]_D^{25}$ +3.5° (*c* 0.85 $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.00 (d, $J=6.9$ Hz, 3H), 1.08 (d, $J=6.9$ Hz, 3H), 1.27 (s, 3H), 1.47 (m, 1H), 1.70 (m, 1H), 1.87–2.06 (m, 4H), 2.05 (s, 3H), 2.12 (d, $J=2.9$ Hz, 1H), 2.16 (dsep, $J=4.0$, 6.9 Hz, 1H), 2.24 (s, 3H), 2.29 (dd, $J=9.5$, 7.5 Hz, 1H), 2.39 (ddd, $J=10.6$, 6.9, 4.0 Hz, 1H), 2.63 (d, $J=9.5$ Hz, 1H), 3.67 (dd, $J=7.7$, 6.9 Hz, 1H), 5.40 (dd, $J=10.6$, 2.4 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 19.8, 20.2, 21.5, 26.8, 29.0, 30.5, 32.2, 32.9, 37.8, 42.5, 48.0, 49.7, 53.7, 64.6, 71.9, 73.8, 121.8, 170.1. IR (neat) 2233, 1744 cm^{-1}. MS (IC) *m*/*z* 319 (MNH_4^+), 305 (MH^+), 261, 245, 248, 232.

5.19. Imino-lactone (**35**)

To a solution of **33** (5 mg, 1.6×10^{-5} mol) in MeOH (0.5 ml) was added sodium methoxide (2 N in MeOH, 0.5 ml), and the solution was heated in a sealed tube at 100°C for 24 h. The solution was cooled to r.t., water was added, and the solution was extracted with CH_2Cl_2 (4 × 5 ml). Concentration gave a 1:1 mixture of **34a** and **34b**, which was directly treated with PTSA (20 mg, 0.1 mmol) in toluene (1 ml) at 110°C for 5 h. The mixture was then cooled to r.t., neutralised with satd. aq. $NaHCO_3$, and extracted with CH_2Cl_2 (4 × 5 ml). Concentration and column chromatography (silica gel, CH_2Cl_2–MeOH, 95:5) afforded imino-lactone **35** (2 mg, 50%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.96 (d, $J=6.5$ Hz, 3H), 0.97 (d, $J=6.5$ Hz, 3H), 1.37 (s, 3H), 1.63–2.53 (m, 9H), 2.51 (s, 3H), 2.60 (d, $J=3.0$ Hz, 1H), 2.71 (t, $J=8.6$ Hz, 1H), 3.12 (t, $J=8.6$ Hz, 1H), 4.71 (dd, $J=5.5$, 3.1 Hz, 1H).

5.20. (−)-Dendrobine (**1**)

To a solution of **33** (21 mg, 6.9×10^{-5} mol) in MeOH (1.5 ml) was added sodium methoxide (2 N in MeOH, 1.5 ml), and the solution was heated in a sealed tube at 100°C for 24 h. The solution was cooled to r.t., water was added, and the solution was extracted with CH_2Cl_2 (4 × 10 ml). Concentration gave a 1:1 mixture of **34a** and **34b**, which was directly treated with PTSA (100 mg, 0.5 mmol) in dioxane (3 ml) and water (0.3 ml) at 120°C for 24 h (sealed tube). The mixture was then cooled to r.t., neutralised with satd. aq. $NaHCO_3$, and extracted with CH_2Cl_2 (4 × 10 ml). Concentration and column chromatography (silica gel, heptane–AcOEt–MeOH, 25:25:2) to afford unreacted **34a** (7.5 mg, 41%) and (−)-dendrobine **1** (8 mg, 44%, 75% based on recovered **34a**) as colourless crystals (m.p. 131–132°C, pentane–ether, lit. [5e]; m.p. 133.0–133.5°C, hexane–ether). $[\alpha]_D^{25}$ −45 9° (*c* 0.44 CH_3OH), lit. $[\alpha]_D^{25}$ 46.7° (*c* 1.98 CH_3OH). ^{1}H-NMR (300 MHz, $CDCl_3$) 60.97 (d, $J=6.5$ Hz, 3H), 0.98 (d, $J=6.5$ Hz, 3H), 1.39 (s, 3H), 1.50–1.60 (m, 1H), 1.76–1.89 (m, 2H), 1.99–2.15 (m, 4H), 2.36 (m, 1H), 2.45 (dd, $J=5.6$, 4.2 Hz, 1H), 2.51 (s, 3H), 2.67 (d, $J=3.1$ Hz, 1H), 2.69 (dd, $J=8.9$, 7.5 Hz, 1H), 3.16 (t, $J=8.7$ Hz, 1H), 4.85 (dd, $J=5.5$, 3.1 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 20.6, 21.3, 24.7, 30.9, 32.8, 32.9, 36.6, 43.2, 44.1, 51.7, 52.6, 53.8, 62.1, 67.0, 79.4, 179.1. IR (neat) 1765.



Scheme 9.

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