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Chemoenzymatic approaches to the montanine alkaloids: a total synthesis of (+)-nangustine

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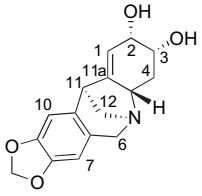
ABSTRACT

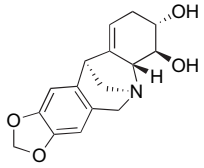
The synthesis of (+)-nangustine [(+)-**2**] has been achieved, for the first time, using the enantiomerically pure *cis*-1,2-dihydrocatechol **3** as starting material. The latter compound is available, in multi-gram quantities, through a whole-cell-mediated biotransformation of chlorobenzene using genetically engineered organisms that over-express the responsible enzyme, namely toluene dioxygenase. Since the enantiomer of compound **3** is available by related means, the present work also represents a formal total synthesis of the montanine alkaloid (−)-nangustine [(−)-**2**]. Single-crystal X-ray analyses of compounds **13** and (+)-**2** are reported.

1. Introduction

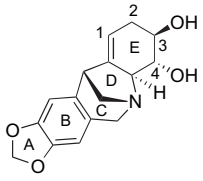
(−)-Brunsvigine [(−)-**1**][1–3] is a representative member of the montanine class of Amaryllidaceae alkaloid, a small group of natural products characterised by the presence of a 5,11-methanomorphanthridinone framework.[4] These compounds, which normally incorporate hydroxy and/or methoxy groups at C2 and C3 (in varying configurations) as well as a $\Delta^{1(11a)}$-double bond, have been isolated from a variety of plant sources. The isolation of (+)-montabuphine from the Amaryllidaceae species *Boophane flava* found in Southern Africa suggests that both enantiomeric forms of the framework can be encountered within this class of natural product.[5] A modest number of biological properties have been attributed to such alkaloids including anxiolytic, antidepressive, anticonvulsive and (weak) hypotensive activities.[5,6] As a result, various efforts have been made to develop syntheses of these compounds with notable successes having been reported by Overman,[7] Pearson,[8] Weinreb,[9] Sha[10] and Hoshino.[11] Our own contributions to the area have involved the development of a formal total synthesis of the racemic modification of pancracine (another member of the montanine alkaloid family)[12] and a total synthesis of (+)-brunsvigine [(+)-**1**].[13] Each of these involved the same end-game as originally established by Overman,[7] namely the preparation of the relevant 3a-arylhexahydroindole and the subjection of such species to a Pictet–Spengler reaction so as to introduce C6 and thus complete the assembly of the required 5,11-methanomorphanthridinone framework.



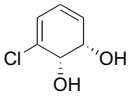
(−)-**1**



(−)-**2**



(+)-**2**



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The montanine alkaloid nangustine [(−)-**2**][14] is the most recently characterised member of the class. It was isolated from the bulbs of *Narcissus angustifolius* subsp. *transcarpathicus* collected in Ukraine and has been assigned the illustrated structure on the basis of extensive NMR analytical studies. Significantly, this compound differs from its congeners in that it possesses a C3,C4- rather than a C2,C3-dioxygenation pattern in the E-ring. Furthermore, the compound has been shown[14] to possess modest but selective activity (IC_{50} 0.7–7.1 μg/mL) against *Trypanosoma brucei rhodesiense*, *Trypanosoma cruzi* and *Plasmodium falciparum*. In contrast, co-occurring pancracine, which incorporates the more conventional C2,C3-dioxygenation pattern, is essentially inactive against the first two of these same parasitic species. On this basis we have sought to adapt our recently reported[13] synthesis of (+)-brunsvigine to the

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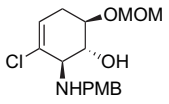
preparation of (+)-nangustine [(+)-**2**]. If successful, such endeavours should serve to confirm the structure assigned to this most unusual member of the montanine alkaloid family. Details of our studies of this matter are reported herein. The reaction sequence used exploits the enantiomerically pure *cis*-1,2-dihydrocatechol **3** as starting material.[15] This compound is available, in multi-gram quantities, through a whole-cell-mediated biotransformation of chlorobenzene using genetically engineered organisms that overexpress toluene dioxygenase.[16]

2. Results and discussion

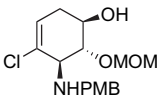
2.1. Part 1: assembly of the 4-deoxyaminoconduritol core

Following the strategy employed in our recently reported[13] synthesis of (+)-brunsvigine, the early stages of our approach to the title compound involved assembling the 4-deoxyaminoconduritol residue corresponding to the E-ring of the target. The route by which this was achieved is outlined in Scheme 1 and started with the readily available PMP-acetal **4** of the *cis*-1,2-dihydrocatechol **3**. Epoxidation of the acetal **4**[17] using *m*-chloroperbenzoic acid (*m*-CPBA) proceeded in both a regio- and diastereo-selective manner to give epoxide **5** (75% from **3**). In a critical step of the reaction sequence, compound **5** was exposed to ca. seven molar equivalents of DIBAL-H and so resulting in reductive cleavage of both the epoxide and acetal residues within the substrate and thus delivering the mono-protected triol **6** (42%) as the only characterisable product of the reaction. The structure of this compound follows from the single-crystal X-ray analysis of a derivative (vide infra). The seemingly selective formation of 4-deoxyconduritol **6** by this means is presumably driven by two factors, namely the preferential cleavage of the allylic C–O bond of the epoxide ring[18] and that benzylic C–O bond of the PMP-acetal remote from the sterically demanding chlorine.[19]

The two free hydroxy groups within diol **6** were protected as the corresponding MOM-ethers using MOM-Cl in the presence of base and the PMB unit within the resulting tris-ether **7** (86%) was selectively cleaved with DDQ to give the allylic alcohol **8** in 81% yield. This last compound was converted into the corresponding mesylate **9** (100%) using modifications of the Crossland and Servis[20] procedure and this ester was then engaged in an S_N2 reaction with sodium azide in DMF. By such means the allylic azide **10** was obtained in 90% yield. The Staudinger reduction[21] of compound **10** was best carried out using polymer-supported triphenylphosphine in aqueous THF because of the ease of separation of the co-produced, and polymer-bound, phosphine oxide from the desired amine **11** (84%). Following protocols established during our synthesis of (+)-brunsvigine, compound **11** was subjected to reductive amination using *p*-methoxybenzaldehyde (*p*-MBA) as electrophile and sodium triacetoxyborohydride as the reducing agent. By such means the secondary amine **12** was obtained in 63% yield. In contrast, if DIBAL-H was used to reduce the intermediate imine then this process was accompanied by cleavage of one or other of the associated MOM-ethers such that a chromatographically separable and 2:5 mixture of compounds **13** and **14** was obtained.



13



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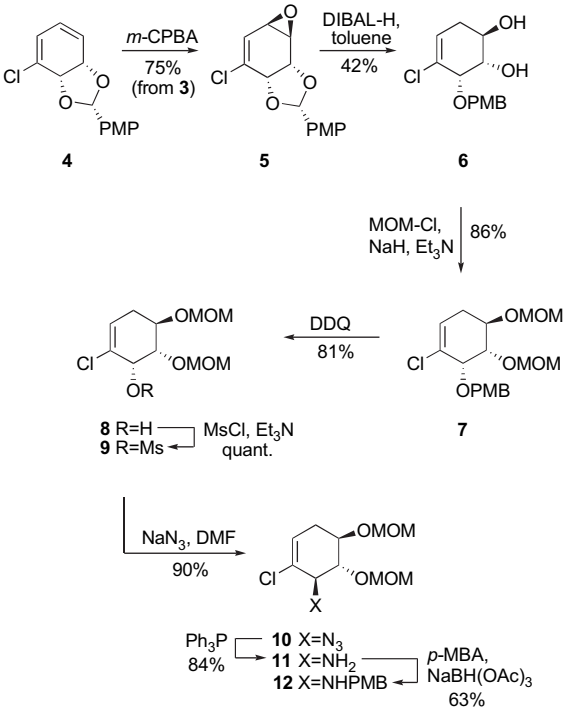
The former product was a solid material that was subjected to a single-crystal X-ray analysis. The derived ORTEP plot is shown in Figure 1 and served to confirm the structures assigned to these compounds and their precursors.

2.2. Part 2: the end-game—coupling of the aromatic and aminocyclitol cores of (+)-nangustine

Compound **12** embodies the E-ring of (+)-nangustine so its annulation with the ABCD-substructure of the target molecule was pursued using the same sorts of protocols as employed in our recently reported synthesis of (+)-brunsvigine.[13] Thus, as shown in Scheme 2, the racemic modification of the known and readily available acid **15**[22] was converted, using standard conditions, into the



Scheme 1.

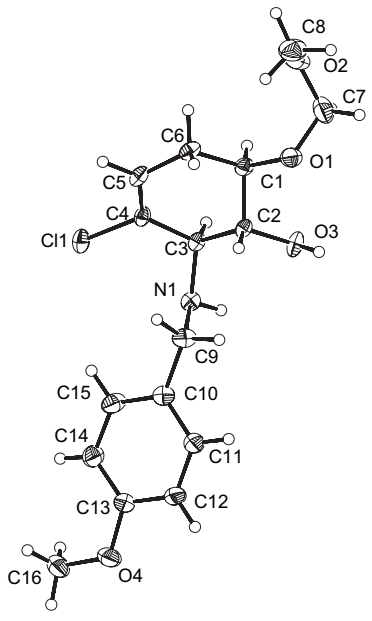
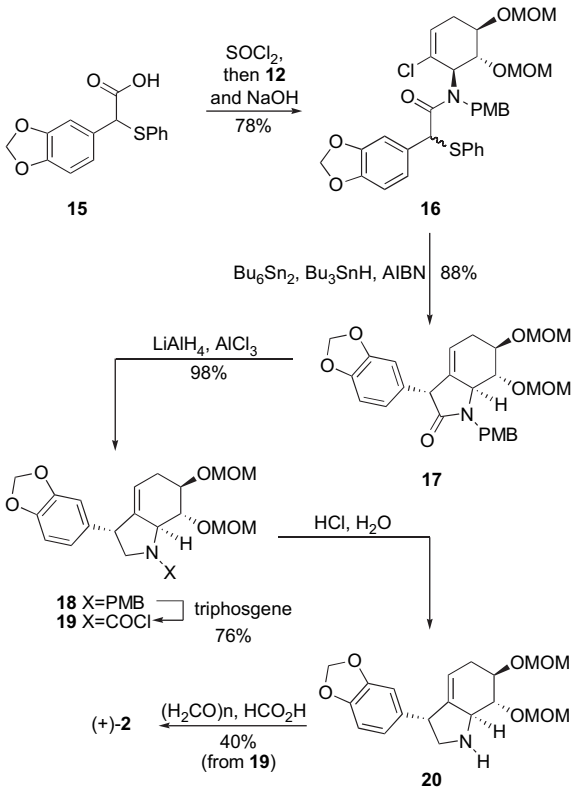


Figure 1. ORTEP plot derived from the single-crystal X-ray analysis of compound **13**.



Scheme 2.

corresponding acid chloride and this was then reacted with amine **12** under Schotten–Baumann conditions so as to produce the amide **16**, as a ca. 1:1 mixture of diastereoisomers, in 78% yield. The ^{1}H and ^{13}C NMR spectra of this mixture proved to be exceptionally complex and rather uninformative due to the presence of amide rotamers. Nevertheless, subjecting this material to reaction with a combination of hexa-*n*-butylditin and tri-*n*-butyltin hydride resulted in the expected radical addition/elimination reaction[13,23] to form, in 88% yield and as a single diastereoisomer, the lactam **17** containing what will become the $\Delta^{1(11a)}$-double bond of (+)-nangustine. The origins of the pleasing diastereoselectivity associated with the conversion **16**→**17** are the subject of ongoing mechanistic and theoretical studies, the results of which will be reported in due course.

In anticipation of carrying out a Pictet–Spengler reaction to establish the C-ring of target (+)-**2**, compound **17** was reduced to the corresponding amine **18** (98%) using in situ generated AlH_3. Reaction of the latter compound with triphosgene[24] in CH_2Cl_2 resulted in cleavage of the PMB-residue within this substrate and formation of the carbamoyl chloride **19** that was obtained in 76% yield after chromatographic purification. Acid-catalysed hydrolysis of compound **19** resulted in the formation of the secondary amine **20** that was immediately subjected to a Pictet–Spengler reaction using a mixture of paraformaldehyde and formic acid. Since this process appeared to produce a mixture of the two mono-formate ester derivatives of (+)-nangustine [(+)-**2**] the crude material obtained on workup was saponified using aqueous potassium hydroxide. The solid material thus produced was then recrystallised from *n*-propanol/hexane to give compound (+)-**2** (40% from **19**), the structure of which follows from a single-crystal X-ray analysis. The derived ORTEP plot is shown in Figure 2.

The MS, NMR and IR spectral data obtained on compound (+)-**2** were fully consistent with the assigned structure and in excellent agreement with those reported for the natural product (−)-**2**.[14] For example, the electron impact-induced mass spectral fragmentation patterns of the two materials were very similar (Table 1). The

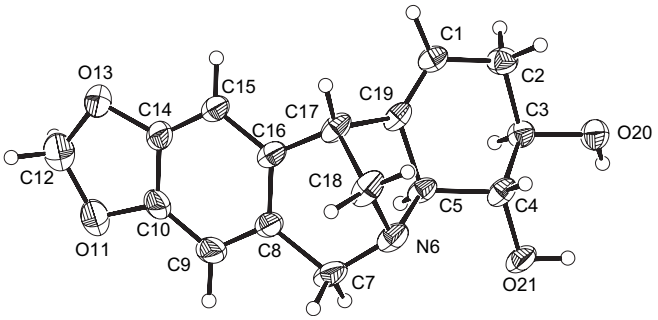


Figure 2. ORTEP plot derived from the single-crystal X-ray analysis of compound (+)-**2**.

origins of the lower intensities of the fragment ions observed in the spectrum of the synthetic material remain unclear at the present time but such variations between these types of data sets are not uncommon. An accurate mass measurement on the molecular ion observed in the electron impact-induced mass spectrum of the synthetic material established that it was of the expected molecular composition, viz. $C_{16}H_{17}NO_4$.

The ^{1}H and ^{13}C NMR spectral data derived from (+)-nangustine (*ent*-**2**) proved essentially identical with those recorded for the natural product[14] (Table 2). Furthermore, the specific rotation of

Table 1
Comparison of the 70 eV electron impact-induced mass spectral fragmentation patterns for naturally occurring (−)-nangustine [(−)-**2**] and synthetically-derived (+)-nangustine [(+)-**2**]

Synthetically-derived (+)-**2**[a]		Naturally occurring (−)-**2**[b,c]	
m/*z*	% of base peak	*m*/*z*	% of base peak
287 ($M^{+\cdot}$)	100	287 ($M^{+\cdot}$)	100
270	6	270	7
241	5	243	1
226	8	226	19
223	10	223	22
215	14	215	22
214	8	214	16
212	10	212	22
199	17	199	35
197	6	197	24
186	8	186	20
185	29	185	87
173	5	173	19
154	3	154	20
141	9	141	43
129	5	129	29
128	9	128	50
127	5	127	30
116	4	116	19
115	12	115	72
103	2	103	19
102	2	102	20
91	3	91	31
89	3	89	32
83	1	83	22
77	7	77	62
76	2	76	32
73	1	73	19
72	3	71	26
69	2	69	24
65	3	65	32
64	2	64	21
63	3	63	40
60	2	60	27
57	2	57	48
55	5	55	60
53	2	53	30
51	2	51	46

[a] Data recorded at 70 eV.
[b] Data derived from Ref. 14.
[c] Data recorded at 70 eV.

Table 2
Comparison of the ^{1}H and ^{13}C NMR data recorded for naturally occurring (−)-nangustine [(−)-**2**] and synthetically-derived (+)-nangustine [(+)-**2**]

^{13}C NMR (δ_C)		^{1}H NMR (δ_H)	
(−)-**2**[a]	(+)-**2**[b]	(−)-**2**[c]	(+)-**2**[d]
148.3	148.2	6.56 (s, 1H)	6.55 (s, 1H)
147.6	147.8	6.51 (s, 1H)	6.50 (s, 1H)
147.5	147.6	5.86 (d, *J*=1.5 Hz, 1H)	5.85 (d, *J*=1.2 Hz, 1H)
133.6	133.7	5.85 (d, *J*=1.5 Hz, 1H)	5.84 (d, *J*=1.2 Hz, 1H)
125.2	125.4	5.52 (dt, *J*=3.5 and 2.5 Hz, 1H)	5.50 (q, *J*=3.0 Hz, 1H)
114.7	114.5	4.32 (d, *J*=16.5 Hz, 1H)	4.29 (d, *J*=16.2 Hz, 1H)
108.3	108.3	3.83 (d, *J*=16.5 Hz, 1H)	3.80 (d, *J*=16.2 Hz, 1H)
107.8	107.7	3.62 (ddd, *J*=9.0, 9.0 and 7.0 Hz, 1H)	3.61 (m, 1H)
102.1	102.1	3.33 (br d, *J*=2.5 Hz, 1H) and 3.31 (t, *J*=9.0 Hz, 1H)	3.30 (br s, 2H) partially obscured by signals due to CD_3OD
75.5	75.6	3.16 (br d, *J*=9.0 Hz, 1H)	3.12 (br d, *J*=9.6 Hz, 1H)
72.3	72.3	3.03 (d, *J*=11.0 Hz, 1H)	3.00 (d, *J*=11.4 Hz, 1H)
70.0	69.9	2.94 (dd, *J*=11.0 and 2.0 Hz, 1H)	2.91 (dd, *J*=10.8 and 2.4 Hz, 1H)
62.0	62.1	2.57 (dddd, *J*=18.0, 7.0, 3.5 and 2.0 Hz, 1H)	2.56 (dddd, *J*=18.0, 6.9, 3.6 and 1.8 Hz, 1H)
56.9	56.9	2.05 (ddt, *J*=18.0, 9.0 and 3.5 Hz, 1H)	2.04 (m, 1H)
46.4	46.5	Signals due to OHs not observed	Signals due to OHs not observed
35.5	35.5		

[a] Data from Ref. 14 (recorded in CD_3OD at 50 MHz).
[b] Data from work reported in this paper (recorded in CD_3OD at 150 MHz).
[c] Data from Ref. 14 (recorded in CD_3OD at 600 MHz).
[d] Data from work reported in this paper (recorded in CD_3OD at 600 MHz).

(+)-nangustine {$[\alpha]_D$ +80.4 (*c* 0.44, methanol)} was of similar magnitude but opposite sign to that reported[14] for the naturally occurring or (−)-enantiomer {$[\alpha]_D$ −69.6 (*c* 0.35, methanol)}.

3. Summary and conclusions

The work presented herein serves to confirm that the structure of the novel montanine alkaloid (−)-nangustine has been correctly assigned. Furthermore, since the enantiomeric form, *ent*-**3**, of the *cis*-1,2-dihydrocatechol used as the starting material in this synthesis is also available,[25] the work described herein constitutes a formal total synthesis of the naturally occurring (−)-form of nangustine. It is also worth noting that the results of the present study, when considered alongside our related earlier work,[13,16b,17–19] highlight the considerable utility of microbially-derived *cis*-1,2-dihydrocatechols such as **3** in the construction of a range of alkaloids and/or their analogues, including those of the montanine-type. Current efforts in our laboratories are directed towards the total synthesis and biological evaluation of various other members of this rather interesting class of alkaloid.

4. Experimental section

4.1. General experimental procedures

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 18 °C in base-filtered $CDCl_3$ on a Varian Mercury or Inova 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei. In certain cases, a Varian Inova 600 spectrometer, operating at 600 MHz for proton and 150 MHz for carbon nuclei, was used. For ^{1}H NMR spectra, signals arising from the residual protio-forms of the solvent were used as the internal standards. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as: s=singlet; d=doublet; t=triplet; q=quartet; m=multiplet or combinations of the above. The residual $CHCl_3$ peak (δ 7.26), residual DMSO peak (δ 2.50) and the residual MeOH peak (δ 3.30) were used as references for ^{1}H NMR spectra. The central peak (δ 77.0) of the $CDCl_3$ 'triplet' and the central peak (δ 49.3) of the CD_3OD 'heptet' were used as references for proton-decoupled ^{13}C NMR spectra. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer. Samples were analysed as KBr disks (for solids) or as thin films on NaCl plates (for oils). A VG Fisons AutoSpec mass spectrometer was used to obtain low- and high-resolution electron impact (EI) mass spectra. Low- and high-resolution electrospray (ESI) mass spectra were obtained on a VG Quattro II triple-quadrupole MS instrument operating in positive ionisation mode. Optical rotations were measured at 18 °C with a Perkin–Elmer 241 polarimeter at the sodium-D line (589 nm) and the concentrations (*c*) (g/100 mL) indicated using spectroscopic grade solvents. The measurements were carried out in a cell with a path length (*l*) of 1 dm. Specific rotations $[\alpha]_D$ were calculated using the equation $[\alpha]_D=100\,a/(c\,l)$ and are given in 10^{-1} deg cm^2 g^{-1}. Melting points were measured on an Optimelt automated melting point system or a Reichert hot-stage microscope apparatus and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminium-backed 0.2 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualised using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (concd)/water (37.5 g:7.5 g:37.5 g:720 mL) or potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g:20 g:5 mL:300 mL). The retardation factor (R_f) values cited here have been rounded at the first decimal point. Flash chromatographic separations were carried out following protocols defined by Still et al.[26] with silica gel 60 (0.040–0.0063 mm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from the Sigma–Aldrich, Merck, TCI, Strem or Lancaster Chemical Companies and were used as supplied. Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium benzophenone ketyl. Methanol was distilled from its magnesium alkoxide salt. Benzene and toluene were distilled from sodium wire. Dichloromethane was distilled from calcium hydride. Triethylamine was distilled from and stored over potassium hydroxide pellets. Where necessary, reactions were performed under a nitrogen or argon atmosphere.

4.2. Specific procedures

*4.2.1. (2S,3aS,5aR,6aR,6bS)-4-Chloro-3a,5a,6a,6b-tetrahydro-2-(4-methoxyphenyl)-7-oxabicyclo[4.1.0]hepta-1(6),2-dieno[5,4-d][1,3]dioxole (**5**)*

A magnetically stirred suspension of *cis*-1,2-dihydrocatechol **3** (10.0 g, 68.3 mmol) and *p*-methoxybenzaldehyde dimethyl acetal

(*p*-BDMA) (12.8 mL, 75.1 mmol) in anhydrous CH_2Cl_2 (150 mL) was cooled to −20 °C then treated with (1*S*)-(+)-camphor-10-sulfonic acid monohydrate (CSA·H_2O) (1.58 g, 6.82 mmol). After 1 h, at which point TLC analysis indicated that all of the starting material had been consumed, the reaction mixture was quenched with sodium hydroxide (200 mL of a 2 M aqueous solution) and the separated aqueous phase was extracted with CH_2Cl_2 (2×200 mL). The combined organic fractions were then washed with brine (1×100 mL) before being dried ($MgSO_4$) and filtered to give a clear and transparent solution that was cooled to 0 °C, treated with *m*-CPBA (30.6 g, 136.5 mmol) then stirred at 0–18 °C for 18 h. The ensuing mixture was treated with sodium metabisulfite (300 mL of a 20% w/v aqueous solution) and the separated aqueous fraction was extracted with CH_2Cl_2 (2×100 mL). The combined organic fractions were washed with $NaHCO_3$ (1×200 mL of a saturated aqueous solution) and brine (1×200 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an oily residue. Subjection of this material to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of appropriate fractions (R_f=0.5; silica, 3:7 v/v ethyl acetate/hexane elution) afforded the *title compound* ***5*** (14.2 g, 75%) as a white, crystalline solid, mp=67–69 °C. [Found: $(M+H)^+$, 281.0590; C, 60.31; H, 4.69. $C_{14}H_{13}^{35}ClO_4$ requires $(M+H)^+$, 281.0581; C, 59.90; H, 4.67%]. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.39 (2H, d, *J*=8.9 Hz), 6.91 (2H, d, *J*=8.9 Hz), 6.28 (1H, dd, *J*=4.2 and 0.9 Hz), 5.96 (1H, s), 4.93 (1H, m), 4.47 (1H, dd, *J*=7.5 and 0.3 Hz), 3.81 (3H, s), 3.64 (1H, m), 3.41 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 160.7, 136.7, 128.3, 128.0, 122.6, 113.8, 105.4, 73.8, 72.9, 55.2, 48.9, 47.7; ν_{max} (NaCl) 3005, 2906, 2838, 1648, 1614, 1589, 1518, 1463, 1437, 1399, 1360, 1304, 1251, 1172, 1082, 1031, 989, 829 cm^{-1}; *m*/*z* (ESI) 283 and 281 [$(M+H)^+$, both <1%], 147 and 145 (4 and 13), 137 (57), 109 (100), 81 (25).

4.2.2. (1R,2S,3S)-3-(4-Methoxybenzyloxy)-4-chlorocyclohex-4-ene-1,2-diol (*6*)

A magnetically stirred solution of epoxide **5** (14.2 g, 50.6 mmol) in anhydrous toluene (300 mL) was cooled to −60 °C then treated with DIBAL-H (350 mL of a 1 M solution in toluene, 350 mmol). The ensuing solution was allowed to warm to −30 °C and after 7 h, at which point TLC analysis indicated that all the starting material had been consumed, the reaction mixture was quenched with sodium potassium tartrate (200 mL of a saturated aqueous solution) [*Caution*: exothermic reaction] and the ensuing mixture was then allowed to warm to 18 °C over a period of 10 h. The separated aqueous fraction was extracted with toluene (3×200 mL) and the combined organic fractions were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, colourless oil. Subjection of this material to flash chromatography (silica, hexane→3:2 v/v ethyl acetate/hexane gradient elution) and concentration of appropriate fractions (R_f=0.4; silica, 3:2 v/v ethyl acetate/hexane elution) afforded the *title compound* ***6*** (6.1 g, 42%) as a clear, colourless oil, $[\alpha]_D$ −56.3 (*c* 2.4, $CHCl_3$). [Found: $M^{+\bullet}$, 284.0815. $C_{14}H_{17}^{35}ClO_4$ requires $M^{+\bullet}$, 284.0815]. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.23 (2H, d, *J*=8.6 Hz), 6.83 (2H, d, *J*=8.6 Hz), 5.81 (1H, m), 4.89 (1H, d, *J*=11 Hz), 4.59 (1H, d, *J*=11 Hz), 4.04 (1H, d, *J*=4.8 Hz), 3.78–3.71 (1H, obscured m), 3.74 (3H, s), 3.49 (1H, m), 2.56 (2H, partially obscured m), 2.51 (1H, partially obscured m), 1.99 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 159.5, 129.9, 129.6, 126.6, 113.9, 78.6, 75.0, 73.7, 66.7, 55.2, 32.4 (one signal obscured or overlapping); ν_{max} (NaCl) 3401, 2909, 1612, 1514, 1464, 1440, 1341, 1302, 1249, 1174, 1102, 1034, 823 cm^{-1}; *m*/*z* (EI, 70 eV) 286 and 284 ($M^{+\bullet}$, 2 and 8%), 137 (21), 121 (100), 109 (7), 78 (8), 77 (8), 65 (5).

4.2.3. 1-{[(1S,5R,6S)-2-Chloro-5,6-bis(methoxymethoxy)cyclohex-2-enyloxy]methyl}-4-methoxybenzene (*7*)

A magnetically stirred solution of diol **6** (190 mg, 0.67 mmol) in anhydrous THF (40 mL) was treated, whilst being maintained at 18 °C, with sodium hydride (60 mg of a 60% w/w mixture with paraffin oil, 1.40 mmol) then triethylamine (194 μL, 1.47 mmol). The ensuing mixture was heated to 65 °C then, after 10 min at this temperature, cooled to 0 °C and methoxymethyl chloride (MOM-Cl) (106 μL, 1.40 mmol) was added dropwise. After the addition was complete, the reaction mixture was re-warmed to 18 °C then kept at this temperature for 0.5 h. This protocol was repeated once more and the resulting mixture then quenched with water (25 mL) [*Caution*: exothermic reaction]. The separated aqueous phase was extracted with ethyl acetate (2×30 mL) and the combined organic fractions were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow residue. This material was subjected, once more, to the reaction conditions outlined above and, after workup in the usual fashion, a yellow residue was obtained. Subjection of this material to flash chromatography (silica, hexane→2:3 v/v ethyl acetate/hexane gradient elution) and concentration of appropriate fractions (R_f=0.3; silica, 2:3 v/v ethyl acetate/hexane elution) under reduced pressure afforded the *title compound* **7** (214 mg, 86%) as clear, light-yellow oil, $[\alpha]_D$ −64.8 (*c* 1.02, $CHCl_3$). [Found: $(M+Na)^+$, 395.1235. $C_{18}H_{25}^{35}ClO_6$ requires $(M+Na)^+$, 395.1237]. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.35 (2H, d, *J*=8.6 Hz), 6.86 (2H, d, *J*=8.6 Hz), 5.79 (1H, m), 4.91–4.62 (6H, complex m), 4.18–4.02 (2H, complex m), 3.87 (1H, m), 3.78 (3H, s), 3.40 (3H, s), 3.34 (3H, s), 2.64 (1H, dm, *J*=18.0 Hz), 2.14 (1H, dm, *J*=18.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 159.1, 130.3, 129.8, 129.6, 125.3, 113.5, 96.7, 96.6, 77.6, 77.4, 74.1, 72.1, 55.6, 55.3, 55.1, 32.0; ν_{max} (NaCl) 2933, 2894, 1612, 1514, 1465, 1441, 1302, 1249, 1151, 1118, 1038, 917, 824 cm^{-1}; *m*/*z* (ESI) 397 and 395 [$(M+Na)^+$, 14 and 39%], 241 (4), 121 (100).

4.2.4. (1S,5R,6R)-2-Chloro-5,6-bis(methoxymethoxy)cyclohex-2-enol (*8*)

A magnetically stirred solution of PMB ether **7** (190 mg, 0.51 mmol) in CH_2Cl_2/water (50 mL of a 3:1 v/v mixture) maintained at 18 °C was treated with DDQ (162 mg, 0.71 mmol) and after 18 h, at which point TLC analysis indicated that all of the starting material had been consumed, the reaction mixture was treated with water (40 mL) and extracted with CH_2Cl_2 (3×40 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an orange oil. Subjection of this material to flash chromatography (silica, hexane→3:7 v/v ethyl acetate/hexane gradient elution) and concentration of the appropriate fractions (R_f=0.3; silica, 2:3 v/v ethyl acetate/hexane elution) afforded the *title alcohol* ***8*** (104 mg, 81%) as a clear, colourless oil, $[\alpha]_D$ −15.9 (*c* 0.98, $CHCl_3$). [Found: $(M-H_2O)^{+\bullet}$, 234.0664. $C_{10}H_{17}^{35}ClO_5$ requires $(M-H_2O)^{+\bullet}$, 234.0659]. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.81 (1H, m), 4.84–4.64 (4H, complex m), 4.32 (1H, m), 4.00 (1H, m), 3.82 (1H, m), 3.40 (3H, s), 3.34 (3H, s), 2.99 (1H, br s), 2.58 (1H, dm, *J*=18.3 Hz), 2.15 (1H, dm, *J*=18.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 130.7, 124.9, 97.1, 96.4, 78.3, 71.4, 70.1, 55.8, 55.4, 31.1; ν_{max} (NaCl) 3450, 2930, 2897, 1654, 1441, 1215, 1151, 1111, 1038, 988, 917 cm^{-1}; *m*/*z* (EI, 70 eV) 236 and 234 [$(M-H_2O)^{+\bullet}$, <1 and 2%], 221 (5), 207 (10), 190 (35), 175 (29), 161 (33), 148 (100), 145 (43), 129 (40), 119 (43), 101 (35), 95 (20), 89 (13), 81 (16), 72 (35), 65 (30), 53 (28), 45 (91), 39 (23).

4.2.5. (1S,5R,6S)-2-Chloro-5,6-bis(methoxymethoxy)cyclohex-2-enyl methanesulfonate (*9*)

A magnetically stirred solution of alcohol **8** (4.0 g, 15.9 mmol), triethylamine (5.5 mL, 39.7 mmol) and DMAP (194 mg, 1.58 mmol) in anhydrous CH_2Cl_2 (160 mL) was cooled to 0 °C then treated, dropwise, with methanesulfonyl chloride (MsCl) (3.1 mL, 39.7 mmol). After 3 h, at which point TLC analysis indicated that all starting material had been consumed, the reaction mixture was warmed to 18 °C then treated with $NaHCO_3$ (300 mL of a saturated

aqueous solution) and the resulting mixture was extracted with CH_2Cl_2 (2×100 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude *title compound* ***9*** as viscous, yellow oil (R_f=0.4; silica, 2:3 v/v ethyl acetate/hexane elution). [Found: $(M+Na)^+$, 353.0489. $C_{11}H_{19}^{35}ClO_7S$ requires $(M+Na)^+$, 353.0438]. ^1H NMR (300 MHz, $CDCl_3$) δ_H 5.97 (1H, m), 5.21 (1H, d, J=3.0 Hz), 4.75–4.60 (4H, complex m), 3.93 (2H, m), 3.38 (3H, s), 3.31 (3H, s), 3.11 (3H, s), 2.65 (1H, dm, J=18.6 Hz), 2.17 (1H, dm, J=18.6 Hz); *m*/*z* (ESI) 355 and 353 [$(M+Na)^+$, <1 and 1%], 257 (4), 123 (99), 102 (100), 74 (47).

This rather unstable material was used, without purification, in the next step of the reaction sequence.

4.2.6. (4R,5R,6R)-6-Azido-1-chloro-4,5-bis(methoxymethoxy)-cyclohex-1-ene (*10*)

A magnetically stirred solution of mesylate **9** in anhydrous DMF (200 mL) was kept at 18 °C then treated with sodium azide (3.1 g, 47.6 mmol). After 15 h, at which point TLC analysis indicated that staring material had been consumed, the reaction mixture was treated with water (600 mL) and extracted with diethyl ether (4×200 mL). The combined organic fractions were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an orange oil. Subjection of this material to flash chromatography (silica, neat hexane→1:9 v/v ethyl acetate/hexane gradient elution) and concentration of appropriate fractions (R_f=0.6; silica, 3:2 v/v ethyl acetate/hexane elution) afforded the *title compound* ***10*** (3.97 g, 90%) as a clear, colourless oil, $[\alpha]_D$+144.8 (*c* 1.26, $CHCl_3$). [Found: $(M+Na)^+$, 300.0734. $C_{10}H_{16}^{35}ClN_3O_4$ requires $(M+Na)^+$, 300.0727]. ^1H NMR (300 MHz, $CDCl_3$) δ_H 5.90 (1H, m), 4.78–4.61 (4H, complex m), 3.79 (3H, m), 3.37 (3H, s), 3.32 (3H, s), 2.48 (1H, dm, J=17.7 Hz), 2.20 (1H, dm, J=17.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 127.9, 125.9, 97.1, 95.9, 78.1, 72.0, 65.5, 56.0, 55.6, 30.0; ν_{max} (NaCl) 2934, 2895, 2105, 1467, 1445, 1329, 1152, 1109, 1039, 1011, 918 cm^{-1}; *m*/*z* (ESI) 302 and 300 [$(M+Na)^+$, 5 and 14%], 258 (5), 220 and 218 (8 and 22), 188 (12), 158 and 156 (28 and 42), 128 (65), 101 (100), 99 (42), 93 (39), 65 (70), 60 (85).

4.2.7. (1R,5R,6R)-2-Chloro-5,6-bis(methoxymethoxy)cyclohex-2-enamine (*11*)

A magnetically stirred solution azide **10** (400 mg, 1.44 mmol) in THF/water (50 mL of a 4:1 v/v mixture) maintained at 18 °C was treated with polymer-supported PPh_3 (886 mg, 1.90 mmol) then heated at 65 °C. After 15 h, when TLC analysis indicated that all the starting material had been consumed, the reaction mixture was cooled to 18 °C and filtered through a pad of Celite®. The resulting filtrate was diluted with water (100 mL), extracted with diethyl ether (3×100 mL) and the combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the *title compound* ***11*** (305 mg, 84%) as a clear, light-yellow oil, $[\alpha]_D$+75.7 (*c* 1.87, $CHCl_3$) (R_f=0.3; silica, 1:11:8 v/v MeOH/ethyl acetate/$CHCl_3$ elution). [Found: $(M+H)^+$, 252.1000. $C_{10}H_{18}^{35}ClNO_4$ requires $(M+H)^+$, 252.1003]. ^1H NMR (300 MHz, $CDCl_3$) δ_H 5.74 (1H, m), 4.77 (2H, d, J=1.2 Hz), 4.71 (1H, d, J=6.8 Hz), 4.65 (1H, d, J=6.8 Hz), 3.92 (1H, m), 3.85 (1H, m), 3.40 (3H, s), 3.37 (3H, s), 2.52 (1H, dm, J=18.0 Hz), 2.26 (1H, dm, J=18.0 Hz), 2.10 (2H, br s) (one signal obscured or overlapping); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 134.1, 120.8, 96.8, 95.5, 80.1, 72.2, 56.3, 55.6, 55.3, 29.4; ν_{max} (NaCl) 3384, 3307, 2931, 2894, 1653, 1586, 1469, 1441, 1214, 1150, 1104, 1035, 992, 917 cm^{-1}; *m*/*z* (ESI) 254 and 252 [$(M+H)^+$, 6 and 20%], 222 and 220 (32 and 100), 190 (49), 188 (49), 178 and 176 (7 and 21).

4.2.8. (1R,5R,6R)-N-(4-Methoxybenzyl)-2-chloro-5,6-bis-(methoxymethoxy)cyclohex-2-enamine (*12*)

A magnetically stirred solution of primary amine **11** (620 g, 2.46 mmol) and *p*-MBA (894 μL, 7.38 mmol) in anhydrous toluene (100 mL) maintained at 18 °C was treated with activated molecular sieves 4 Å (~2 g) and the ensuing mixture heated at 120 °C in an apparatus fitted with a Dean–Stark trap. After 34 h, at which point TLC analysis indicated that all the starting material had been consumed, the reaction mixture was cooled to 18 °C, filtered through a pad of Celite® and the resulting filtrate concentrated under reduced pressure to give a yellow oil containing the imine derivative of compound **11**. A magnetically stirred solution of this material in anhydrous CH_2Cl_2 (20 mL) was cooled to 0 °C then treated with $NaBH(OAc)_3$ (930 mg, 4.92 mmol) and the ensuing mixture allowed to warm to 18 °C. After 20 h at this temperature the reaction mixture was treated with water (20 mL) and sodium hydroxide (20 mL of a 2 M aqueous solution) then stirred for 5 min at 18 °C. The separated aqueous phase was extracted with CH_2Cl_2 (3×20 mL) and the combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (silica, hexane→2:3 v/v ethyl acetate/hexane gradient elution) and concentration of appropriate fractions (R_f=0.8; silica, 2:3 v/v ethyl acetate/hexane elution) afforded the *title compound* ***12*** (578 mg, 63%) as a viscous, colourless oil, $[\alpha]_D$+48.9 (*c* 2.00, $CHCl_3$). [Found: $(M+H)^+$, 372.1580. $C_{18}H_{26}^{35}ClNO_5$ requires $(M+H)^+$, 72.1578]. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.31 (2H, d, J=8.7 Hz), 6.84 (2H, d, J=8.7 Hz), 5.83 (1H, m), 4.76 (2H, q, J=6.6 Hz), 4.71 (1H, d, J=6.9 Hz), 4.65 (1H, d, J=6.9 Hz), 3.98 (1H, m), 3.87 (1H, m), 3.81 (1H, m), 3.77 (3H, s), 3.71 (1H, d, J=12.1 Hz), 3.36 (3H, s), 3.35 (3H, s), 3.32 (1H, m), 2.49 (1H, dm, J=17.7 Hz), 2.22 (1H, dm, J=17.7 Hz), 2.11 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 158.5, 132.8, 132.1, 129.5, 123.2, 113.6, 96.8, 95.8, 75.7, 73.3, 62.0, 55.7, 55.4, 55.1, 49.0, 29.8; ν_{max} (NaCl) 3347, 2933, 2894, 2836, 1611, 1513, 1464, 1442, 1301, 1247, 1150, 1106, 1036, 917, 833 cm^{-1}; *m*/*z* (ESI) 396 and 394 [$(M+Na)^+$, 38 and 80%], 378 (19), 360 (50), 338 (26), 306 (5), 201 (11), 181 (10), 121 (100).

4.2.9. (1R,2R,6R)-2-(4-Methoxybenzylamino)-3-chloro-6-(methoxymethoxy)cyclohex-3-enol (*13*) and (1R,5R,6R)-5-(4-methoxybenzylamino)-4-chloro-6-(methoxymethoxy)cyclohex-3-enol (*14*)

A magnetically stirred solution of primary amine **11** (1.00 g, 3.97 mmol) and *p*-MBA (482 μL, 3.97 mmol) in anhydrous benzene (100 mL) maintained at 18 °C was treated with activated molecular sieves 4 Å (~10 g) and the ensuing mixture heated at 80 °C in an apparatus fitted with a Dean–Stark trap. After 14 h, at which point TLC analysis indicated that all the starting material had been consumed, the reaction mixture was cooled to 18 °C, filtered through a pad a Celite® and the resulting filtrate was concentrated under reduced pressure to give a yellow oil containing the imine derivative of compound **11**. A magnetically stirred solution of this material in anhydrous toluene (100 mL) was cooled to 0 °C then treated with DIBAL-H (20 mL of a 1 M solution in toluene, 20.0 mmol) and the ensuing mixture allowed to warm to 18 °C. After 14 h at this temperature the reaction mixture was quenched with sodium potassium tartrate (40 mL of a saturated aqueous solution) [*Caution*: exothermic reaction]. Stirring was continued at 18 °C for 16 h then the separated aqueous phase was extracted with toluene (2×50 mL) and the combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow residue. Subjection of this material to flash chromatography (silica, hexane→2:3 v/v ethyl acetate/hexane gradient elution) provided fractions **A** and **B**.

Concentration of fraction **A** (R_f=0.5; silica, 2:3 v/v ethyl acetate/hexane elution) afforded the *title compound* ***13*** (190 mg, 22%) as a white, crystalline solid, mp=85–87 °C, $[\alpha]_D$+59.7 (*c* 1.60, $CHCl_3$). [Found: $(M+H)^+$, 328.1316. $C_{16}H_{22}^{35}ClNO_4$ requires $(M+H)^+$, 328.1316]. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.29 (2H, d, J=8.7 Hz), 6.85 (2H, d, J=8.7 Hz), 5.86 (1H, m), 4.81 (1H, d, J=6.8 Hz), 4.74 (1H, d, J=6.8 Hz), 3.85–3.62 (7H, complex m), 3.43 (1H, m), 3.40 (3H, s),

2.55 (1H, dm, J=17.4 Hz), 2.18 (1H, dm, J=17.4 Hz) (two signals obscured or overlapping); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 158.6, 132.5, 132.0, 129.6, 124.2, 113.7, 96.6, 76.6, 72.4, 63.8, 55.6, 55.2, 47.8, 31.1; ν_{max} (NaCl) 3436, 3350, 2930, 2905, 2836, 1612, 1513, 1464, 1301, 1248, 1106, 1034, 842 cm^{-1}; m/z (ESI) 352 and 350 [$(M+Na)^+$, 45 and 100%], 330 and 328 [$(M+H)^+$, 5 and 15], 121 (70).

Concentration of fraction **B** (R_f=0.7; silica, 2:3 v/v ethyl acetate/hexane elution) afforded the *title compound* ***14*** (510 mg, 58%) as a clear, colourless oil, $[\alpha]_D$+33.1 (c 0.88, $CHCl_3$). [Found: $(M+H)^+$, 328.1318. $C_{16}H_{22}^{35}ClNO_4$ requires $(M+H)^+$, 328.1316]. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.25 (2H, d, J=8.7 Hz), 6.87 (2H, d, J=8.7 Hz), 5.93 (1H, m), 4.68 (2H, q, J=6.8 Hz), 4.08 (1H, m), 4.02 (1H, m), 3.92 (1H, d, J=12.9 Hz), 3.80 (3H, s), 3.73 (1H, d, J=12.9 Hz), 3.36 (3H, s), 2.52 (1H, dm, J=18.3 Hz), 2.33 (1H, dm, J=18.3 Hz) (three signals obscured or overlapping); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 159.0, 130.4, 129.6, 129.5, 125.4, 113.9, 96.3, 73.5, 66.4, 61.2, 55.7, 55.2, 50.6, 32.0; ν_{max} (NaCl) 3306, 2904, 2837, 1611, 1513, 1463, 1248, 1177, 1150, 1106, 1037, 990, 917, 832 cm^{-1}; m/z (ESI) 352 and 350 [$(M+Na)^+$, 35 and 100%], 330 and 328 [$(M+H)^+$, <1 and 2], 122 (2).

*4.2.10. N-(4-Methoxybenzyl)-2-{benzo[d][1,3]dioxol-6-yl}-N-[(1R,5R,6R)-2-chloro-5,6-bis(methoxymethoxy)cyclohex-2-enyl]-2-(phenylthio)acetamide (**16**)*

A magnetically stirred solution of acid **15**[22] (210 mg, 0.72 mmol) in anhydrous toluene (10 mL) maintained at 18 °C was treated with thionyl chloride ($SOCl_2$) (210 μL, 2.89 mmol) and the ensuing mixture heated at 120 °C for 3 h. The reaction mixture was then cooled to 18 °C and concentrated under reduced pressure to give a brown residue containing the acid chloride derivative of compound **15**. A solution of this material in CH_2Cl_2 (3 mL) was then added, via syringe pump over 0.25 h, to a magnetically stirred mixture of secondary amine **12** (179 mg, 0.48 mmol) and sodium hydroxide (5 mL of a 2.5 M aqueous solution) in CH_2Cl_2 (10 mL) that had been cooled to 0 °C. After stirring at this temperature for 1 h, the reaction mixture was allowed to warm to 18 °C and kept stirring at this temperature for 40 h at which point TLC analysis indicated that all of secondary amine **12** had been consumed. Accordingly, the reaction mixture was treated with CH_2Cl_2 (50 mL) and water (20 mL) then sufficient HCl (2 M aqueous solution) to establish a pH of ca. 0–1 (ca. 5 mL required). The mixture was then treated with sufficient sodium hydroxide (2 M aqueous solution) to establish a pH of ca. 9–10 (ca. 6 mL required). The separated aqueous phase was extracted with CH_2Cl_2 (2×40 mL) and the combined organic fractions were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow residue. Subjection of this material to flash chromatography (silica, hexane→3:7 v/v ethyl acetate/hexane gradient elution) and concentration of appropriate fractions (R_f=0.4; silica, 3:7 v/v ethyl acetate/hexane elution) then afforded the *title compound* ***16*** (242 mg, 78%) as a white foam. [Found: $(M+H)^+$, 642.1931. $C_{33}H_{36}^{35}ClNO_8S$ requires $(M+H)^+$, 642.1928]. ν_{max} (NaCl) 2933, 2896, 2837, 1649, 1611, 1512, 1486, 1441, 1407, 1303, 1247, 1176, 1152, 1108, 1037, 919, 734 cm^{-1}; m/z (ESI) 666 and 664 [$(M+Na)^+$, 43 and 100%], 644 and 642 [$(M+H)^+$, 40 and 88], 534 and 532 (7 and 20), 502 and 500 (5 and 18), 490 and 488 (4 and 12), 458 and 456 (4 and 11), 382 and 380 (1 and 3), 130 (8), 121 (13), 102 (24).

*4.2.11. (3R,6R,7R,7aS)-1-(4-Methoxybenzyl)-3-{benzo[d][1,3]dioxol-6-yl}-5,6,7,7a-tetrahydro-6,7-bis(methoxymethoxy)-1H-indol-2(3H)-one (**17**)*

A magnetically stirred mixture of amide **16** (205 mg, 0.312 mmol) and n-Bu_6Sn_2 (400 μL, 0.798 mmol) in anhydrous benzene (750 mL) was degassed (3×freeze-pump-thaw method) and then maintained under an argon atmosphere. The ensuing mixture was heated to 80 °C then treated, via syringe pump over 3 h, with a degassed solution of n-Bu_3SnH (127 μL, 0.479 mmol) and AIBN (26 mg, 0.159 mmol) in anhydrous benzene (3 mL). The resulting mixture was cooled and concentrated under reduced pressure to give a yellow residue. Subjection of this material to flash chromatography (silica, hexane→2:3 v/v ethyl acetate/hexane gradient elution) and concentration of appropriate fractions (R_f=0.2; silica, 2:3 v/v ethyl acetate/hexane elution) provided the *title compound* ***17*** (142 mg, 88%) as an opaque, viscous oil. [Found: $(M+H)^+$, 498.2132. $C_{27}H_{31}NO_8$ requires $(M+H)^+$, 498.2128]. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H ($CDCl_3$) 7.19 (2H, d, J=8.6 Hz), 6.77 (2H, d, J=8.6 Hz), 6.66 (1H, d, J=8.0 Hz), 6.57 (1H, d, J=1.5 Hz), 6.53 (1H, d, J=8.0 Hz), 5.90 (2H, m), 5.65 (1H, m), 5.06 (1H, d, J=14.4 Hz), 4.88 (2H, q, J=5.7 Hz), 4.72 (2H, q, J=6.9 Hz), 4.52 (1H, d, J=14.4 Hz), 4.09 (1H, m), 4.02 (1H, s), 3.81 (1H, m), 3.77 (3H, s), 3.70 (1H, m), 3.46 (3H, s), 3.37 (3H, s), 3.69 (1H, m), 2.28 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 174.8, 158.8, 147.9, 146.7, 133.1, 131.8, 129.8, 129.0, 121.9, 120.2, 113.6, 108.2, 107.8, 101.0, 98.6, 96.5, 81.9, 59.9, 57.0, 55.6, 55.2, 51.4, 44.4, 33.1, 29.6; ν_{max} (NaCl) 2954, 2925, 2853, 1707, 1686, 1611, 1512, 1488, 1441, 1247, 1176, 1151, 1109, 1035, 930, 812 cm^{-1}; m/z (ESI) 520 [$(M+Na)^+$, 100%], 498 [$(M+H)^+$, <1].

*4.2.12. (3R,6R,7R,7aS)-1-(4-Methoxybenzyl)-3-{benzo[d][1,3]dioxol-6-yl}-2,3,5,6,7,7a-hexahydro-6,7-bis(methoxymethoxy)-1H-indole (**18**)*

A magnetically stirred suspension of aluminium trichloride ($AlCl_3$) (860 mg, 6.44 mmol) in anhydrous THF (20 mL) was cooled to −20 °C then treated, dropwise, with $LiAlH_4$ (6.44 mL of a 1 M solution in THF, 6.44 mmol) before being allowed to warm to 18 °C. After 2 h at this temperature a solution of lactam **17** (210 mg, 0.42 mmol) in anhydrous THF (10 mL) was added, dropwise, and the ensuing mixture was stirred at 18 °C for 13 h. TLC analysis of the reaction mixture after this time indicated that all the starting material had been consumed so it was treated with sodium potassium tartrate (10 mL of a saturated aqueous solution) [*Caution*: exothermic reaction] and stirring continued at 18 °C for 2 h. The separated aqueous phase was extracted with diethyl ether (3×60 mL) and the combined organic fractions were washed with brine (1×20 mL) and ammonium chloride (1×20 mL of a saturated aqueous solution) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford *title compound* ***18*** (201 mg, 98%) as an opaque, viscous oil (R_f=0.4; silica, 2:3 v/v ethyl acetate/hexane elution). [Found: $(M+H)^+$, 484.2329. $C_{27}H_{33}NO_7$ requires $(M+H)^+$, 484.2335]. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.20 (2H, d, J=8.7 Hz), 6.75 (2H, d, J=8.7 Hz), 6.60 (1H, d, J=8.0 Hz), 6.53 (1H, d, J=1.8 Hz), 6.50 (1H, dd, J=8.0 and 1.8 Hz), 5.82 (2H, s), 5.22 (1H, m), 4.93 (1H, d, J=6.2 Hz), 4.85 (1H, d, J=6.2 Hz), 4.73 (1H, d, J=6.8 Hz), 4.66 (1H, partially obscured d, J=6.8 Hz), 4.63 (1H, partially obscured m), 3.85–3.72 (2H, complex m), 3.70 (3H, s), 3.56 (1H, br m), 3.36 (3H, s), 3.32 (3H, s), 3.23–3.10 (3H, complex m), 2.58 (1H, m), 2.15 (1H, m) (one signal obscured or overlapping); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 158.5, 147.6, 145.9, 142.6, 137.1, 130.1, 127.0, 120.9, 118.6, 113.5, 108.0, 100.8, 98.6, 96.4, 83.2, 68.5, 63.4, 59.7, 56.7, 55.4, 55.1, 45.7, 33.2, 29.6 (one signal obscured or overlapping); ν_{max} (NaCl) 2924, 2851, 1611, 1511, 1487, 1441, 1374, 1247, 1148, 1107, 1035, 918, 810 cm^{-1}; m/z (ESI) 484 [$(M+H)^+$, 100%], 452 (10), 362 (10), 332 (5), 300 (7), 254 (6), 121 (83).

*4.2.13. (3R,6R,7R,7aS)-3-{Benzo[d][1,3]dioxol-6-yl}-2,3,5,6,7,7a-hexahydro-6,7-bis(methoxymethoxy)indole-1-carbonyl chloride (**19**)*

A magnetically stirred solution of tertiary amine **18** (200 mg, 0.413 mmol) and pyridine (134 μL, 1.65 mmol) in anhydrous CH_2Cl_2 (20 mL) was cooled to 0 °C then treated with triphosgene (245 mg, 0.826 mmol). The ensuing mixture was allowed to warm to 18 °C and after 10 h at this temperature it was concentrated under reduced pressure to give a brown residue that was subjected to flash

chromatography (silica, 1:9→3:7 v/v ethyl acetate/hexane gradient elution). Concentration of appropriate fractions (R_f=0.2; silica, 3:7 v/v ethyl acetate/hexane elution) then afforded the *title compound* ***19*** (134 mg, 76%) as an opaque, viscous oil. [Found: $(M+Na)^+$, 448.1145. $C_{20}H_{24}^{35}ClNO_7$ requires $(M+Na)^+$, 448.1139]. ^1H NMR (300 MHz, $CDCl_3$) δ_H 6.75 (1H, d, J=7.8 Hz), 6.65 (1H, d, J=1.5 Hz), 6.61 (1H, dd, J=7.8 and 1.5 Hz), 5.94 (2H, s), 5.76 (1H, m), 4.86 (1H, d, J=6.8 Hz), 4.80 (1H, d, J=7.1 Hz), 4.74 (1H, d, J=7.1 Hz), 4.68 (1H, d, J=6.8 Hz), 4.51 (1H, br s), 4.33 (1H, d, J=10.8 Hz), 3.98 (1H, m), 3.75 (3H, br s), 3.41 (3H, s), 3.37 (3H, s), 2.75 (1H, br m), 2.31 (1H, m) (one signal obscured or overlapping); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 148.1, 146.6, 137.9, 133.5, 121.5, 119.1, 108.4, 106.9, 101.0, 97.1, 96.4, 78.4, 74.9, 61.6, 57.4, 56.0, 55.4, 47.2, 32.3 (one signal obscured or overlapping); ν_{max} (NaCl) 2895, 1746, 1503, 1489, 1440, 1366, 1320, 1253, 1235, 1149, 1105, 1032, 918 cm^{-1}; m/z (ESI) 450 and 448 [$(M+Na)^+$, 15 and 45%], 444 (100), 394 (5), 390 (20), 314 (28), 298 (30), 284 (10), 101 (10), 80 (39).

4.2.14. (+)-Nangustine [(+)-*2*]

A magnetically stirred solution of carbamoyl chloride **19** (130 mg, 0.305 mmol) in dioxane/water (20 mL of a 1:1 v/v mixture) maintained at 18 °C was treated with HCl (drop of a concentrated aqueous solution) then heated at 70 °C. After 21 h at this temperature, the reaction mixture was cooled to 18 °C, treated with water (20 mL) and sodium hydrogen carbonate (20 mL of a saturated aqueous solution) then extracted with ethyl acetate (3×30 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a grey residue presumably containing compound **20**. A magnetically stirred solution of this material in formic acid (10 mL) maintained at 18 °C was treated with paraformaldehyde (80 mg, 2.54 mmol) and the ensuing mixture heated at 80 °C for 16 h then cooled to 18 °C, diluted with water (100 mL), treated with sufficient sodium hydroxide (2 M aqueous solution) to attain a pH of ca. 9 then extracted with ethyl acetate (5×50 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a brown residue. A magnetically stirred solution of this material in MeOH (20 mL) maintained at 18 °C was treated with potassium hydroxide (5 mL of a 2.5 M aqueous solution) and after 3 h the reaction mixture was diluted with water (100 mL) and treated with sufficient HCl (1 M) aqueous solution to attain a pH of ca. 7–8 then extracted with ethyl acetate (5×50 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-brown solid. Recrystallisation (*n*-propanol/hexane) of this material then afforded the *title compound (+)-**2*** (35 mg, 40%) as a white, crystalline solid, mp=255–257 °C {lit.[14] mp [for (−)-**2**]=261 °C}, $[\alpha]_D$ +80.4 (*c* 0.44, MeOH). [Found: $M^{+\bullet}$, 287.1158. $C_{16}H_{17}NO_4$ requires $M^{+\bullet}$, 287.1158]. ^1H NMR (600 MHz, CD_3OD) δ_H see Table 2; ^{13}C NMR (150 MHz, CD_3OD) δ_C see Table 2; ν_{max} (NaCl) 3435, 2898, 1632, 1502, 1483, 1337, 1235, 1039, 930 cm^{-1}; m/z (EI, 70 eV) see Table 1.

4.3. X-ray crystallographic studies

4.3.1. Crystal data for compound (+)-*2*

$C_{16}H_{17}NO_4 \cdot 1.25H_2O$, M=309.83, T=200(1) K, orthorhombic, space group $C222_1$, Z=8, a=7.4746(2), b=17.1338(5), c=24.0329(6) Å, V=3077.85(14) $Å^3$, D_x=1.337 g cm^{-3}, 1545 unique data ($2\theta_{max}$=50°), 1213 with $I>1.5\sigma(I)$; R=0.039, Rw=0.041, S=1.19.

4.3.2. Crystal data for compound *13*

$C_{16}H_{22}ClNO_4$, M=327.81, T=200(1) K, monoclinic, space group $P2_1$, Z=2, a=12.5255(4), b=5.0041(1), c=13.5776(4) Å, β=106.574(1), V=815.67(4) $Å^3$, D_x=1.335 g cm^{-3}, 3726 unique data ($2\theta_{max}$=55°), 3108 with $I>3.0\sigma(I)$; R=0.026, Rw=0.027, S=1.13.

4.3.3. Structural determinations

Images were measured on a Nonius Kappa CCD diffractometer (Mo Kα, graphite monochromator, λ=0.71073 Å) and data extracted using the DENZO package.[27] Structure solution was by direct methods (SIR92).[28] The structures of compounds (+)-**2** and **13** were refined using the CRYSTALS program package.[29] Crystallographic data (excluding structure factors) for these compounds have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. 675210 and 675211, respectively. 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, email: data_request@ccdc.cam.ac.uk or web: www.ccdc.cam.ac.uk/data_request/cif).

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